Check for updates

DOI: 10.1002/pds.5114

WILEY

ICPE All Access conference abstracts

Benefit-Risk Assessment, Communication, and Evaluation (BRACE)

102 | Evaluation of the effectiveness of direct healthcare professional communication regarding new dosage of paracetamol paediatric syrup

Françoise Wuillaume, Martine Sabbe, Javier Sawchik and Jamila Hamdani

Federal Agency for Medicines and Health Products, Brussels, Belgium

Background: In April 2018, a new posology of paracetamol paediatric syrup was introduced in the Belgian market. The composition of the syrup remained unchanged but the dosing pipette was recalibrated to provide 15 mg/kg instead of 10 mg/kg. This change in posology was selected as a case-study to evaluate the effectiveness of Direct Healthcare Professional Communication (DHPC).

Objectives: To determine the proportion of healthcare professionals (HCP) who were informed of the change in posology of paracetamol paediatric syrup in Belgium.

Methods: A cross-sectional online survey was conducted one month after the introduction of the new paracetamol dosage. HCPs were asked if they were aware of the change in posology, source of information and opinion regarding the most reliable source of information. Dissemination of the survey was through email-lists of professional associations and through their websites. The estimated source population was over 8 700 community pharmacists, 1 050 hospital pharmacists, 2 370 paediatricians and 4 500 general practitioners (GPs). Frequencies and percentages of item response were calculated, including 95% confidence interval (95%CI), for the number of respondents overall and per professional category.

Results: Overall, 1 032 HCP responded, including community pharmacists (45%), paediatricians (30%), GPs (18%), and hospital pharmacists (4%). A total of 812 (79%, 95%CI 76-81) respondents reported that they were informed of the change. Awareness was greatest among community pharmacists (92%, 95%CI 89-94) followed by hospital pharmacists (87%, 95%CI 74-94), and paediatricians (77%, 95%CI 72-81). Only 53% (95%CI 45-60) of the GPs reported that they were aware of the change. Professional media (website or newsletters) and DHPC were the most frequently cited information sources. The DHPC was the primary source among 46% (95%CI 31-62) of hospital pharmacists, 42% (95%CI 36-48) of paediatricians, 34% (95%CI 23-45) of community pharmacists, and 25% (95%CI 16-34) of GPs. The DHPC was also cited as the most reliable source of information by 39% (95%CI 36%-43%) of informed respondents.

Conclusions: Although responder bias could have influenced the results, this survey indicates pharmacists and paediatricians were well aware of the new posology. The DHPC and professional information sources played an important role in this communication. We also confirmed the importance to maintain multiple sources of information. However, almost half of GPs were not aware of this change and further investigations are recommended in this professional group.

2372 | Medication storage and disposal in Saudi Arabia: Opportunities for public health improvement

Rasha Almubark, Aljoharah Algabbani, Nora Althumairi and Nasser Bin Dhim

Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: Inappropriate drug storage (IDS) and inappropriate drug disposal (IDD) has previously been observed to lead to inappropriate use, accidental poisoning and medication errors. Therefore, many studies have examined patterns and methods of disposing medication and risks associated with it. These studies were carried out in the USA, UK, New Zealand, Russia among other countries worldwide, but almost none in the Kingdom of Saudi Arabia (KSA).

Objectives: This study aims to describe the distribution of IDS and IDD in KSA population, and to describe the characteristic associated with it.

Methods: A cross-sectional national survey using quota sampling, population-based of residents of KSA conducted via in-person interviews.

Results: A total of 801 surveys were available for analysis, the mean age of respondents was 33 (±11). Majority of respondents reported having diabetes and hypertension (58.8% and 31.5%, respectively). Most of respondents reported (fridge 69.1%) as their preferred location for medication storage, (52.1%) reported that stored medications were not kept in a box or cabinet dedicated for medication only. In addition, 48.4% indicated that they store medications at home for emergency uses. Additionally, 71.3% reported throwing medication in the trash, is the method they are using for medication disposal.

Conclusions: Approximately half of KSA residents do not store the medications in a dedicated location, which is contrary to the current Saudi Food and Drug Authority regulations. Future studies are needed to better characterize the distribution and determinants of storing medications at home across KSA. Moreover, existing guidelines need improvement for better disposal options within KSA community.

© 2020 The Authors. *Pharmacoepidemiology and Drug Safety* © 2020 John Wiley & Sons, Ltd.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2588 | Proton pump inhibitor use and the risk of hepatocellular carcinoma: A systematic review of real-world data

Ambrish Singh[1], Robin Jha[2], Salman Hussain[3] and Benny Antony[1]
[1]*University of Tasmania, Hobart, Australia;* [2]*Independent Researcher, Delhi, India;* [3]*Jamia Hamdard, Delhi, India*

Background: Proton pump inhibitors (PPIs) are one of the most frequently used prescription drugs globally. Recently, there have been concerns that PPI therapy is associated with an increased risk of cancer such as hepatocellular carcinoma (HCC). However, the results of real-world clinical studies are conflicting.
Objectives: A systematic literature review was conducted to identify all the evidence and determine the effect of the use of PPI on the risk of HCC based on the published real-world data (RWD) studies.
Methods: We performed a systematic review and meta-analysis of RWD studies, adhering to the PRISMA guidelines, to evaluate the risks of HCC with PPI use. All RWD studies that assessed the risk of HCC in PPI users compared to PPI nonusers were included. We used the generic inverse variance method and RevMan (5.3.5) to meta-analyses the risk ratios (RRs) using a random-effects model. We used Newcastle-Ottawa scales (NOS) to assess the study quality. The study protocol was registered at PROSPERO [CRD42019109885].
Results: Of the identified studies, six (4 cohort and 2 case-control) with more than 33,102 HCC cases were included in our analysis. In PPI users, compared with PPI nonusers, the unadjusted and adjusted risk ratio (RR) for HCC (studies, n= 4) was 1.80 [95 % confidence interval (CI): 1.03 - 3.14, p<0.05] and (n= 6) 1.55 [CI: 1.17-2.82, p<0.05], respectively. When stratified by study design, the risk of HCC, in PPI users compared to PPI nonusers, was significant for cohort studies (n= 4) [1.51 (CI: 1.23-1.86, p<0.05)], and non-significant [1.64 (CI: 0.55-4.87, p=0.38)] for the case-control studies (n= 2). There was a significant heterogeneity (I^2>88%) among the studies and the majority (n= 5) of the studies were of moderate to high quality, based on NOS.
Conclusions: This meta-analysis found a significantly increased risk of HCC in PPI users compared to PPI nonusers; however, the results should be interpreted with caution owing to the inclusion of observational studies with significant heterogeneity.

2600 | Process indicators and outcomes to assess the effectiveness of additional risk minimisation measures in Europe

Esther Artime[1], Nawab Qizilbash[2,3], Rafael Herruzo[1] and Macarena Garrido-Estepa[4]
[1]*Universidad Autónoma de Madrid, Madrid, Spain;* [2]*OXON Epidemiology, Madrid, Spain;* [3]*London School of Hygiene & Tropical Medicine, London, United Kingdom;* [4]*Ministry of Science and Innovation, Madrid, Spain*

Background: Good Pharmacovigilance Practice XVI recommends the evaluation of additional risk minimisation measures (aRMMs) with process indicators and outcomes.
Objectives: To describe study designs, measures and results in risk minimisation evaluation plans (RM Plans) that include process indicators and outcomes in Europe.
Methods: A systematic search was conducted using the EU PAS Register, PubMed, and grey literature to identify RM Plans for products involving one or multiple studies to assess the effectiveness of aRMMs via process indicators and outcomes, between 1Jan2011 and 12Oct2019. Process indicators include measures of awareness, receipt, use, knowledge, and self-reported behaviour via surveys. Outcome measures include health outcomes and behavioural outcomes via measures of prescribing, investigations and monitoring. Data were abstracted from study reports, manuscripts and abstracts.
Results: A total of 129 studies involving 102 products were identified. Eighteen products (18%) with RM Plans assessed process indicators and outcomes; 10/18 plans included process indicators and outcomes within the same study. Most products belonged to the antineoplastic and nervous system groups (61%). Two thirds had HCP educational materials, while patient cards were implemented in half of the products. The 18 RM Plans included 29 studies: cross-sectional surveys (66%; 47% targeted patients and 90% HCPs), retrospective designs (59%; 47% using a pre/post approach) and prospective designs (10%). While 62% measured process indicators [receipt (n=14) or use of aRMMs (n=12), level of knowledge (n=17) and self-reported behaviour (n=15)], prescribing behaviour was assessed via drug utilisation studies in 41% of cases and health outcomes were measured in 28%. The proportion of patients receiving the target drug under on-label/off-label conditions, over time, before and after the aRMMs or at a specific data point, was evaluated by 11 of 29 studies. Monitoring of metabolic parameters, reading errors and inappropriate use were assessed by one study each. Outcomes measured were adverse events. Drug utilisation and health outcomes data were mostly obtained from existing healthcare databases (10 of 29). In four RM Plans a correlation between process indicators and outcomes was noted. Study results were available for 14/18 RM Plans.
Conclusions: Only one in five RM Plans identified in this review assessed both process indicators and outcomes, with health outcomes being measured in a minority. Few within-patient correlations between process indicators and outcomes were noted.

2615 | Digital tools for the communication of risk minimization measures for medicines

Michael Forstner
Mesama Consulting, Bärschwil, Switzerland

Background: The primary goal of a Risk Minimization Plan (RMiP) is to develop activities that help patients and healthcare providers understand important risks associated with a drug and to reduce the chance that a serious side effect might occur. The activities implemented by a drug company as part of this plan are called risk minimization measures (RMM). Implementing an RMiP consists of implementing the RMMs, assessing the usefulness of those

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

activities, and using the assessment results to decide if the RMiP needs to be changed.

Objectives: Despite the widespread use of mobile phone apps and other electronic means for the dissemination of information to patients, RMMs are still mostly implemented as paper-based tools, consisting of e.g., educational material packs or patient alert cards. Numerous evaluations by regulators and companies have shown the relative inefficiency of these tools. In addition, paper based tools require an offline means of effectiveness evaluation, such as a survey, and they do not lend themselves to two-way communication. Early attempts to design electronic tools for RMMs consistent mostly of web-versions of the paper material used for educational purposes but did not make use of the full capabilities of digital tools.

Methods: We review different approaches and show that apps designed to deliver information about the safe use of medicines can also be used to allow patients to report experiences pertaining to the safety of the drug and to quality-of-life related issues they may experience in connection with their disease and/or the drug.

Results: The two-way communication allows for a personalized delivery of safety relevant messages to patients and for a real-time evaluation of the benefit-risk profile by feeding into safety signal management tools directly. The evaluation of process and outcome related parameters to demonstrate the effectiveness of risk minimization is simplified as the collection of these parameters is linked to the use of the tool. Furthermore, the collection of meta-data related to the use of the app, e.g., geo-spatial data, behavioral aspects concerning the use of the app, or the frequency, time and duration of use may help to evaluate important real-world parameters associated with the safe and efficacious use of the medicine. The inherent biases associated with data obtained from such sources and ways of accounting for them are discussed as well.

Conclusions: The use of truly digital tools for patient and HCP education has the potential to change the communication on benefits and risks of drugs substantially and integrate risk management of medicines better into clinical care.

2627 | Association between dose and duration patterns of opioid and benzodiazepine use and risk of overdose among U.S. medicare beneficiaries: A group-based multi-trajectory model

Weihsuan Jenny Lo-Ciganic[1], Ting Wang[2], Yong Ge[3], Bobby Jones[4], James Huang[1], Gary Reisfield[1], Jeanne Lee[3], C. Kent Kwoh[3], Juan Hincapie-Castillo[1], P. Chris Delcher[5], Ching-Yuan Chang[1], Debbie Wilson[1] and Walid Gellad[6]

[1]University of Florida, Gainesville, FL;[2]Chinese Academy of Agricultural Sciences, Beijing, China; [3]University of Arizona, Tucson, AZ; [4]University of Pittsburgh Medical Center, Pittsburgh, PA; [5]University of Kentucky, Lexington, KY; [6]University of Pittsburgh, Pittsburgh, PA

Background: Concurrent opioid and benzodiazepine (OPI-BZD) use continues to rise despite clinical guidelines and US Food and Drug Administration black box warnings opposing such. Over 30% of OPI overdose deaths involve concurrent BZD use. Yet, little is known about OPI-BZD dose and duration patterns most associated with OPI overdose risk.

Objectives: To investigate the dose and duration patterns of OPI-BZD use most associated with OPI overdose risk.

Methods: A retrospective cohort study included fee-for-service, non-cancer Medicare beneficiaries initiating prescription OPIs from 2011-2016. During the first 6 months following OPI initiation (i.e., trajectory period), group-based multi-trajectory models identified distinct OPI-BZD dose and duration patterns, based on average daily morphine milligram equivalents (MME) for OPIs and diazepam milligram equivalents for BZDs. We estimated the risk of time to first OPI-related overdose within 6 months following the trajectory period using inverse-probability-of-treatment-weighted Cox proportional hazards models.

Results: Among 337,879 beneficiaries (age≥65=59.3%, female=71.9%, white=87.6%, having OPI overdose=0.31%), we identified 9 distinct trajectories: low-dose OPIs with low or medium-dose BZDs (n=4 trajectories), medium-dose OPIs with medium or high-dose BZDs (n=3), and high-dose OPI-BZD (n=2). The 6-month overdose risk varied by trajectory when compared to beneficiaries with the lowest-dose OPI-BZD trajectory (25.8% of the cohort). The 4 trajectories for low-dose OPIs (<25 MME) with low or medium-dose BZD and medium-dose (25-50 MME) OPIs with medium-dose BZDs were not associated with an overdose risk (42.5%; adjusted hazard ratios [aHR] range=0.32-1.02). An increased risk of OPI overdose was observed in the following 4 higher-dose trajectories: medium-dose OPIs (25-50 MME) with very-high-dose BZDs (9.9%; aHR=2.70, 95% CI=1.12-6.51); medium-dose (50-100 MME) OPIs with medium-dose BZDs (7.9%; aHR=4.95, 95%CI=1.65-14.84); high-dose OPI-BZD use (7.7%; aHR=8.30, 95%CI=2.36-29.11); and very-high-dose OPIs (>250 MME) with high-dose BZD use (5.1%; aHR=7.63, 95% CI=2.44-23.91).

Conclusions: Among Medicare fee-for-service beneficiaries, OPI overdose risks varied substantially across OPI-BZD trajectories. Compared to the lowest-dose OPI-BZD trajectories, individuals with consistently high-dose OPI-BZD use were associated with 2 to 8 times the overdose risk.

2639 | Hypoglycemia-related ED visits and hospitalizations among initiators of insulin analogues compared to NPH insulin

Marie C. Bradley[1], Yoganand Chillarige[2], Hana Lee[1], Xiyuan Wu[2], Shruti Parulekar[2], Stella Muthuri[2], Michael Wernecke[2], Thomas E. MaCurdy[2], Jeffrey A. Kelman[3] and David Graham[1]

[1]FDA, Silver Spring, MD; [2]Acumen LLC, Burlingame, CA; [3]Centers for Medicare & Medicaid Services, Washington, DC

Background: In clinical trials the risk of severe hypoglycemia did not differ between insulin analogues and neutral protamine hagedorn insulin (NPH) for patients with type II diabetes mellitus (T2DM). A recent observational study examining emergency department

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(ED) visits and hospitalizations for hypoglycemia in T2DM patients found similar results.

Objectives: To examine the risk of ED visits and hospitalizations for hypoglycemia among older T2DM patients who initiated long acting insulin or NPH in real world settings.

Methods: A retrospective new-user cohort study of Medicare beneficiaries aged ≥65 years initiating insulin glargine (407,018), insulin detemir (141,588) or NPH (26,402) who did not use other insulins, from January 2007 to July 2019 was conducted. The primary outcome was time to first hypoglycemia-related ED visit or hospitalization, defined using a modified validated algorithm. Propensity score weighted Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). In the secondary analysis, recurring hypoglycemia events were modeled using the Anderson-Gill model.

Results: There were 7,347 hypoglycemia-related ED visits or hospitalizations during the study period; 5,194 for glargine, 1,693 for detemir, and 460 for NPH with a median follow-up across the three cohorts of 0.37 years (interquartile range: 0.20 to 0.76). Crude incidence rates (with 95% CIs) were 1.74 (1.69, 1.78), 1.67 (1.59, 1.75), and 3.07 (2.79, 3.35), for glargine, detemir and NPH, respectively. Initiators of glargine and detemir had reduced risk of an outcome event compared to NPH initiators, HRs (95% CIs) 0.69 (0.61-0.77) and 0.69 (0.61-0.79), respectively. When adjusting for concomitant use of oral diabetes medication the HRs did not change substantially; 0.71 (0.63-0.80) and 0.72 (0.63-82). The HR remained unchanged for the recurrent event analysis and the risk of recurrent ED visits and hospitalizations increased with the number of prior events.

Conclusions: Initiation of long acting insulin analogues was associated with a lower risk of hypoglycemia-related ED visits and hospitalizations compared with NPH in older T2DM patients.

3699 | Real-world data collection in early access programs: An additional source of data to inform benefit-risk assessment in the pre-approval phase

Mira Soni[1], Delphine Saragoussi[2], Dara Stein[1], Doug Eckley[3] and Jodie Block[4]

[1]Evidera, London, United Kingdom; [2]Evidera, Paris, France; [3]PPD, Cambridge, United Kingdom; [4]PPD, Wilmington, NC

Background: Early access programs (EAPs) provide patients with life-threatening diseases with access to investigational products prior to market approval. Across EAPs, safety data collection is usually required, but guidance on effectiveness data is limited and can vary by local regulations. The 'real-world data' (RWD) collected in EAPs could supplement trial data in the pre-approval phase, as the investigational drug is provided to a wider range of populations than would be eligible for a trial and patients are monitored as per expected usual practice. However, careful consideration of RWD collection ahead of EAP implementation is needed to ensure data quality to support pre-approval benefit-risk assessment.

Objectives: We developed an RWD framework to collect long-term effectiveness and quality of life (QoL) outcomes as part of an oncology EAP in the United Kingdom (UK). To our knowledge this was the first UK EAP with a voluntary observational study component. Our aim is to share knowledge on optimization of RWD collection in EAPs for future use in benefit-risk assessment.

Methods: During RWD framework development, input/approval on the observational study were sought from the ethics committee and regulatory body stakeholders. As drug supply requests in the UK EAP were physician-led, it was not possible to know in advance which sites would participate, so special circumstances were required to set-up and train sites for data collection within a couple of days of them submitting a drug supply request. For physicians, data collection was limited to key outcomes [disease progression, survival] collected from patient medical records. QoL questionnaires were completed by patients at home.

Results: To ensure data quality to support pre-marketing benefit-risk assessment, the following aspects should be considered ahead of EAP implementation: (1) primary research objectives should be planned and vetted with key stakeholders; (2) expected sample size should be accounted for and ways to improve the reliability of data (e.g. data pooling in multi-country EAPs); (3) a robust data collection platform should be utilized that is easy and convenient for physicians; (4) electronic questionnaires are recommended rather than paper questionnaires; (5) a rigorous safety reporting plan should be in place.

Conclusions: Regulatory bodies are increasingly looking to incorporate RWD in pre-approval benefit-risk assessment. EAPs could contribute RWD, however the related setting and challenges need to be taken into account to ensure quality data that can be considered for drug approval.

3723 | Risk of stroke and bleeding in atrial fibrillation treated with apixaban compared to warfarin

Marie C. Bradley[1], Emily C. Welch[2], Efe Eworuke[1], David Graham[1], Rongmei Zhang[1] and Ting-Ying Huang[2]

[1]FDA, Silver Spring, MD;[2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: Apixaban use has been increasing in recent years in the US. A previous FDA study reported a favorable benefit risk for apixaban compared to warfarin for stroke prevention in older non-valvular atrial fibrillation (NVAF) patients. However, that study was restricted to those aged 65 years or more and it remains unclear whether this favorable benefit risk profile persists in other populations including younger users. We examined if a similar benefit risk profile was observed in the Sentinel Distributed Database (SDD), and if it varied by age group.

Objectives: To examine if a similar benefit risk profile was observed in the Sentinel Distributed Database (SDD), and if it varied by age group.

Methods: Patients, 21 years and older initiating apixaban or warfarin for NVAF, between December 28, 2012 and June 30, 2018, were identified in the SDD. Cox proportional hazards regression was used to estimate the hazard ratios (HR) and 95 % confidence intervals (95%

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

CI) for each outcome [ischemic stroke, gastrointestinal (GI) bleeding and intracranial hemorrhage (ICH)] in propensity score matched apixaban users compared to the warfarin users. A subgroup analysis by age (21-64, 65-74 and 75+ years) was conducted.

Results: After matching, 55.3% and 58.4% (n=55,038) of the apixaban and warfarin users were included in the main analysis. GI bleeding was the most common outcome. The HR (95%CI) for GI bleeding, ICH and ischemic stroke in apixaban users compared to warfarin users was 0.57 (0.50-0.66), 0.53 (0.40-0.70) and 0.56 (0.45-0.71) respectively. The reduced risk of these outcomes in apixaban compared to warfarin users persisted across age groups and was lowest in those aged 21-64 years.

Conclusions: In NVAF patients initiating either apixaban or warfarin for stroke prevention, apixaban was associated with a decreased risk of GI bleeding, ICH and ischemic stroke compared to warfarin, and this reduced risk was seen in all age groups.

3736 | Comparative risk assessment of severe abnormal uterine bleeding associated with non-vitamin K oral anticoagulants

Efe Eworuke[1], Laura Hou[2], Rongmei Zhang[1], Hui-Lee Wong[1], Peter Waldron[1], Abby Andersen[1], Audrey Gassman[1], David Moeny[1] and Ting-Ying Huang[2]

[1]US Food and Drug Administration, Silver Spring, MD;[2]Harvard Pilgrim Health Care Institute, Boston, MA

Background: Clinically relevant uterine bleeding has been reported among women of reproductive age, exposed to oral anticoagulants including Non-Vitamin K Oral Anticoagulants (NOACs).

Objectives: To conduct a pairwise NOAC risk assessment for severe abnormal uterine bleeding (SAUB) defined as vaginal bleeding (VB) requiring same-day transfusion and VB requiring surgery (hysterectomy, hysteroscopy, hysteroscopic polypectomy, myomectomy, dilation/curettage, endometrial ablation, or uterine artery embolization) within 30 days after starting NOAC or warfarin.

Methods: We conducted a retrospective cohort study in the Sentinel Distributed Database. Females 18+ years with venous thromboembolism (VTE), or atrial flutter/fibrillation (AF) who newly initiated a NOAC (rivaroxaban [R], apixaban [A], dabigatran [D]) or warfarin [W] from 01/2010 to 09/2015 were included. Patients with hysterectomy, VB, use of oral contraception/antifibrinolytics/vaginal packing, insertion of intrauterine device or study outcome within 183 days were excluded. We followed patients from dispensing date until the earliest of transfusion or surgery following VB, disenrollment, exposure or study end date, initiation of other NOAC or warfarin, or recorded death. Using Cox proportional hazards regression via propensity score stratification, we estimated the hazard ratios (HRs) overall and by age (18-50 and 51+ years), past gynecological disorder, low vs. high NOAC dose, and NOAC indication. Four pairwise comparisons were conducted; R-D, R-A, D-A and R-W for each intervention.

Results: We identified 194,400 rivaroxaban, 80,074 dabigatran, 97,784 apixaban and 722,772 warfarin new users. Overall, there was an increased risk of surgical intervention with rivaroxaban when compared to dabigatran (HR: 1.19; 95% CI:1.03-1.38), apixaban (1.23; 1.04-1.47) and warfarin (1.34; 1.22-1.47). No difference in risk was observed for the D-A comparison. Increased risk of transfusion was observed for rivaroxaban compared to dabigatran (1.43; 1.03-2.17) only. For patients with no gynecological history, rivaroxaban was associated with risk of surgical intervention compared to dabigatran (1.22; 1.05-1.42), apixaban (1.25; 1.04-1.49) and warfarin (1.36; 1.23-1.50). No difference in risk was observed for R-D, R-A and D-A comparisons stratified by age and dose for both outcomes.

Conclusions: Our study found increased SAUB risk with rivaroxaban users compared to other NOACs or warfarin. The increased risk was present among women without underlying gynecological conditions.

3739 | Risk of neuropsychiatric adverse events among montelukast users

Efe Eworuke[1], Nicole Haug[2], Andrew Mosholder[1], Noelle Cocoros[2], Marie Bradley[1], Dinci Pennap[1], Elizabeth C. Dee[2], Sengwee Toh[2], Ella Prestine[2], Andrew Petrone[2], Ivone Kim[1], Yong Ma[1], Jennifer G. Lyons[2] and Veronica V. Sansing[1]

[1]US Food and Drug Administration, Silver Spring, MD;[2]Harvard Pilgrim Health Care Institute, Boston, MA

Background: There have been conflicting results from observational studies regarding the risk of neuropsychiatric adverse events (NAEs) with montelukast use.

Objectives: To determine if there are associations of depressive disorders, self-harm, and suicide with use of montelukast compared to inhaled corticosteroid (ICS) use.

Methods: We conducted a retrospective cohort study (01/2000-09/2015) using data from the Sentinel Distributed Database. We identified montelukast and ICS new users, aged 6 years and older, with a diagnosis of asthma (ICD-9-CM: 493.xx) in the six months prior to index dispensing. We excluded patients with chronic obstructive pulmonary disease during the baseline period but allowed comorbid allergic rhinitis. We matched montelukast to ICS users 1:1 on propensity score. Patients were followed from the day after the cohort entry date until a diagnosis of depression, self-harm, or suicide; exposure end date; dispensing of comparator drug, other leukotriene antagonists, long-acting-beta-agonists (LABA), oral corticosteroids, or a combination ICS/LABA product; asthma-related hospitalization; death; disenrollment; or data end date. We estimated hazard ratios (HRs) and 95% confidence intervals (CI) for each study outcome overall and by age, sex, psychiatric history, and pre- and post-2008 labeling updates using Cox proportional hazards regression.

Results: We matched 457,377 montelukast users with 457,377 ICS users. Most NAEs (93%) occurred in patients with a history of a psychiatric disorder. Exposure to montelukast was associated with a lower risk of treated outpatient depressive disorder (HR: 0.91; CI: 0.89-0.93) compared to ICS exposure. No increased risks of inpatient depressive disorder (HR: 1.06; CI: 0.90-1.24), self-harm (HR: 0.92; CI:

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

0.69-1.21), or self-harm using a modified algorithm (HR: 0.81; CI: 0.63-1.05) were observed with montelukast use compared to ICS use.
Conclusions: When compared to use of ICS, no associations between montelukast use and hospitalizations for depression or self-harm events were found. Psychiatric comorbidity was common, and the majority of NAEs occurred in patients with a psychiatric history. Our study outcomes were limited to severe NAEs and early termination of montelukast use to resolve depressive symptoms may have impacted the results.

3744 | Heterogeneity of patient preferences for benefits and risks of antiplatelet therapies

Cathy Anne Pinto[1], Gin Nie Chua[2], Ella Brookes[2], Johanna Hyacinthe[1] and Tommi Tervonen[2]
[1]*Merck & Co., Inc, Kenilworth, NJ;*[2]*Evidera, London, United Kingdom*

Background: Benefit-risk (B-R) profiles of antiplatelet treatments for cardiovascular (CV) disease depend on patient risk factors and preferences for ischemic and bleeding risk, which may also be affected by patient characteristics.
Objectives: To understand myocardial infarction (MI) patient preferences associated with antiplatelet therapies.
Methods: An online discrete choice experiment (DCE) survey was used to elicit MI patients' preferences for ischemic and bleeding risk for antiplatelet therapy: CV death; non-fatal ischemic stroke (IS), recurrent MI, intracranial hemorrhage (ICH) and other non-fatal severe bleeding (OSB). DCE data was analysed using a heteroscedastic multinomial logit model (HMNL), controlling for scale heterogeneity between patients recruited from different sources (access panels vs NHS sites) and preference heterogeneity in subgroups (e.g. age, bleeding risk factors). Maximum acceptable risk of CV outcomes was estimated for a 1% decrease in mortality risk.
Results: 353 patients completed the survey. Majority were male (84%), with median (IQR) age of 65 (59-71) years. Approximately one-third (38%) experienced their most recent MI <1 year prior to completing the survey. Internal validity was high with most patients correctly answering a dominance test (93%), stability test (82%) and trading across choice tasks (99%). The HMNL model had good fit (adj. R^2=0.27) with no significant scale heterogeneity detected between patients recruited from the two sources. For a 1% decrease in mortality risk, patients were willing to accept an increased risk (95% CI) of 0.7% (0.6 - 0.8) for ICH, 1.0% (0.8 - 1.2) for OSB, 1.9% (0.8 - 2.9) for IS. Significant (p<0.001) interactions of MI and age and bleeding risk factors were observed. Older patients (≥65 years) were willing to accept significantly lower increase (1.1%, 95% CI 0.8 - 1.3) in MI risk for 1% mortality risk reduction compared to younger patients (2.1%, 95% CI 1.4 - 2.8). Older patients with ≥1 bleeding risk factor cared less about MI risk than those without bleeding risk factors.
Conclusions: The acceptability of MI risk depends on age and bleeding risk factors. This heterogeneity may impact BR profiles for MI patients receiving antiplatelet therapy.

3786 | Can monitoring instructions provided in direct healthcare professional communications (DHPCs) be applied in clinical practice? - A retrospective analysis of DHPCs sent out between 2007 and 2018

Christine E. Hallgreen, Arnela F. Boskovic, Maja-Marie G. Højer and Marie Louise de Bruin
Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Background: Direct to Healthcare Professional Communications (DHPC) are one of the most used additional risk minimisation measures. Around 10% of all drugs require regulatory action to inform healthcare professionals about new safety concerns that appear after marketing approval. Often DHPCs include instructions to monitor patients. However, the effectiveness of DHPCs and their usability in clinical practice has been criticised.
Objectives: In this study we assessed whether DHPCs are applicable in clinical practice and how the applicability differs according to safety concerns and type of monitoring.
Methods: A retrospective cohort study of DHPCs containing monitoring instructions issued in Denmark between 2007 and 2018 was conducted. Clinical applicability of monitoring instructions was assessed according to the Systematic Information for Monitoring (SIM) score. Associations between different characteristics of instructions and the SIM score were compared with analysis of variance (ANOVA) and the post hoc test Tukey's HSD if significant.
Results: In total, 297 DHPCs were issued, of which 97 contained 134 monitoring instructions. For 95% of these DHPCs the European Medicines Agency was involved. The average SIM score was 2.551.57 (range 0-6) and only 47% were considered applicable in clinical practice (SIM score 3). In addition, even fewer (11%) instructions were considered a "sufficient instruction" which also reported about facts and risks. Differences between clinical applicability according to type of monitoring were observed, specifically between clinical monitoring (SIM score 1.9) and biomarker monitoring (physical SIM score 2.9, p=0.029, and laboratory SIM score 3.4, p<0.0001).
Conclusions: Monitoring instructions were found not to be clinically applicable according to the SIM score. Our study concludes the need for further research and regulatory steps to ensure clinical applicability of safety communications.

3818 | Evaluation of spontaneous adverse event reports for hepatocellular carcinoma attributed to sofosbuvir and its combinations within the FDA adverse events reporting system

Mai M. Salama[1], Ahmed M. Elkersh[2] and Mohamed A. Mekkawy[3]
[1]*Biomedical Informatics and Medical Statistics Department, Medical Research Institute, Alexandria University, Alexandria, Egypt;*
[2]*Epidemiology Department, High Institute of Public Health, Alexandria University, Alexandria, Egypt;* [3]*Medical Statistics Department, High Institute of Public Health, Alexandria University, Alexandria, Egypt*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Few trials have reported conflicting results about development or recurrence of hepatocellular carcinoma (HCC) among patients treated with direct-acting antivirals (DAAs). However, no study has analyzed spontaneous reports of HCC with these drugs.

Objectives: To describe and evaluate spontaneous adverse event reports of HCC attributed to sofosbuvir and its combinations.

Methods: We identified adverse events reports listing sofosbuvir or sofosbuvir and its combinations in the FDA Adverse Events Reporting System (FAERS) from July 2014 to September 2019. We used the terms "sofosbuvir," "voxilaprevir," "glecaprevir," "pibrentasvir," "ledipasvir," "dasabuvir," "ombitasvir," "paritaprevir," "ritonavir," "elbasvir," "grazoprevir" and "velpatasvir" to identify sofosbuvir and its combinations. Hepatocellular carcinoma (HCC) MedDRA term was used to identify HCC events. We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) for each drug.

Results: Among 3,258,771 FAERS reports between July 2014 and September 2019, 28,894 (0.9 %) reports mentioned DAAs, 5546 (19 %) mentioned sofosbuvir, 16131 (56 %) mentioned sofosbuvir /ledipasvir, 6609 (23 %) mentioned sofosbuvir/velpatasvir, and 608 (2.0 %) mentioned sofosbuvir/velpatasvir/voxilaprevir. There were 2642 (9 %) HCC reports during the same period of which 602 reports (22.8 %) were attributed to sofosbuvir combinations, 301 (50 %) were attributed to sofosbuvir, 244 (40.5%) were attributed to sofosbuvir /ledipasvir, 42 (7 %) to sofosbuvir/velpatasvir, and 15 (2.5 %) to sofosbuvir/velpatasvir/voxilaprevir. The PRR for sofosbuvir was 75.42 (95% CI: 67.09, 84.79), for sofosbuvir /ledipasvir was 20.45 (95% CI: 17.95, 23.31), for sofosbuvir/velpatasvir was 7.95 (95% CI: 5.86, 10.77), and for sofosbuvir/velpatasvir/voxilaprevir was 30.6 (95% CI: 18.54, 50.51) respectively, and the ROR were 79.69 (95% CI: 70.47, 90.13), 20.75 (95% CI: 18.18, 23.7), 7.99 (95% CI: 5.8, 10.8), and 31.35 (95% CI: 18.75, 52.4) respectively.

Conclusions: Although FAERS is subject to significant limitations, the results suggest that sofosbuvir and its combinations have a statistically significant association with an increased incidence of HCC. Further studies are promptly needed to investigate this risk.

3826 | Risk of non-melanoma skin cancer associated with hydrochlorothiazide-containing products in the United States

Efe Eworuke[1], Nicole Haug[2], Marie Bradley[1], Austin Cosgrove[2], Elizabeth C. Dee[2], Sruthi Adimadhyam[2], Hana Lee[1], Tiffany Woodworth[2] and Sengwee Toh[2]

[1]US Food and Drug Administration, Silver Spring, MD;[2]Harvard Pilgrim Health Care Institute, Boston, MA

Background: Recent studies conducted in Europe report an increased risk of non-melanoma skin cancer (NMSC) with hydrochlorothiazide-containing (HCTZ) products. It remains unclear whether the observed risk applies to the US.

Objectives: To determine whether there is an increased risk of NMSC among patients exposed to HCTZ compared to patients exposed to angiotensin-converting-enzyme inhibitors (ACEIs).

Methods: We conducted a retrospective cohort study (January 2000-August 2018) in the Sentinel Distributed Database. Patients at the time of dispensing were followed until a diagnosis of squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) (ICD-9: BCC: 173.x1; SCC: 173.x2; ICD-10: BCC/SCC: C44.xxx) requiring excision; destruction; Mohs microscopic chemosurgery or topical chemotherapy treatment on or within 30 days after the diagnosis date; or a censoring event (non-outcome cancer, radiation or chemotherapy, disenrollment, or death). Using Cox proportional hazards regression analysis via 1:1 propensity score matching, we estimated the hazard ratios (HRs) of NMSC overall and separately by age, gender, and race. We also examined site- and age-adjusted incidence rate ratios (IRRs) by cumulative HCTZ dose within the matched cohort.

Results: After propensity score matching, 5.2 million HCTZ and 5.2 million ACEI users were retained for analyses. Overall, there was no difference in risk between HCTZ and ACEI of BCC (HR: 0.99; 95% CI: 0.97-1.00) but an elevated risk of SCC (1.04; 1.02-1.06). Elevated risks of BCC (1.09; 1.07-1.11) and SCC (1.15; 1.12-1.17) were observed among Whites. An increased risk of SCC was also observed in males (1.06; 1.03-1.09) and older patients (1.05; 1.02-1.08 for 60-74 and 1.04; 1.01-1.07 for ≥75 year-olds). Cumulative HCTZ dose of ≥50,000mg was associated with an increased risk of SCC (IRR: 1.19; 1.05-1.35 in all patients and 1.27; 1.10-1.47 in Whites) but not BCC (IRRs 0.93; 0.84-1.02 in all patients; and 0.92; 0.81-1.04 in Whites)

Conclusions: We identified a small increased risk of NMSC associated with HCTZ use. This magnitude of risk should not alter the risk-benefit profile for HCTZ use in the treatment of hypertension. Instead, risk mitigation strategies such as reducing prolonged sun exposure and following up clinically on new skin lesions should be considered while on HCTZ.

3969 | Changes in zolpidem exposure cases in the national poison data system after FDA drug safety communications

Esther Zhou, Zhou Feng, Ellen Pinnow, Joann Lee, Amarilys Vega and Gerald DalPan

Food and Drug Administration (FDA), Silver Spring, MD

Background: The US Food and Drug Administration (FDA) issued two Drug Safety Communications (DSCs) concerning the sleep aid zolpidem, first in January and a follow-up in May 2013, after emerging data from post-approval clinical experience demonstrated a high risk of next-morning impairment.

Objectives: To evaluate the long-term impact of the 2013 zolpidem DSCs, we assessed trend changes in nation-wide zolpidem exposure cases reported to the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS).

Methods: We used the NPDS data to conduct a retrospective study of zolpidem-related call cases in the United States, from 2009 to 2018. We calculated monthly rate of single-product zolpidem exposures per 1,000 AAPCC single-product human exposures.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

We evaluated long-term impact of the FDA's zolpidem DSCs, using interrupted time series (ITS) analysis with seasonal adjustment. We also assessed concomitant exposures for multiple-product exposures involving zolpidem. Cases related to sedating antidepressants (ADs), commonly used for sleep disorders, were used as a comparison group.

Results: During the 10-year period, we identified 74,958 zolpidem and 78,101 sedating ADs single-product exposures; and 87,996 zolpidem and 140,854 sedating ADs multiple-product exposures. Among the single-product zolpidem cases, 25% were children, 59% were female; 40% reported "Intentional - Suspected Suicide"; 31% were admitted to critical care unit or psychiatric care facility. Before the 2013 DSCs, monthly trend for single zolpidem rate was constant with approximately 5 cases per month per 1,000 single-product exposures. The rate dropped to 4 cases immediately after May 2013 (-0.9, 95% CI -1.1, -0.7; P <0.0001); then continuously decreased afterwards compare to baseline (monthly change: -0.03, 95% CI -0.03, -0.02, P <0.0001). Even though there was a significant but smaller increase in AD rate immediately after May 2013 (0.4, 95% CI 0.25, 0.60, P <0.0001), the trend afterward did not change compare to baseline (0.00, 95% CI -0.01, 0.01, p =0.97). Among multiple-product exposures, benzodiazepines were the most frequently reported concomitant drugs involving both zolpidem or sedating AD, in approximately 40% of the cases.

Conclusions: The FDA's zolpidem-DSCs have significant immediate and long-term impact on nation-wide monthly trend of single zolpidem exposure cases. Partial switching from zolpidem to sedating ADs may have occurred in early 2013.

4069 | Retirement of statistical significance testing

Olaf Klungel[1], Kenneth J. Rothman[2], Hans Hillege[3] and John Fletcher[4]
[1]*Utrecht University, Utrecht, Netherlands;* [2]*Research Triangle Institute, Research Triangle Park, NC;* [3]*Dutch Medicines Evaluation Board/ University Medical Center Groningen, Utrecht/Groningen, Netherlands;* [4]*BMJ, London, United Kingdom*

Background: For decades, science has relied on an arbitrary p-value of 0.05 to make a distinction between a statistically significant study result, or not. However, there has been more and more debate about abandoning statistical significance testing in its current form, leading to a recent call by three statisticians to abandon statistical significance (Amrhein V, Greenland S, McShane B,. Retire statistical significance. Nature 2019;567:305-7). The call has been signed by more than 800 researchers, many of which from our society, clearly showing the urgency scientists feel to get rid of the current situation.

Objectives: To identify and understand misconceptions of statistical significance testing. To understand the role of significance testing in decision making on drug approvals from the regulatory perspective and decision making on scientific papers from the perspective of medical journals. To provide alternative ways of interpreting study findings for decision making.

Description: To set the stage, Kenneth Rothman will speak (20 min) about misconceptions related to statistical significance. Using examples of published studies, the audience will get an understanding of why statistical significance testing is misleading. In addition, alternatives for significance testing will be discussed. The second speaker, Hans Hillege will discuss (20 min) the role of significance in regulatory decision making. Lastly, John Fletcher, research editor of BMJ, will speak (20 min) about significance testing from the perspective of a major medical journal.

A panel discussion will be moderated by Olaf Klungel (30 min).

4097 | Evaluation of the physician education component of the ozurdex risk management plan

Laurie Zografos[1], Elena Rivero-Ferrer[2], Staci Abramsky[3], Jean Lou[3], Eric Davenport[1] and Daniel Wolin[4]
[1]*RTI Health Solutions, Research Triangle Park, NC;*[2]*RTI Health Solutions, Barcelona, Spain;* [3]*Allergan, Irvine, CA;*[4]*RTI Health Solutions, Marshall, MI*

Background: In 2014, a survey was conducted to evaluate physician understanding of educational materials (Injector's guide and patient's guide) developed as part of the risk management plan (RMP) for Ozurdex. The educational materials were revised according to regulatory requirements and were redistributed beginning in 2014.

Objectives: To assess the effectiveness of the revised educational materials, a new survey was conducted from October through December 2018.

Methods: In this noninterventional, cross-sectional study, physicians in France, Germany, Spain, and the United Kingdom who administered Ozurdex in the previous 6 months were eligible to complete a web-based, multiple-choice questionnaire designed to evaluate physicians' knowledge and understanding of the educational materials on six knowledge areas: contraindications to Ozurdex injection (6 items), patient preparation for injection (5 items), proper injection technique (7 items), important injection-associated risks (12 items), patient monitoring post-injection (4 items), and importance of counselling patients on symptom reporting (5 items). For each area, the number of physicians considered to have knowledge of that area was determined. Correctly answering $\geq$80% of questions in an area was considered the threshold for knowledge in that area.

Results: Of 4,162 physicians invited to participate, 401 (9.6%) completed the questionnaire. Knowledge of proper injection technique was the highest at 76%. Knowledge of injection-associated risks, the importance of counselling patients on symptom reporting, and contraindications to Ozurdex injection reached 68%, 65%, and 61%, respectively. Physicians were least knowledgeable of patient preparation for Ozurdex injection and patient monitoring post-injection with 31% and 3%, respectively. Only 31% of physicians reported receiving the Ozurdex injector's guide, of whom 82% reported having read it. Variation in knowledge by country was minimal, as were differences in knowledge between physicians who reported receiving the materials and those who did not.

Conclusions: Knowledge varied considerably across information categories, and the proportion of physicians who reportedly received the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

injector's guide was low. Knowledge was high for most key areas covered by the guide, particularly about injection technique and risks. Knowledge of material from the injector's guide, and recall of receipt of it, may have been affected by the length of time between distribution of the revised materials and the survey, which could have been as much as four years.

4138 | Attitudes of pharmacy students towards patient safety: A multinational cross-sectional study

Abdallah Y. Naser[1], Zahra Khalil Alsairafi[2], Ahmed Awaisu[3], Hassan Alwafi[4], Oriana Awwad[5], Salman Hussain[6], Avinash Kumar Singh[6], Alaa Alsharif[7,8], Fatima B. Jeragh-Alhaddad[2], Angga Prawira Kautsar[9] and Amal Khaleel AbuAlhommos[10]

[1]Isra University, Amman, Jordan; [2]Kuwait University, Kuwait, Kuwait; [3]Qatar University, Doha, Qatar; [4]Umm Alqura University, Mecca, Saudi Arabia; [5]University of Jordan, Amman, Jordan; [6]School of Pharmaceutical Education and Research, New Delhi, India; [7]University College London, London, United Kingdom; [8]Princess Norah bint Abdul Rahman University, Riyadh, Saudi Arabia; [9]Universitas Padjadjaran, Bandung, Indonesia; [10]King Faisal University, Alhasa, Saudi Arabia

Background: Patient safety is one of the main concerns of healthcare systems during the provision of healthcare. Pharmacy programmes globally include content related to patient safety in their curricula. Attitudes of pharmacy students towards patient safety can substantially impact their behaviours.

Objectives: To evaluate the attitudes of undergraduate pharmacy students towards patient safety in six developing countries.

Methods: A cross-sectional study using a pre-validated questionnaire (Walpola et al.) was conducted among undergraduate pharmacy students between October 2018 and September 2019 in six developing countries (Jordan, Saudi Arabia, Kuwait, Qatar, India, and Indonesia). Walpola et al. questionnaire was used in this study. This questionnaire contains five subscales: being quality improvement focused, internalising errors regardless of harm, value of contextual learning, acceptability of questioning more senior healthcare professionals' behaviour, and attitude towards open disclosure, using a five-point Likert scale (range 0-4). Multiple-linear regression analysis was used to identify predictors of positive attitudes towards patient safety.

Results: A total of 2,595 students participated in this study (1,044 from Jordan, 514 from Saudi Arabia, 145 from Kuwait, 61 from Qatar, 416 from India, and 434 from Indonesia). Overall, the pharmacy students had good attitudes towards patient safety with a mean score of 37.4 (SD= 7.0) out of 56 (66.8%). "Being quality improvement focused" scale had the highest score, 75.6%. The scale with the lowest score was "internalising errors regardless of harm", 49.2%. Female students had better attitude towards patient safety score (p= 0.001). Being at a higher level of study and involved in or witnessed harm to patients while practicing were important predictors of negative attitude towards patient safety (p= 0.000).

Conclusions: Patient safety content should be covered comprehensively in pharmacy curricula and reinforced at each year of study. This should focus more on students at their final years of study and who started their training. This will enhance our confidence that the next generation of pharmacists are equipped with the requisite knowledge, core competencies, and attitudes to ensure optimal patient safety when they practice.

4176 | Participation in survey studies of the effectiveness of risk minimisation measures in Europe

Esther Artime[1], Nawab Qizilbash[2,3], Rafael Herruzo[1] and Macarena Garrido-Estepa[4]

[1]Universidad Autónoma de Madrid, Madrid, Spain; [2]OXON Epidemiology, Madrid, Spain; [3]London School of Hygiene & Tropical Medicine, London, United Kingdom; [4]Ministry of Science and Innovation, Madrid, Spain

Background: One main challenge of survey studies assessing the effectiveness of risk minimisation measures (RM studies) is country selection and participant recruitment which may result in selection bias.

Objectives: To describe country selection and subject participation in RM survey studies in Europe

Methods: A systematic literature search was conducted using the EU PAS Register, PubMed, and grey literature to identify RM studies to assess the effectiveness of aRMMs via process indicators and/or outcomes, between 1 January 2011 and 12 October 2019. Survey studies that included at least one European country with process indicators were selected. Participation data were abstracted from study reports, manuscripts and abstracts. Response rate was calculated as the proportion of participants among invited.

Results: Of 129 RM studies, 45 surveys of HCPs and 14 surveys of patients and caregivers were identified. Twenty-eight different European countries were included in the HCP surveys with an average of 5 (Range: 1 to 18) countries per survey. In patient surveys 17 different countries were involved with an average of 5.8 (Range: 3 to 10) countries per survey. The total number of participants was 18316 HCPs and 4129 patients; 17611 and 2996, respectively, with country-specific participation data. The highest recruiting countries in HCP surveys were the UK (34/45), Spain (29/45), France (29/45) and Germany (29/45), contributing 64.3% (by country range: 18.2% to 12.6%) of all participants with country-specific data. Italy, Sweden, Netherlands, Belgium, Austria and Portugal participated in 19, 17, 11, 10, 10 and 4 HCP surveys, respectively, recruiting 21.9% (Range: 2.2% to 6.3%) of all participants. The other 18 countries participated in 1 to 15 studies and provided 13.7% (Ranging from 0% to 2%) of the HCP participants. The median HCP response rate by country ranged from 22.0% to 0.3%, being highest in Greece (22.0%), Italy (19.0%) and Czech Republic (18.4%). The UK (13/14), Germany (10/14), France (9/14) and Spain (7/14) were also the top recruiters in the 14 patient surveys, recruiting 65.7% of all participants with country-specific data. The median patient response rate by country ranged

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

from 90.3% to 10.0%, being highest in Spain (90.3%) and Germany (78.9%)

Conclusions: Some countries are overrepresented in HCP and patient RM survey studies. Subject participation remains low, especially in patient surveys. Strengthened recommendations to guide country selection and participation are warranted.

4187 | Pregnancy outcomes among women exposed to potentially harmful drugs

Thuy Thai[1], Amir Sarayani[1], Yasser Albogami[1,2], Xi Wang[1], Sabina Nduaguba[1], Preya Patel[1] and Almut Winterstein[1,3,4]

[1]College of Pharmacy, University of Florida, Gainesville, FL;[2]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [3]College of Medicine and College of Public Health and Health Professions, University of Florida, Gainesville, FL;[4]Center for Drug Evaluation and Safety (CoDES), University of Florida, Gainesville, FL

Background: Only 12 out of hundreds of potentially teratogenic drugs are approved with risk mitigation strategies (REMS) aimed at preventing fetal exposure in the US. The public health impact of potentially harmful but non-REMS drugs on adverse pregnancy outcomes is unclear.

Objectives: To evaluate the risk for pregnancy loss and malformation associated with potentially harmful non-REMS, REMS and non-potentially harmful drug exposures during early pregnancy.

Methods: We conducted two retrospective cohort studies using the IBM MarketScan Commercial Claims data 2005-2018. Women aged 12-55 years old had a continuous enrollment from 180 days before conception to pregnancy end date for non-livebirth or 30 days after pregnancy end date for livebirth. Linked infants had ≥30 days enrollment after birth or ≥90 days enrollment after birth for malformation evaluation. Potentially harmful drugs were based on the Teratogen Information System including drugs with ≥moderate level evidence on teratogenicity or with indication for potential teratogenicity from animal studies and labeled pregnancy contraindication (269 drugs). Women with any drug fill from conception to first trimester end were classified into three groups: REMS (REMS), potentially harmful non-REMS (non-REMS), and non-potentially harmful (non-harmful) drug users. Pregnancy loss and major malformation were compared between non-REMS vs non-harmful drugs and between REMS vs non-harmful drugs in cohort 2. We adjusted for maternal age, gestational age at first prescription fill, demographics, and a variety of maternal characteristics using clinical classification software condition categories. We used standardized mortality ratio weighting and generalized estimating equation models to estimate adjusted absolute risk difference (ARD) and risk ratio (RR).

Results: A total 1,038,584 pregnancies were included: REMS (0.03%), non-REMS (8.7%), and non-harmful (91.2%) drugs. Adjusted ARD between non-REMS and non-harmful drug users was 8.0% (95%CI 7.5-8.4%) and 0.4% (95%CI -0.03 to 0.9%) and RR was 1.30 (95%CI 1.28-1.32) and 1.06 (95%CI 1.00-1.13) for pregnancy loss and malformation, respectively. In cohort 2 comparing REMS and non-harmful drug users, ARD was 22.0% (95%CI 12.3-31.8%) and RR was 1.78 (95%CI 1.36-2.37) for pregnancy loss. Due to small number of livebirths in REMS users, malformation was not evaluated.

Conclusions: Both REMS and non-REMS potentially harmful drugs showed increases in adverse pregnancy outcomes but despite broad adjustment, confounding may contribute to this finding. More studies should address non-REMS drugs individually to quantify teratogenic burden.

4239 | Medication errors current situation in Saudi Arabia; A nationwide observational study

Khalidah A. Alanazi[1], Yasser Alatawi[2], Ali F. Altebainawi[3] and Thamir M. Alshammari[4,5]

[1]Ministry of Health, Tabuk, Saudi Arabia; [2]University of Tabuk, Collage of Pharmacy, Tabuk, Saudi Arabia; [3]Ministry of Health, Hail, Saudi Arabia; [4]Saudi Food and Drug Authority, Riyadh, Saudi Arabia; [5]Medication Safety Research Chair, King Saud University, Saudi Arabia

Background: Medication errors is a global concern that lead the World Health Organization to have an initiative aiming to reduce the medication errors worldwide.

Objectives: The objective of this nationwide study was to estimate the prevalence of medication errors, characterize the type of errors and determine the stages of the medication process in which the errors occurred. In addition, we aimed to identify the groups of healthcare providers who detect and report errors, as well as the potential causes of the errors and classes of medication involved.

Methods: A retrospective observational study that assessed all medication errors reports that were submitted to the general pharmaceutical care department database from 265 government hospitals and primary care centers for the period of March 2018 to June 2019. The database was structured to include information regarding all aspects of medication errors, including patient information, medication information, error information, causing the error and reporter information. The medication use process was categorized into ordering/prescribing, transcribing, dispensing, administration, and monitoring. All data were analyzed by using the Statistical Analysis Software (SAS), version 9.4

Results: About 71,332 medication errors reports were submitted to the pharmaceutical care in ministry of health database during the period between March 2018 to June 2019. The medication error rate was estimated to be 0.15% and most of errors were frequently made by physicians 63120 (88.5%) and were primarily detected by pharmacists (75.9%). The majority of errors were detected at the prescribing stage (84.8%), followed by the transcribing (5.8%), dispensing (5.7%) stage and only 4,182 (5.8%) errors reached patients. Medication errors were frequently reported for medication taken orally (56.5%). Antimicrobials were the most commonly associated drugs with a medication error (24.3%). Work overload of the staff was associated with one-third of the reported error (31.6%) and 22.7% of the errors were due to lack of experiences and training among health care providers.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: This study found that medication errors were more likely to occur in the prescribing phase and mainly detect by pharmacists. The majority of factors contributing to medication errors were human-related, such as increased workload and non-compliance with policy and procedure. It is important that we focus on improving our understanding of the scope and nature of errors and implement policies and procedures that will improve patient safety.

4295 | How patient preferences can inform net clinical benefit: A personalized, patient-centered, benefit risk assessment using real-world and clinical trial data

Tommi Tervonen[1,2], Thibaud Prawitz[1], Gin Nie Chua[1], Johanna Hyacinthe[3] and Cathy Anne Pinto[3]

[1]Evidera, London, United Kingdom; [2]University of Groningen, University Medical Center Groningen, Groningen, Netherlands; [3]Merck & Co., Inc, Kenilworth, NJ

Background: Drug benefit-risk (BR) assessments have traditionally been informed with clinical trial data with equal or arbitrary weighting of outcomes. Characterization of the expected BR profile in the real-world (RW) requires additional understanding of how risks and their tolerance vary within the population receiving treatment.

Objectives: To estimate the patient-centered net clinical benefit (NCB) of an oral antiplatelet, vorapaxar, in terms of key treatment outcomes including ischemic benefit and bleeding risks.

Methods: A database study identified patients with a prior myocardial infarction (MI) in the Clinical Practice Research Datalink, linked to the Hospital Episode Statistics and Office of National Statistics databases. Risk prediction models were developed to estimate baseline risk of each NCB outcome for each patient over 3-years of follow-up. A separate preference study using a Discrete Choice Experiment (DCE) to elicit trade-offs among these outcomes from MI patients was conducted with recruitment via access panels and National Health Service (NHS) in England. DCE data was analyzed using a heteroscedastic logit model. The drug's hazard ratios relative to placebo, as observed in the pivotal RCT, were applied to baseline risk estimates to compute expected attributable risks which were weighted to estimate the per-patient NCB. Attributable risks were weighted equally and with patient preference data.

Results: Complete-case database sample included 22,125 adults with median (IQR) age of 72 (61-81) yrs, 64% male. The DCE was completed by 353 MI patients with a median (IQR) age of 65 (59-71) yrs, and 84% male. In the DCE, patients >=65 yrs of age with no other bleeding risk factors valued reduction of MI risk higher than younger patients or those with additional bleeding risk factors. Using equal weighting and preference weighting, the relative NCB for patients within the highest and lowest deciles of baseline cardiovascular risk ranged between 9-12% and 2-3%, and between 8-11% and 1-2%, respectively. Mean NCB was significantly lower in the preference weighted than in the equal weighted analysis (4.3 vs 5.7; p<0.001). Sensitivity analyses showed that 100% of patients would maintain a positive NCB in the equal- and preference-weighted analyses, if bleeding risk increased 12-fold and 7-fold, respectively.

Conclusions: Patient preferences can have a significant effect on the treatment NCB and is an important consideration for patient-centric decision-making processes.

4301 | Handling information about new drug safety issues in Dutch hospitals: A mixed-methods approach

Esther de Vries[1,2], Elisabeth Bakker[1], Peter G.M. Mol[1,2] and Petra Denig[1]

[1]University of Groningen, University Medical Center Groningen, Groningen, Netherlands; [2]Dutch Medicines Evaluation Board, Utrecht, Netherlands

Background: Risk communication by regulators through Direct Healthcare Professional Communications (DHPC) is primarily focussed at individual healthcare professionals (HCPs). Many new safety issues concern hospital based HCPs but little is known about the routines hospitals have to handle such information. To optimise communication about new drug safety issues it is crucial to align with current ways of handling drug information in hospital settings.

Objectives: Which routines for handling information about new drug safety issues exist in Dutch hospitals?

Methods: We used a mixed-methods design. Semi-structured focus group interviews were conducted with hospital specialists and pharmacists. Based on the focus group results and literature review, a survey was developed, which was distributed among the heads of hospital pharmacies. The survey included questions to assess whether and how new safety issues and DHPCs were addressed in hospital committees, policies, procedures, and agreements.

Results: Of the 15 hospitals approached, 6 agreed to participate in a focus group within their hospital, 3 academic, 2 top clinical and 1 general hospital. The survey was completed by 38 of 79 pharmacies, 2 academic, 16 top clinical and 20 general hospitals. From the focus groups it became clear that safety issues were sometimes discussed in drug formulary committees but DHPCs seldom. New drug safety issues were introduced by individuals at department meetings. The survey showed that only 11 hospitals had hospital wide agreements how to deal with new safety information. Drug safety aspects were considered in drug formulary committees in 24 hospitals, but DHPCs were discussed in only 7. In 30 hospitals, there were agreements on how to deal with new safety information at pharmacy level. DHPCs were evaluated by one of the pharmacists in 27 hospitals. In 4 of them DHPCs were also discussed at department meetings, 3 other hospitals did this solely. 18 of the 27 hospitals with a committee for treatment protocols, considered drug safety aspects in these committees. Only 3 hospitals mentioned that DHPCs could change protocols. Although DHPCs are sent to all relevant HCPs, in 13 hospitals pharmacists forwarded the DHPC to prescribers and in 5 to relevant departments. 5 hospitals archived the DHPCs in a quality system.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: In most hospitals, there are no clear routines to handle new drug safety information. DHPCs are at best discussed in the drug formulary committee and/or handled by one of the hospital pharmacists. Currently, individual hospital specialists need to decide for themselves what to do with new safety information.

4372 | Measuring the uptake of pharmacoepidemiologic research through bibliometric analysis: A pilot study from the Canadian network for observational drug effect studies

Robyn L. Traynor[1], Wusiman Aibibula[2], Melissa Helwig[1], Kristian B. Filion[3], Ingrid S. Sketris[1] and Samuel A. Stewart[1]
[1]Dalhousie University, Halifax, NS, Canada; [2]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada; [3]McGill University, Montreal, QC, Canada

Background: Drug safety research findings are communicated to policy makers, researchers, and health care professionals, in part, by being cited in academic and clinical publications. Understanding how research findings are cited, interpreted, and used is helpful for determining research impact.
Objectives: The objective of this pilot study is to describe the uptake of findings from a Canadian Network for Observational Drug Effect Studies (CNODES) study of the heart failure risk of incretin-based drugs using a bibliometric approach.
Methods: We searched Scopus® (March 24, 2016 - August 8, 2018) for articles citing the CNODES study, Filion et al. 2016 (doi:10.1056/NEJMoa1506115). We downloaded all records to REDCap, removing any that were duplicates or non-English. We conducted content analysis, using a piloted extraction form, to retrieve data related to the citing article and its journal. We applied the Becker Medical Library Model for Assessment of Research Impact and the Canadian Academy of Health Sciences return on investment model to further assess potential impact.
Results: A total of 79 articles citing the CNODES study were analyzed, including 43 reviews, 19 original research articles, and 17 'other' publications, including editorials. The review citations were largely narrative (91%); four were systematic reviews. The CNODES study results were often cited as rationale in background and discussion sections; less commonly, the study's methods were cited. Twenty-four of the citing articles included calculations or reported numbers from the original CNODES study. The majority (96%) of the citing articles were classified as contributing to the "advancement of knowledge" under the Becker Model.
Conclusions: The CNODES study of the heart failure risk of incretin-based drugs was cited in original research and review articles, contributing to a change in understanding and an advancement of knowledge in the field. Further work is needed to determine how results from drug safety studies can be better communicated to policy makers, researchers, and health care professionals to contribute to improving policies, programs, and patient care.

4449 | Patient perceptions on transplant with organs from donors with hepatitis C virus infection

M. Elle Saine[1,2], Erin M. Schnellinger[1], Michaella Moore[3], Ashley J. Woodards[1], Caitlin Phillips[1], David S. Goldberg[4], Peter P. Reese[1] and Frances K. Barg[1]
[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]University of Pennsylvania, Philadelphia, PA; [3]Howard University, Washington, DC; [4]University of Miami Miller School of Medicine, Miami, FL

Background: Historically, many organs from deceased donors with hepatitis C virus (HCV) were discarded. The advent of highly-curative direct acting antiviral (DAA) therapies motivated transplant centers to conduct pilot trials of transplanting HCV-infected organs into uninfected recipients, followed by DAA treatment. These therapies create the potential to significantly increase the number of organ transplants each year. However, factors that influence patients' decisions regarding acceptance of transplant with HCV-viremic organs are unknown.
Objectives: To explore patient-level perceptions, influences, and experiences that inform recipient decision-making regarding transplant with organs from HCV-positive donors.
Methods: We are conducting an ongoing qualitative semi-structured interview study embedded within clinical trials investigating the safety and efficacy of transplanting lungs (Open-Labeled Trial of Zepatier for Treatment of Hepatitis C-Negative Patients who Receive Lung Transplants from Hepatitis C-Positive Donors [SHELTER]) and kidneys (Multi-center Study to Transplant Hepatitis-C Infected Kidneys [MYTHIC]) from HCV-positive donors into HCV-negative recipients. Thematic domains include: 1) chronic illness experience; 2) infection and stigma concerns; and, 3) decision-making processes. Interviews are conducted via telephone and last 20-30 minutes. All interviews are transcribed and systematically analyzed for common themes.
Results: Preliminary data indicate that the curability of HCV with DAA therapies had varying impact on patients' decisions to receive transplant from HCV-positive donors. Some participants feel that curative DAA treatment made the risk of receiving HCV-positive organs comparable to other transplant risks (e.g. receiving organs from older donors), while others are concerned about the limited clinical trial data. Participants frequently express concerns regarding the risk of transmitting HCV to loved ones post-transplant, specifically during DAA treatment.
Conclusions: The potential to cure HCV through DAA therapies offers promising opportunities to patients in need of transplant, as it could dramatically increase the number of donor organs available. However, preliminary qualitative interview data suggest that patients' willingness to accept HCV-positive organs varies, as do their perspectives on the attendant risks of receiving such organs. Ongoing research aims to further elucidate factors informing patient decision-making regarding transplant with HCV-positive organs.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4852 | Stakeholders' perspective in implementation of additional risk minimization measures: reflection on challenges and solutions

Harshil Patel
APCER Life Sciences, Ahmedabad, India

Background: Additional risk minimization measures (ARMMs) are developed as regulatory commitment to inform healthcare professionals and patients on the risks associated with a particular product including measures to mitigate them. Any non-compliance in implementation, and effectiveness assessment of the ARMMs have a critical impact on safety and well-being of the patients. The implementation and determination of effectiveness for ARMMs can be a challenge as it involves multiple stakeholders.

Objectives: 1) To understand the pharmaceutical industry Stakeholders' perspective to meet the legal obligation of global ARMM commitments including implementation and effectiveness assessment. 2) To identify the root cause of non-compliance of RMP commitments and related solutions

Methods: To understand the challenges faced by industry for RMP commitments, three-way analysis of MHRA GPvP metrics 2017-18, author's experiences and Stakeholders' perspectives through anonymous survey was undertaken using online SurveyMonkey® application.

Results: Three-way analyses revealed critical lack in adherence to RMP commitments [failure in additional risk minimization measures (aRMMs) implementation and effectiveness assessment, specific data monitoring in lieu of a Post Authorization Safety Studies (PASS) and targeted follow-up of events] and lack of robust process (including aRMM tracking, outreach to target audience, lack of awareness and resource crunch) for RMP implementation at Marketing Authorization Holders' end. Challenges like aRMM translation and version management during national approval (36%); distribution, stakeholders training and budget during implementation of aRMMs (40%); and higher chances of manual miss due to use of excel based tracking tools (55%) were identified from survey results of 38 respondents comprehend author's experiences and GPvP metrics. Effectiveness assessment included post-marketing incidence and reporting rates, and drug utilization studies. Possible challenges in RMP commitments implementation and tracking require collaborative approach. Solutions focusing on ARMM education, local market alliance and multi-faceted IT tools can be supportive aids to ensure that legal obligations are met and risk to the patients are adequately communicated and mitigated.

Conclusions: Maintenance of products with complex risk management systems is always a challenge and such systems are under the scanner of the inspectors. Multi-prong solutions would increase visibility of measures reaching target and achieve the objective of risk reduction.

4880 | Deprescribing of inappropriately consumed proton pump inhibitors and its clinical consequences: A prospective study

Eswaran Maheswari
M.S. Ramaiah University of Applied Sciences, Bangalore, India

Background: Deprescribing is the process of ceasing, tapering or substituting inappropriate medication(s). Proton Pump Inhibitors (PPI) are consumed inappropriately which may lead to increased occurrence of Adverse Drug Reactions (ADR).

Objectives: The aim of the study is to deprescribe inappropriate consumption of PPI among PPI chronic users and assess the clinical consequences of deprescribing.

Methods: This is a prospective interventional study carried out for a period of 11 months after obtaining ethical approval. Patients more than 18 years of age consuming PPI were included. Based on endoscopic report, medical records and expert opinion the patients were classified as "clearly appropriate", "likely appropriate" and "potentially inappropriate". The "potentially inappropriate" patients were counseled on harms of inappropriate PPI usage, impact of healthy dietary and lifestyle habits employing a Patient Information Leaflets (PIL). The patients deprescribed were followed up through telephonic communication. Global Overall Symptom scale (GOS) was utilized to assess gastric discomfort before and after deprescribing.

Results: From the 745 patients recruited, 226 (30.33%) were classified under "potentially inappropriate", out of which 113 (15.16%) were deprescribed. When paired t-test was applied, GOS scale indicated significant difference in symptoms before and after deprescribing (P- value<0.01).

Conclusions: Deprescribing of PPI decreased the incidence of long-term ADR, cost burden and promoted healthy lifestyle and therefore, may help improve the Quality of Life (Q0L).

4983 | Establishing drug safety and effectiveness strategies in low and middle income countries

Edward Mills[1], Nathan Ford[2] and Sabin Nsanzimana[3]
[1]Bill and Melinda Gates Foundation, Seattle, WA; [2]World Health Organization, Geneva, Switzerland; [3]Rwanda Biomedical Centre, Kigali, Rwanda

Background: Low and middle income countries now have emerging markets for medical products that have not been evaluated in their local setting. There is a need for local evaluations assessing the appropriateness of drug availability, efficacy, safety and cost-effectiveness. These settings are unique as the efficacy and safety data is rarely from LMICs and the quality of medical components varies widely.

Objectives: This session will address the need and process to develop local administrative skills for the assessment of safety, efficacy, and economic evaluations of external data for local settings in LMICs.

Description: Low and middle income countries represent an emerging pharmaceutical market and established drugs are now being marketed in these settings. Many LMICs do not have oversight agencies to assess the efficacy, safety or applicability of these drugs in their markets. This is unique to LMICs as the efficacy and safety data has rarely been collected in similar settings. The World Health Organization (WHO) offers guidance on the use of drugs for low income settings but does not take into consideration the heterogeneity of markets within countries and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the use of drugs without local guidance. This session will debate whether there is a need for a general (WHO like) oversight agency, regional agencies, or national agencies. There is limited infrastructure in many settings to evaluate drug applicability and a need for specialized human resources for drug technology evaluations. The panel will begin (10 minutes) with an overview of capabilities in LMICs addressing current strategies for drug evaluations. We will then have representation from global funders, the WHO, and regional leaders. After the presentations, questions and ideas from the session attendees will be addressed.

5049 | Benefit-harm balance of fingolimod in patients with MS: A modelling study based on FREEDOMS

Alessandra Spanu
University of Zurich, Zurich, Switzerland

Background: Multiples sclerosis is a chronic condition that requires a life long treatment.
Objectives: Our aim was to assess the benefits and arms of fingolimod, an agent employed in MS management, using individual patient data from FREEDOMS trial.
Methods: We modelled each patient health in a scale from 100 (maximum health) to 0 (minimum health/death) including EDSS measurements, relapses, adverse events with their relative drop (loosing of health points) in the scale. We averaged the health status in all arms and compared the difference between them with a predefined Minimal Important Difference (MID). We computed the proportion of patients who profited or declined in health during the treatment. We performed several analyses to evaluate the impact of relapse and AEs different drops in our model.
Results: The main analysis showed that Fingolimod 0.5mg benefits significantly outweighed its harms compared to placebo. The average health status difference of 2.7 (95% CI 2.2 to 3.2, p<0.001) over two years of study. The risk ratio for preventing a relevant decline in health status with fingolimod 0.5mg was 0.53 (95% CI 0.40-0.72, p<0.001), the number needed to treat to prevent one relevant decline in health status was 8. Sensitivity analyses favoured Fingolimod 0.5.
Conclusions: Fingolimod net benefit was not significant when compared to the MID, but the decreased risk in health deterioration could be relevant for patients. This method based on IPD could be useful to evaluate other MS drugs and gives an objective evidence base for guideline recommendations.

5070 | A comprehensive analysis of the characteristics of external control arms in approved oncology therapies

Caitlin Knox, Cherise Wong, Lewis Raynor and Asieh Golozar
Regeneron, Tarrytown, NY

Background: In recent years, there has been a rise in the approval of oncology therapies based on non-randomized clinical trials. The use of historic or external control (EC) arms may provide additional context/supplementary evidence to support the clinical efficacy in the submission of these non-randomized pivotal trials, however the frequency of their application is unknown.
Objectives: To systematically review and characterize the current landscape of EC in the submission of non-randomized oncology trials approved by the European Medicines Agency (EMA).
Methods: A comprehensive search on the EMA's database of European public assessment reports (EPAR) was conducted to extract approvals with single arm trials for anti-neoplastic and immune-modulating agents that were granted accelerated approval, conditional approval, exceptional circumstances or orphan drug designation. No time limitation was imposed. Data elements were extracted by one abstractor and confirmed by the second abstractor.
Results: A total of 27 eligible indications approved between 2001 and 2019 were identified though the EMA EMAR system; 16 indications for hematologic malignancies and 11 for solid tumors. Twenty (74%) of approvals occurred during the past five years; 13 (48%) through the conditional mechanism and three via exceptional circumstances. Use of non-randomized evidence as EC was observed in 14 (52%) approvals. The types of EC submitted included data from retrospective observational studies (9 approvals), literature review (two approvals), pooled or meta-analyses of published literature (six approvals) or a combination of these approaches. Efficacy data was directly compared with the external controls in three approvals and indirectly, in one approval. The choice of EC, description of the EC studies in which they were originally used, and their use in the submission varied across all approved medicines.
Conclusions: Submission of EC as supporting efficacy evidence in non-randomized oncology trials to the EMA is increasing, with the majority occurring in the last five years. There is variability in the design, conduct, and reporting as observed within the systematic review of the EPARs. Additional guidance on the appropriate use of EC and methodological applications may be beneficial and improve the consistency of EC utilization.

Biologics/Biosimilars

27 | Why not biosimilars: Biologic and biosimilar utilization trends in Japanese RA patients

Lu Zhang, Tiffany S. Woodworth and Joseph Menzin
Boston Health Economics, Boston, MA

Background: Lower-costing biosimilars offer opportunities to increase access to biologic treatment for patients with rheumatoid arthritis (RA) and to lower overall health care expenditures in these patients. Since the 2014 market entry in Japan, the impact of biosimilars is largely unknown.
Objectives: To assess the impact of biosimilars and describe utilization trends and patient characteristics in Japanese RA patients.
Methods: We identified patients with ≥1 RA treatment, prior RA diagnosis and 1 year of continuous enrollment in the JMDC Inc. database

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

between January 1, 2005 and May 31, 2019. We calculated annual prevalence of RA treatments: biologics, including biosimilars for etanercept, infliximab, and rituximab; non-biologic DMARDs; glucocorticoids; and methotrexate (MTX). Among new users of biologics, defined as no prior biologic use in prior year, we examined treatment and switching patterns between reference biologics and associated biosimilars. Finally, we examined patient characteristics among those initiating reference biologics vs biosimilars.

Results: Among treated Japanese RA patients, prevalent biologic use steadily increased from 2.7% in 2005 to 18.5% in 2019. MTX use also increased (24.0 to 46.7%). Use of glucocorticoids and other DMARDs decreased (78.1 to 57.9% and 40.2 to 26.6%, respectively). Biosimilars had low uptake (0.1% in 2015 to 1.0% in 2019) despite overall increase in biologics. While prevalence of newer biologics without associated biosimilars increased (0.6% in 2008 to 11.7% in 2019), prevalence of reference biologics peaked to 10.5% in 2011 and have been steadily declining to 6.3% in 2019. Further, new initiators of reference biologics (N=536) stayed on reference for 541 days on average, and 7.3% switched to biosimilars, while new biosimilar initiators (N=37) stayed on biosimilars for 95.5 days on average, and 10.8% switched to reference. Biosimilar initiators tended to be older (50.8 [11.7] vs 47.4 [13.1] years), male (32.4 vs 27.1%), had less outpatient visits in the 12 month baseline period (19.6 vs. 24.6), and were more likely to use MTX at baseline (73.0 vs. 63.1%).

Conclusions: While biosimilars are presumed to increase utilization of biologics due to better affordability, preliminary analysis of biosimilar and biologic uptake and utilization patterns indicate hesitancy to use biosimilars in Japan. Early results seem to indicate that new initiators of biosimilars may have different clinical and demographic attributes compared to initiators of reference biosimilars. Further research should be conducted examine these differences and their impact on biosimilar uptake.

2324 | Monoclonal antibody induced progressive multifocal leukoencephalopathy and cytokine release syndrome: Analysis of Eudravigilance and FAERS databases and risk minimisation measures

Kalindi N. Hapani
APCER LIFESCIENCES, Ahmedabad, India

Background: Monoclonal antibodies (MABs) are used in different therapeutic areas. There has been increased concern for spontaneous reports of progressive multifocal leukoencephalopathy (PML) and cytokine release syndrome (CRS) attributed to MABs that modulate the immune system.

Objectives: 1. To detect the cases of PML & CRS with MABs from FAERS and EudraVigilance safety database and to apply signal detection algorithms to identify significant signals for PML & CRS. 2. To identify the risk minimization measures (RMMs) prevailing in EU & US for PML and CRS with MABs and to discuss the need of awareness in healthcare professionals (HCP) regarding RMMs.

Methods: EudraVigilance and FAERS database were searched using each MAB name approved by EMA & USFDA as suspect drug and adverse reaction of PML and CRS. Proportional reporting ratios (PRR) and 95% confidence intervals (CI) were calculated for MABs with ≥2 case reports. European public assessment reports (EPARs) and REMS database were further explored for the type of RMMs implemented in EU and US.

Results: 72 and 81 MABs were identified by searching the EPARs & Purple Book respectively. About 70% of PML cases and 34% of CRS cases retrieved from both databases were found with MABs. MABs with highest number of PML cases (n=EVD, FAERS) were natalizumab (n=1223, 1658), rituximab (n=847, 1374) and alemtuzumab (n=50, 86). Similarly, MABs with highest number of CRS cases were blinatumomab (n=195, 186), rituximab (n=107, 114) and obinutuzumab (n=6, 45). The percentages of PML & CRS versus all EVD cases for each drug ranged from 0.034% (adalimumab) to 5.28% (natalizumab) and 0.025% (alemtuzumab) to 13.14% (blinatumomab). Similarly, percentages of PML & CRS versus all FAERS cases for each drug ranged from 0.008% (adalimumab) to 1.77% (rituximab) and 0.12% (nivolumab) to 6.06% (blinatumomab). Both EU & US product labels of natalizumab describes PML with guidance on detection and mitigation of PML. Additional RMMs (aRMMs) and REMS are implemented in EU & US respectively for natalizumab. However, no aRMMs or REMS exist for PML for other 4 MABs. For blinatumomab, one of the goals included in REMS is to inform HCPs about the risk of CRS which may be life-threatening or fatal. However, there are no aRMMs in place for blinatumomab in EU.

Conclusions: Our results expand the knowledge of the relationship of MABs with PML and CRS. Calculated statistics and further analysis may reveal a strong signal which requires further study so that patients and HCPs can be communicated regarding these ADRs and its minimisation strategies.

2477 | Long-term safety and effectiveness of etanercept in pediatric psoriasis patients: Results from a prospective observational cohort study

Yun Gu[1], Emma Brinkley[2], Rachel E. Sobel[3], Joel M. Gelfand[4], Marieke Seyger[5], Zsuzsanna Szalai[6], Jean-Philippe Lacour[7] and Mona Ståhle[8]
[1]Pfizer Inc., Collegeville, PA;[2]IQVIA, Durham, NC;[3]United BioSource Corporation, Blue Bell, PA;[4]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA;[5]Universitair Medisch Centrum St, Nijmegen, Netherlands; [6]Heim Pál Children's Hospital, Budapest, Hungary; [7]Hôpital de l'Archet II, Nice, France; [8]Karolinska Institutet, Stockholm, Sweden

Background: Etanercept is a soluble TNF receptor fusion protein indicated for treatment of severe plaque psoriasis, and can be prescribed from 6 years of age.

Objectives: The study aimed to evaluate long-term safety and effectiveness of etanercept in pediatric plaque psoriasis patients.

Methods: It was a long-term, prospective, observational study of pediatric psoriasis patients prescribed etanercept and followed for up to 5 years in 8 EU countries. Patients were classified as prospective (starting etanercept within 30 days pre-enrolment or any time after) or retrospective (starting etanercept > 30 days pre-enrolment).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Incidence rate and relative risk were estimated for defined outcomes, with patients classified by timing of AE relative to etanercept: current/recent or previous treatment.

Results: There were 72 patients (32 prospective and 40 retrospective) enrolled at 28 sites, with 51% males. Mean age was 14.5 years with average disease duration of 7.1 years. Patients were followed for a mean of 3. 8 years, with 29 (40%) completing 5 years follow-up. No serious or opportunistic infections or malignancies were reported. There were 25 serious adverse events (SAEs), including 15 SAEs in 11 (15.3%) patients with current/recent etanercept treatment and 10 SAEs in 7 (13.0%) previously exposed, with an incidence rate of 6.21 (95% CI: 3.48 - 10.24) and 8.54 (95% CI: 4.09 - 15.70) per 100 person-years, respectively. Among them, 7 (28.0%) were considered possibly related to etanercept (1 Cholesteatoma, 1 hepatic steatosis, 3 psoriasis and 2 drug ineffective). Infections and infestations were most frequently reported treatment-emergent AE (TEAEs) with 49 events in 19 (26.4%) and 7 events in 5 (9.3%) patients with current/recent exposure and previous exposure, respectively. Among 32 prospective patients, 28 (87.5%) completed at least 24 weeks of therapy, and 5 (15.6%) required ≥ 1 subsequent course of etanercept. Sixteen (50%) required > 1 treatment period with other systemic treatments. After treatment with etanercept, 93.8% (30/32) had a decrease in disease severity. Twenty six (81.3%) prospective patients had ≥ 1 dose change/discontinuation during initial treatment period, with drug ineffective being the most common reason (32.4%).

Conclusions: In this one of the largest studies with the longest follow-up of pediatric psoriasis patients treated with etanercept in the real-world setting, no serious or opportunistic infections or malignancies were observed, and the majority of prospective patients had a decrease in disease severity after etanercept treatment.

2511 | Infliximab use in the Netherlands: Uptake and characteristics of originator and biosimilars over time

Jetty A. Overbeek[1], Josephina G. Kuiper[1,2], Marina Bakker[1], B.J.F. (Bart) van den Bemt[3,4] and Ron M.C. Herings[1,5]

[1]*PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands;* [2]*Erasmus MC University Medical Centre, Rotterdam, Netherlands;* [3]*Sint Maartenskliniek, Nijmegen, Netherlands;* [4]*Radboud University Medical Center, Nijmegen, Netherlands;* [5]*VU University Medical Center, Amsterdam, Netherlands*

Background: To date there is limited data available regarding the general utilization of infliximab and the uptake of its biosimilars in Europe. The nature of the data of PHARMO's In-patient Pharmacy Database allows for distinction between originator and biosimilar and the assessment of multiple centres and indications at once.

Objectives: To provide an overview of the utilization of originator and biosimilar infliximab in the Netherlands in terms of uptake over time and switching patterns.

Methods: All dispensings for infliximab were selected from the In-patient Pharmacy Database of the PHARMO Database Network from 2002 through 2018. Descriptive analyses were performed in order to characterize initiators of originator and biosimilar infliximab and to characterize patients switching from originator infliximab to biosimilar infliximab and patients not switching.

Results: In total, 3,840 patients with 61,274 infliximab dispensings were identified. 2,496 patients initiated an originator infliximab and 777 patients initiated a biosimilar infliximab. Overall, 57% of the patients was female and mean (± standard deviation [SD]) age was 43.2 (± 17.5) years. Both originators and biosimilars were mostly prescribed by gastroenterologists, followed by internists and rheumatologists. After market authorization of the first biosimilar in 2015 the proportion of new patients initiating the biosimilar increased from 39% in 2015 to 91% in 2018. 704 patients were eligible for switching as they had at least one dispensing of infliximab after 01 January 2015. Among these patients 34% switched. Among switchers, the proportion of females was 60% and mean (±SD) age at index was 45.1 (±16.7) years. Among non-switchers, 55% was female and mean age was 39.8 (±17.0) years. The median (interquartile range [IQR]) time to switch was 1.7 (0.6-2.1) years and switchers were most frequently initiated on infliximab by a rheumatologist (42%), while non-switchers were most frequently initiated by a gastroenterologist (42%).

Conclusions: The results of this large population-based cohort show an increase in biosimilar initiation in daily clinical practice. The number of switchers remains relatively low as non-medical switch is not encouraged in the Netherlands. Complete traceability of originator or biosimilar and indication and expansion of PHARMO's In-patient Pharmacy Database would increase the applicability and validity of the current results. Linkage to other databases in the PHARMO Database Network would create possibilities to study outcomes among originator and biosimilar infliximab users.

2605 | Association between biologics and risk of herpes zoster in patients with psoriasis

Chaw-Ning Lee[1,2], Hsing-Chun Hsieh[2], Tzu-Chi Liao[2] and Edward Chia-Cheng Lai[2]

[1]*Department of Dermatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Tainan, Taiwan;* [2]*School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Tainan, Taiwan*

Background: Previous studies indicated patients with psoriasis posed a higher risk of herpes zoster (HZ). It raised a concern that use of biologics and other immunosuppressants may increase the risk of HZ. However, only limited evidences on this issue were available and conclusions of the studies remained controversial.

Objectives: To evaluate the association between biologics and risk of HZ in patients with psoriasis.

Methods: We conducted a retrospective cohort study by analyzing the Taiwan's National Health Insurance Database (NHID). We included adult patients aged 18+ diagnosed with psoriasis or psoriatic

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

arthritis receiving biologics (etanercept, adalimumab, ustekinumab, secukinumab) between 2000 and 2016. Patients with biologics were 1:5 matched to patients with non-biologic treatments (methotrexate, cyclosporine, acitretin) by using propensity score, which was derived from logistic regressions considering patients' age, sex, comorbidities and co-medications. The outcome of study was diagnosis of HZ with subsequent use of antivirus agents. We followed up patients for 2 years from initiation of biologics or non-biologic treatments. We censored patients at the date of diagnosis of HZ or death. We used Cox proportional hazards models to examine the risk of HZ between patients with biologics vs. non-biologic treatments.

Results: We identified a total of 4142 and 20,710 patients with psoriasis receiving biologics and non-biologic treatments, respectively. The mean age of patients were 47.6 (SD 16.5) years old and similar between groups. We found the incidence rates of HZ were 175.4 and 127.4 per 10000 person-years for biologics and non-biologic users, respectively. Compared to patients with non-biologic treatments, the adjusted hazard ratio of HZ to patients receiving biologics were 1.56 (95% CIs, 1.27 to 1.92).

Conclusions: We found patients with psoriasis receiving biologics were associated with the risk of HZ. The finding warrants clinical attentions and strategies to prevent the occurrence of HZ infection while using the biologics.

3709 | Different safety reporting profiles of infliximab biosimilar from originator: Comparison among countries

Kimie Sai, Yoshiko Aoki and Yoshiro Saito
National Institute of Health Sciences, Kawasaki, Japan

Background: Usage of biosimilar (BS) of infliximab (IFX) has been encouraged worldwide. One important issue of BS usage is a possible interpopulation difference in its safety profiles; e.g., similar to the originator, immunogenicity of BS might be different among individual/populations and could lead to different efficacy/safety profiles among regions. However, information of safety profiles of BS in real world and possible regional differences is still limited.

Objectives: To examine possible differences in adverse drug reaction (ADR) reporting profiles between IFX originator and BS, and to explore those regional differences.

Methods: ADRs reports of IFX originator (Remicade) and its CT-P13 BS (Remsima/Inflectra/BS 1) were examined. JADER was used in analysis for Japan (Apr 2015 - Dec 2019) and VigiBase (serious report type) was used for global analysis, i.e., Korea, UK, France and USA (Jan 2014 - Dec 2019). Number/percent for ADR reports of either IFX (originator or BS) and reporting odds ratios (RORs) (target vs. non-target drugs) based on MedDRA preferred terms and 27 categories for System Organ Class (SOC) were compared between the originator and the BS. For evaluation of differences in ADR reporting profiles, lower limit of 95% confidence intervals (> 1) for ROR (BS vs. originator) was used.

Results: Major ADRs (either the top or top two SOC) for both originator and BS was "Infections and infestations" in Japan, Korea and UK, "Skin and subcutaneous tissue disorders" in France, and "General disorders and administration site conditions" in USA. Significantly higher ROR (BS vs. originator) was observed in 5 SOC categories in Japan, 2 for Korea, 3 for France, 1 for UK and 7 for USA, of which profile was different among regions. "Injury, poisoning and procedural complications", attributed to "infusion related reaction" was raised to the second BS ADRs in Japan [ROR (95%CI):2.98 (1.70-5.23)], and to the third, but not due to infusion related reaction, in Korea [2.10 (1.08-4.10)]. "General disorders and administration site conditions" was raised to the top BS ADRs, mainly "drug ineffective", in France [2.33 (1.75-3.12)] and, mainly "pain" and "death", in USA [1.36 (1.05-1.76)].

Conclusions: This study suggests that the major ADRs (the top or top two) by IFX would be mostly consistent between originator and BS in each country, but different ADRs might be also raised as major BS ADRs in a region-specific manner. The reason of regional difference might be due to differences in medical practice and population differences among regions. However, further confirmation study is still needed in a larger number of case reports.

3751 | Switching from originator infliximab to biosimilar: Missed dose and discontinuation in a population-based cohort

Cristiano S. Moura[1], Jeffrey R. Curtis[2], Denis Choquette[3], Gilles Boire[4], Gilles Boire[4], Vivian P. Bykerk[5], Walter P. Maksymowych[6], Peter L. Lakatos[7], Waqqas Afif[7] and Sasha Bernatsky[1]
[1]McGill University Health Center, Montreal, QC, Canada; [2]University of Alabama at Birmingham, Birmingham, AL;[3]Institut de Rhumatologie de Montréal, Montreal, QC, Canada; [4]University of Sherbrooke, Sherbrooke, QC, Canada; [5]Hospital for Special Surgery, New York, NY;[6]University of Alberta, Edmonton, AB, Canada; [7]McGill University, Montreal, QC, Canada

Background: Observational studies of patients switching from originator biologic to biosimilar are limited.

Objectives: To compare persistence on therapy between switchers from originator to biosimilar infliximab, versus non-switchers.

Methods: We used Marketscan data (Jan 2017-Dec. 2018) from the United States (US) to study adult individuals (age≥18), switching from infliximab originator to biosimilar. A group of infliximab originator users remaining on the therapy was also identified. Both groups were required to have 3 or more originator infusions (no gap > 90 days between them) in the past six months before the index date (date of first biosimilar infusion). We assessed time to first missed dose (allowing a grace period of 7 days) based on the maintenance schedule (infusion Q8 weeks) and time to complete therapy discontinuation (first 90-day gap between infusions without restarting). We used multivariate Cox regression to compare both outcomes among switchers and non-switchers. Models were adjusted for age, sex, prior use of DMARDs and biologics, baseline systemic glucocorticoids, duration of prior infliximab, calendar period of index date, and underlying disease (inflammatory arthritis [rheumatoid arthritis, ankylosing spondylitis, or

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

psoriasis/psoriatic arthritis], and inflammatory bowel disease [Crohn's disease, or ulcerative colitis]).

Results: We identified 178 switchers to biosimilar and 3,704 who remained on originator. Female sex was 51% among switchers and 56% in the originator group; age was 46±17 in switchers and 42 ±14 years in the originator group. Among switchers, 32.6% missed at least one dose, versus 42.2% in the non-switcher group (9.6% difference, 95% confidence interval, CI 2.2 to 16.2). Complete infliximab discontinuation occurred in 11.0% of non-switchers (11.6% in switchers, difference of 0.6%, 95% CI -3.5 to 6.7). The adjusted hazard ratio (HR) suggested a trend for longer time to first missing dose with biosimilar versus originator (adjusted HR 0.81, 95% CI 0.62-1.06). We were unable to determine if complete discontinuation differed between the two groups (HR 1.54; 95% CI: 0.97-2.44).

Conclusions: Switching from originator to biosimilar infliximab remains very infrequent in this US sample. We noted a trend for lower risk of missed dose in switchers biosimilar but our results were not precise enough for conclusions regarding relative persistence with biosimilar versus originator. These 'real-world' results may reflect true underlying effects although we cannot rule out residual confounding (e.g. differences in time of originator use or disease duration).

3900 | Persistence in rheumatoid arthritis patients on biosimilar and bio-originator etanercept: A pooled analysis of pan-Canadian cohorts

Cristiano S. Moura[1], Denis Choquette[2], Louis Coupal[2], Orit Schieir[3], Vivian Bykerk[4], Marie-France Valois[5], Gilles Boire[6] and Walter P. Maksymowych[7]

[1]McGill University Health Center, Montreal, QC, Canada; [2]Institut de Rhumatologie de Montréal, Montreal, QC, Canada; [3]University of Toronto, Toronto, ON, Canada; [4]Hospital for Special Surgery, New York, NY; [5]McGill University, Montreal, QC, Canada; [6]University of Sherbrooke, Sherbrooke, QC, Canada; [7]University of Alberta, Edmonton, AB, Canada

Background: Biosimilar etanercept (ETA-B) was recently introduced in Canada but real-world data descriptions of drug persistence (and comparisons with the originator product, ETA-O) are still scarce.

Objectives: To describe and compare persistence of ETA-B and ETA-O in RA.

Methods: We used data from four ongoing, prospective cohorts in Canada: the Canadian Early Arthritis Cohort (CATCH), the Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics (RAPPORT), the Early Undifferentiated Polyarthritis (EUPA) cohort, and the RHUMADATA® registry. We studied biologic-naïve and biologic-experienced RA adult initiating ETA-B or ETA-O between Jan. 2015 and Oct. 2019. Switchers from ETA-O to ETA-B (or vice-versa) were included. We assessed persistence of therapy in the first 12 or 24 months, measured as time from therapy initiation (time zero) to discontinuation. Individuals switching between products could contribute further person-time to the new exposure category. Multivariable Cox regression models were performed with each cohort dataset separately, following a common protocol. Model variables included age, sex, comorbidity, past biologic use, and disease duration. After testing for between-study heterogeneity (Higgin's I^2), cohort-estimated hazard ratios (HR) were pooled using random-effects meta-analysis.

Results: We identified 262 episodes of etanercept use (118 ETA-B and 144 ETA-O) from 250 RA patients. Sex distribution (% of female) on the four cohorts ranged from 63% to 73% in the ETA-B group and 67%-77% in the ETA-O group; mean age ranged from 51±15 to 59 ±15 in the ETA-B group and 51±13 to 59±15 in the ETA-O group. Across cohorts, there was considerable variation in RA duration at the time of initiating ETA-B or ETA-O. In the pooled analysis, the HR for discontinuation at 24 months comparing ETA-B to ETA-O was 0.51 (95% confidence interval, CI: 0.26-0.98). The pooled analysis for therapy discontinuation at 12 months adjusted HR in this analysis was 0.82 (95% CI: 0.42-1.60).

Conclusions: Despite wide confidence intervals, the 24-month data suggested potential better persistence with ETA-B versus ETA-O, with a similar trend at 12 months. Some of the observed associations may be related to residual confounding (e.g. disease activity, time-dependent effects of concomitant medications) and/or survivorship bias (in patients transitioning from ETA-O to ETA-B).

3916 | Machine learning coupled with patient reported outcome data to classify & predict RA disease activity: Results from the AWARE trial

Jeffrey R. Curtis[1], Fenglong Xie[1], Shelly Kafka[2] and Shawn Black[1]

[1]University of Alabama at Birmingham, Birmingham, AL; [2]Janssen Scientific Affairs, LLC, Horsham, PA

Background: Patient reported outcome (PRO) data have assumed increasing importance in the care of rheumatoid arthritis (RA) patients.

Objectives: Physician-derived disease activity measures such as CDAI remain the most-accepted metrics to assess RA. The possibility that newer, longitudinal PRO might proxy for the CDAI has not been evaluated.

Methods: Setting: Using data from the Comparative and Pragmatic Study of Golimumab IV vs. Infliximab (AWARE), we evaluated RA patients initiating one of these two therapies who started in moderate or high disease activity and remained under observation through 6 months. Interventions: The primary prediction target was CDAI and CDAI disease activity category at Month 6. Outcome measures: Candidate predictors included baseline CDAI, baseline PROs including those from the NIH PROMIS system (e.g. Pain Interference, Fatigue, Physical Function, Sleep Disturbance), and follow up PROs at month 1 and 6 (+-30 days). Data were randomly partitioned into a training (2/3) and test (1/3) datasets. Multiple machine learning (ML) methods (e.g. Gradient Boosting, (XGBoost), RandomForests, SVM, ensemble approaches) and traditional statistics (e.g. LASSO, logistic regression) were used to classify both CDAI, and CDAI disease activity category

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(remission/low vs. moderate/high). Statistical Analysis: Model performance evaluated cross-validated error comparing different ML approaches using the test data.

Results: A total of 388 AWARE patients were analyzed. Of these, the distribution of disease activity by CDAI at month 6 was remission (4.9%), low (26.8%), moderate (31.7%), and high (36.6%). The more optimal analytic approaches were gradient boosting (XG), LASSO and RandomForests, and resulted in c statistics of 0.83 (XG), 0.80 (LASSO) and 0.78 (RF) for the binary outcome. In univariate analysis examining outcomes at 6 months, and depending on which modeling method was used, the most important features included pain intensity, PROMIS measures (social participation, pain interference, pain intensity, physical function), baseline CDAI, and age. Requiring a minimum PPV of 80%, sensitivity ranged from 74-92% (depending on ML method) to identify LDA/remission.

Conclusions: Machine learning methods coupled with longitudinal PRO data appear useful and accurate to classify RA disease activity over time among patients starting a new biologic. This approach has promise to support real-world evidence generation in the circumstance where PRO measures are available but physician-derived disease activity data is yet.

3930 | Variation in definitions of granulocyte colony stimulating factor prophylaxis and patient outcomes: A scoping review of observational studies

Cara L. McDermott[1], Pamala A. Pawloski[2], Prasad Gawade[3], Cynthia Holmes[4], Edward Li[5], Aaron Mendelsohn[6], Gary Yee[7] and Catherine M. Lockhart[1]

[1]Biologics and Biosimilars Collective Intelligence Consortium, Alexandria, VA; [2]HealthPartners Institute, Bloomington, MN; [3]Amgen, Inc, Thousand Oaks, CA; [4]AbbVie, North Chicago, IL; [5]Sandoz, Princeton, NJ; [6]Harvard Pilgrim Health Care Institute, Boston, MA; [7]University of Nebraska Medical Center, Omaha, NE

Background: The uptake of granulocyte colony stimulating factor (G-CSF) biosimilars has started in clinical practice, but limited comparative research exists on safety and effectiveness in real-world settings.

Objectives: To conduct a scoping review to examine exposure and outcome definitions used in observational studies of long and short-acting G-CSFs. Our findings will inform the design of future comparative effectiveness research (CER) with G-CSF products, including biosimilars.

Methods: Our review identified observational studies of G-CSF use in patients with cancer age 18y+, who received myelosuppressive chemotherapy. We included studies in humans, published in English between January 1, 2012 and December 31, 2019 in Medline. This time period was selected to include study populations from 2011 and beyond to allow for adoption of the 2010 European Organization for Research and Treatment of Cancer (EORTC) clinical practice guidelines. We describe definitions, algorithms and analytic methods used in studies to determine and analyze G-CSF prophylaxis, neutropenia, and healthcare utilization.

Results: The initial search strategy identified 385 studies for title review. After reviewing the abstracts of 136 studies, excluding non-observational studies and those outside our timeframe of interest, we included 13 studies in this review. Of included studies, five were conducted in the U.S., four in Europe, two in multiple countries, one in Canada and one in China. Eight (61%) studies were retrospective, using insurance claims or electronic health records and five (39%) were prospective. Studies evaluated solid tumors (38%), non-Hodgkin's lymphoma (8%), or a combination of solid and hematologic malignancies (54%). Definition of G-CSF prophylaxis administration varied between 1 and 7 days after initial chemotherapy receipt. Comparators to G-CSF administration included no G-CSF receipt, biosimilar G-CSF product, or G-CSF receipt outside the study definition of prophylaxis. Studies varied in the definition of neutropenia, e.g. with or without fever, with or without other signs of infection. The most common healthcare utilization evaluated was inpatient hospitalization for neutropenia. No studies reported patient-related quality of life.

Conclusions: To allow for comparisons across studies, future CER should use standardized definitions for primary G-CSF prophylaxis receipt and for neutropenia-related outcomes. Future observational research is needed to evaluate patient quality of life.

4057 | Do labels of drugs with the same mechanism of action describe the same adverse drug reactions? A case study on TNF-alpha inhibitors

Lotte A. Minnema[1,2], Thijs J. Giezen[2,3,4], Jarno Hoekman[1], Toine C.G. Egberts[1,5], Hubert G.M. Leufkens[1] and Helga Gardarsdottir[1,5,6]

[1]Utrecht University, Utrecht, Netherlands; [2]Medicines Evaluation Board, Utrecht, Netherlands; [3]Foundation Pharmacy for Hospitals in Haarlem, Haarlem, Netherlands; [4]Spaarne Gasthuis, Haarlem, Netherlands; [5]University Medical Centre Utrecht, Utrecht, Netherlands; [6]University of Iceland, Reykjavik, Iceland

Background: The drug label is an important information source to guide prescribers and patients on safe drug use. The labels of drugs with the same mechanism of action are expected to show consistency in mechanism of action related adverse drug reactions (ADRs).

Objectives: To assess the consistency in mechanism of action related ADRs described in the label of TNF-α inhibitors.

Methods: We included all TNF-α inhibitors that were approved in the European Union (EU). We extracted, through validated text mining techniques, the ADRs that were described in all versions of the label (section 4.8 of the summary of product characteristics) from date of approval until 31 December 2019. ADRs were characterized using a standard dictionary (Medical Dictionary for Regulatory Activities version 22.1 on the preferred term level). ADRs not related to the mechanism of action (hypersensitivity and administration site reactions) were excluded. We performed Kaplan-Meier analysis to assess the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

time from first description of an ADR in any of the labels to the first description of the same ADR in the label of another TNF-α inhibitor. The analysis was restricted to TNF-α inhibitors that were approved at the time an ADR was first described. Using a univariable Cox regression analysis, we studied which determinants were associated with an ADR being described in a second label. The following determinants were assessed: a) serious vs. non-serious ADRs; b) important risk vs. non-important risk; and c) ADR first described in the label of the first-in-class product vs. ADR first described in follow-on drug label.

Results: We assessed the labels of five TNF-α inhibitors: adalimumab, certolizumab, etanercept, golimumab, and infliximab. At the end of follow-up, a total of 488 unique ADRs were described in the labels, of which 287 (59%) ADRs were described in one label, 84 (17%) in two, 55 (11%) in three, 32 (7%) in four and 30 (6%) in all five labels. Approximately 5% of the ADRs were described in a second label one year after the ADR was first described in a label. Serious ADRs and ADRs that were classified as important risks were significantly more often described in a second label (HR=3.61 (95%CI: 1.83-7.12), HR=3.01 (95%CI: 1.52-5.94), respectively). Also, ADRs that were first described in the first-in-class product label were significantly more often described in a second label (HR=2.30, 95%CI: 1.28-4.14).

Conclusions: Mechanism of action related ADRs described in the label differ considerably among drugs with the same mechanism of action. This may hamper the provision of safety information to health care professionals and patients.

4167 | Insulin glargine and hypersensitivity reactions as an example of biosimilars pharmacovigilance

Ayad K. Ali and Martin S. Bohm
Eli Lilly and Company, Indianapolis, IN

Background: Hypersensitivity reactions (HSR) are concerns for all biologics and biosimilars, including insulin. In rare circumstances HSR could be serious and life-threatening.

Objectives: To describe a pharmacovigilance approach to monitor HSR for biosimilar insulin glargine (BIG) compared to the original insulin glargine (OIG).

Methods: Adverse event reports submitted to FDA Adverse Event Reporting System (FAERS) between Apr 2000 and Dec 2018 were analyzed. BIG and OIG products were identified by corresponding brand names. HSR were defined by custom narrow and algorithmic structured MedDRA queries (SMQ) of Preferred Terms: 'hypersensitivity'; 'angioedema'; 'anaphylactic reaction'; and 'anaphylactic/anaphylactoid shock conditions'. Multi-item Gamma Poisson Shrinker disproportionality analysis was applied to estimate Empirical Bayes Geometric Mean (EBGM) and corresponding 95%CI (EB05-EB95) as a signal detection metric (EB05≥2.0 denote potential signal that warrants further review). To account for reporting bias due to Weber effect, analyses were restricted to 2 years post-launch for both products (Jan 2017-Dec 2018 for BIG; Apr 2000-Jan 2002 for OIG). To minimize masking effect, adverse event reports submitted for all insulin products—regardless of brand were used as the background during corresponding analysis periods.

Results: A total of 191 and 56 HSR reports were submitted for BIG and OIG, respectively; corresponding to 6.7% and 10% of all adverse events reported during the period for these products, respectively. Serious events accounted for 19.4% (n=37) of HSR reports submitted for BIG and 8.9% (n=5) of HSR reports submitted for OIG. Among all HSR reported for BIG, about 40% (n=77) reported concomitant treatment with other medicinal product, including 20% (n=39) of reports mentioned concurrent treatment with other insulin product (including OIG, n=10) at the time of HSR occurrence. There was no disproportionate reporting of HSR in relation with either product (BIG: EBGM=0.70, EB05-EB95=0.62-0.79; OIG: EBGM=0.67, EB05-EB95=0.53-0.83). Among all insulin products as the background, the disproportional reporting of HSR for insulin glargine was similar between either product (BIG: EBGM=1.30, EB05-EB95=1.15-1.46; OIG: EBGM=1.16, EB05-EB95=0.97-1.38).

Conclusions: There was no difference in reporting of HSR between BIG and OIG. No HSR signal was identified for either product. This pharmacovigilance methodology can be applied to monitor HSR for other biosimilars.

4275 | Trends in formulary coverage of and point-of-sale prices for short-acting filgrastim products

Shelley A. Jazowski[1] and Stacie B. Dusetzina[2]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC;* [2]*Vanderbilt University School of Medicine, Nashville, TN*

Background: Adoption of biosimilars has been slower than anticipated in the United States. Commonly cited barriers, including limited formulary coverage and non-competitive prices, have spurred debate around policy solutions and ultimately the future of biosimilar development and utilization.

Objectives: To compare trends in Medicare Part D formulary coverage of and point-of-sale prices for short-acting filgrastim products.

Methods: We used prescription drug formulary and pricing data from the Centers for Medicare and Medicaid Services for Q1-2015 to Q3-2019. We used National Drug Classification and Concept Unique Identifier codes to identify filgrastim (originator biologic), tbo-filgrastim (follow-on biologic approved prior to the implementation of the US biosimilar licensure pathway), filgrastim-sndz (biosimilar approved in Q1-2015) and filgrastim-aafi (biosimilar approved in Q3-2018). For each product, we summarized Medicare Part D formulary coverage and point-of-sales prices (amount paid by beneficiaries and plans to the pharmacy, excluding discounts and rebates).

Results: Prior to filgrastim-sndz entry in Q3-2015, originator filgrastim and tbo-filgrastim were included on 81% and 48% of Medicare Part D formularies, respectively. Filgrastim-sndz was first included on formularies in Q1-2016 (40% coverage). By Q1-2017, formulary inclusion of filgrastim-sndz increased to 45% while coverage of originator filgrastim decreased to 63%. In the quarter following filgrastim-aafi

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

entry (Q1-2019), filgrastim-aafi was included on 9% of formularies, whereas formulary inclusion for originator filgrastim, tbo-filgrastim and filgrastim-sndz was 74%, 51% and 49%, respectively.

Average point-of-sale prices for originator filgrastim were consistently higher than biosimilar and follow-on products. Originator filgrastim's mean price increased from $5,233 in Q1-2016 to $5,430 in Q3-2019, while filgrastim-sndz's average price remained approximately $4,500 during this same period

Conclusions: Formulary coverage of biosimilars lagged behind that of originator filgrastim, while prices for the first biosimilar were comparable to those of the originator product. To increase formulary inclusion, reduce prices and ultimately ensure adoption, Part D plans should consider preferred placement of biosimilars or incorporating biosimilars into existing incentives and cost-savings programs (e.g., Medicare Star Ratings and Shared Savings Programs).

4421 | Changes in patient-reported outcome (pro) scores for nausea and fatigue following weekly methotrexate dose in a real-world sample of RA and PsA patients in the ArthritisPower registry

W. Benjamin Nowell[1], Elaine Karis[2], Kelly Gavigan[1], Laura Stradford[1], Scott Stryker[2], Huifeng Yun[3], Shilpa Venkatachalam[1], Gregory Kricorian[2], Lang Chen[3], Hong Zhao[3], Fenglong Xie[3] and Jeffrey R. Curtis[3]

[1]Global Healthy Living Foundation/CreakyJoints, Upper Nyack, NY; [2]Amgen, Thousand Oaks, CA; [3]University of Alabama at Birmingham, Birmingham, AL

Background: Methotrexate (MTX) is frequently used in patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA). Despite known benefits of MTX, it has potential side effects, including nausea and fatigue, which can be severe and are often temporally related to weekly MTX administration. The combined patient-reported side effects, along with potential long-term toxicity, may make use of MTX more burdensome. Currently, there is a gap in patient-centered studies focusing on patients' experience with MTX.

Objectives: Using self-controlled case series study design, examine fatigue and nausea associated with oral MTX (with or without biologics) in RA/PsA.

Methods: Participants (pts) are members of the ArthritisPower (AP) registry who self-reported RA or PsA and taking MTX for <10 yrs. Each completed a screener and brief online survey. In an ancillary study, pts were asked to complete ≤8 assessments within 6-36 hours ('risk') and 96-144 hours ('control') after a weekly MTX oral dose, for ≤4 weeks. Risk and control windows were selected based on expected temporal relationship between MTX use and peak onset of symptoms. Assessments included PROMIS short forms for same-day Fatigue, Nausea/Vomiting, and Patient Global. Descriptive statistics were conducted using paired t-tests 2-way comparisons. Within-person change in PROMIS scores between risk (1-2 days post MTX) and control (4-6 days post MTX) windows were analyzed using mixed models for repeated measures, stratified by pt reported baseline fatigue or nausea.

Results: As of December 2019, 91 pts participated (76.9% RA and 28.6% PsA) with mean baseline PROMIS Patient Global score (SD) of 39.5 (7.1). Mean age (SD) was 50.9 (12.0) yrs, 84.6% female, 92.3% White, and mean BMI 33.7 (8.8). Mean MTX treatment duration was 2.1 (2.8) yrs. Among pts, 41.8% were on a biologic DMARD and 58.2% on non-biologic DMARDs only. Among pts reporting baseline nausea (n=30, 33.0%), where paired within-week measures were observed (n=64 observations/20 pts), the mean increase in PROMIS Nausea was 4.5 (adj p=0.003) units. Among those reporting baseline fatigue (n=39, 42.9%), where paired within-week measures were observed (n=96 observations/28 pts), the mean increase in PROMIS Fatigue was 4.7 (adj p=0.004) units. In those pts, the proportion of pts with worsened nausea and fatigue with minimally important difference of >5 units was 40.0% (nausea), and 60.7% (fatigue).

Conclusions: One-third or more pts experienced nausea or fatigue shortly after MTX dosing, many of them with clinically meaningful symptoms.

4544 | Risk of preterm delivery and small for gestational age among women with inflammatory bowel disease using TNF alpha inhibitors during pregnancy

Xi Wang[1], Ellen Zimmerman[2], Joshua Brown[1,3], Amie J. Goodin[1,3] and Almut Winterstein[1,3]

[1]College of Pharmacy, University of Florida, Gainesville, FL; [2]College of Medicine, University of Florida, Gainesville, FL; [3]Center for Drug Evaluation and Safety(CoDES), University of Florida, Gainesville, FL

Background: There is limited evidence on the benefit (in controlling disease) and risk (e.g., due to immune-modulatory properties) of TNF-alpha inhibitors (anti-TNFs) use during pregnancy for women with inflammatory bowel disease (IBD).

Objectives: To investigate the association between anti-TNF use during pregnancy and the risk of preterm or small for gestational age (SGA) delivery.

Methods: A retrospective cohort study established from the 1999-2012 Medicaid Analytic eXtract and the 2005-2015 IBM MarketsSan Databases. We included pregnant women with IBD enrolled in insurance plans from 6 months before the last menstrual period through 1 month after delivery and linked infants enrolled for at least 1 month after birth. The exposure of interest was treatment with anti-TNFs (adalimumab, certolizumab pegol, infliximab), or immunomodulators (azathioprine, mercaptopurine, cyclosporine). Preterm and SGA were defined with validated claim-based algorithms. We estimated risk ratios (RRs) after balancing exposure groups with stabilized inverse probability of treatment weights (SIPTW) to control for confounders. To assess the impact of anti-TNFs use during late pregnancy, we used a cox regression model with SIPTW adjustment to assess the hazard ratio (HR) of preterm in exposure to anti-TNFs vs. immunomodulators in the third trimester.

Results: Among 6,045 pregnancies with IBD, 498 (8.2%) were exposed to anti-TNFs, and 398 (5.6%) to immunomodulators during

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

pregnancy. Overall, 67 (13.5%) anti-TNFs exposed and 69 (20.1%) immunomodulators exposed infants were preterm births and 13 (2.6%) anti-TNFs exposed and 14 (4.1%) immunomodulators exposed infants were SGA. The adjusted RR for preterm was 0.65 (95% confidence interval (CI), 0.47-0.89) and the adjusted RR for SGA was 0.54 (95% CI, 0.26-1.14). The adjusted HR for preterm risk in the third trimester was 0.49 (95% CI, 0.35 to 0.67).

Conclusions: Use of anti-TNF during pregnancy was associated a decreased risk of preterm among pregnant women with IBD. The current findings also suggest that third trimester use of anti-TNF could decrease the risk of preterm delivery relative to the use of immunomodulators.

4575 | Effect of biosimilar market entry on cost of biologics in the United States: The case of filgrastim

Morgane Mouslim, Caleb Alexander and Jodi Segal
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Background: Biosimilars, lower cost, highly similar but inexact copies of referent (brand name) biologics, have been put forth as a promising cost containment strategy for mounting drug prices. However, since their introduction in the United States market, few studies have investigated whether they have been an effective tool in curbing pharmaceutical expenditures with regards to biologic medications. The launch of filgrastim-sndz, the first Food and Drug Administration approved biosimilar, provides a natural experiment with which to empirically evaluate and quantify biosimilar generated cost savings in the United States.

Objectives: To estimate the effect of filgrastim-sndz market entry on cost of filgrastim in the United States.

Methods: This study used a single interrupted time series approach and data from the IBM MarketScan® Commercial Claims and Encounters database to assess the impact of filgrastim-sdnz market entry on cost of filgrastim in the U.S. Study population consisted of outpatient prescription claims for filgrastim, and filgrastim-sndz from January 1, 2014 to December 31, 2017. Our exposure of interest was the September 2015 U.S. launch of filgrastim-sndz. Our primary outcome was the monthly mean reimbursement cost to third party payers (insurers) for filgrastim. Cost was adjusted for inflation using the Consumer Price Index for Medical Care Commodities and was standardized to cost per 480 mcg vial. To the extent that filgrastim-sndz market entry did not translate into immediate market penetration, we used a test of unknow break point to test for an intervention point post filgrastim-sndz launch. Analyses were adjusted for autocorrelation and seasonality

Results: Following filgrastim-sndz launch there was an immediate level decrease in the cost of filgrastim of approximately $5.38 dollars per 480 mcg vial (95% CI, -9.22 to - 1.55; p=0.007) but no significant decrease in monthly cost trend (β= -0.11; 95% CI, -0.61 to -0.38 ; p=0.634). Results of our structural break analysis show a significant discontinuity in utilization of filgrastim 16 months post filgrastim-sndz launch (sup-Wald, 38.25, p<0.001). After this estimated "market penetration intervention point" we observed a significant decrease in the monthly cost trend of a 480-mcg vial of filgrastim (β= -1.22; 95%CI, -2.30 to -0.13, p=0.029).

Conclusions: Among commercially insured patients, filgrastim biosimilar availability led to an immediate decrease in price level and a lagged decrease in price trend for filgrastim. The delay in price trend decrease is likely due to the lag between biosimilar availability and biosimilar adoption.

4583 | Traceability of biosimilar and reference products in adverse drug events reports in Saudi Arabia

Fares Alrubaish, Rayan Alolayet, Muhanad Alharbi, Hamad Alnomay and Fawaz Alharbi
Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: Product trade name and batch number are essential elements in reporting Adverse Drug Events (ADEs) of biologics (reference and biosimilar products) due to the variability of biomanufacturing process.

Objectives: To assess the availability of biologics (reference and biosimilar) trade name and batch number in ADE reports on the National Pharmacovigilance Center (NPC) database at the Saudi Food and Drug Authority (SFDA).

Methods: We performed a descriptive analysis of ADE case reports of biosimilars and reference products in Saudi Arabia reported to the NPC by healthcare providers and the public from January 2010 to January 2020. The analysis examined the reporting frequency of the product trade name, batch number, and the type of reporter.

Results: We identified 322 ADE case reports of biosimilars and reference products. The product trade name was only included in 97 (30%) ADE case reports. The majority of case reports (303; 94%) did not include the batch number. 224 (70%) ADE case reports did not specify the reporter type. The remaining cases (98; 30%) were reported by pharmacists.

Conclusions: The analysis demonstrates the need for improving the traceability of biosimilars and reference products in Saudi Arabia. The product trade name and batch number are essential elements in post-marketing safety surveillance of biosimilars and reference medicines.

4586 | Cardiovascular risk in patients receiving ranibizumab therapy for exudative age-related macular degeneration: A nationwide self-controlled case-series study

Ha-Lim Jeon[1], Seong Jun Byun[1], Nicole L. Pratt[2], Janet Sultana[3], Sang Jun Park[4] and Ju-Young Shin[1]
[1]Sungkyunkwan University (SKKU), Suwon, Republic of Korea; [2]University of South Australia, Adelaide, Australia; [3]University of Messina, Messina, Italy; [4]Seoul National University Bundang Hospital, Seongnam, Republic of Korea

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Ranibizumab is a vascular endothelial growth factor (VEGF) inhibitor, which is developed for the treatment of exudative age-related macular degeneration (AMD). Although cardiovascular complications are identified by systemic use of anti-VEGF in oncology, it is still unclear whether intravitreal anti-VEGF injection is associated with the systemic cardiovascular events.

Objectives: To examine the association between ranibizumab use and the risk of stroke and acute myocardial infarction (AMI) using a self-controlled case-series design.

Methods: We identified patients aged ≥45 years who received ranibizumab for exudative age-related macular degeneration (AMD) between January 2009 and December 2015 using the Korean National Health Insurance database. Of these, we selected patients suffering stroke or AMI for the self-controlled case-series. We estimated age-adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for stroke or AMI by comparing incidence rates of ranibizumab-exposed periods to that of baseline periods using conditional Poisson regression. We also calculated the risks of hemorrhagic and ischemic strokes separately to examine potential differences due to physiological mechanism.

Results: Among 33,134 patients receiving ranibizumab for exudative AMD, 2,397 patients had stroke or AMI; 1,943 had stroke and 762 had AMI. The median duration of exposure was 4.6 (interquartile range [IQR], 2.7-6.2) and median age at first exposure was 76 (IRQ, 70-81). The risk of stroke (IRR=0.83, 95% CI=0.75-0.91) was not increased during overall exposed period compared to baseline period; however, there was a marginally elevated risk in ≥57 days exposed period (IRR=1.14, 95% CI=1.001-1.31). When analyzing by the types of stroke, no increased risk of hemorrhagic (IRR=1.01, 95% CI=0.80-1.26) and ischemic stroke (IRR=0.78, 95% CI=0.71-0.86) was observed during the exposed period, although the risks of ischemic and hemorrhagic stroke were slightly elevated during ≥57 days exposed period (ischemic: IRR=1.15, 95% CI=1.00-1.32; hemorrhagic: IRR=1.26, 95% CI=0.90-1.76). We could not find an association between ranibizumab and AMI.

Conclusions: This study shows ranibizumab intravitreal injections did not increase the overall risk of stroke or AMI. Although the cardiovascular risk in patient with ranibizumab therapy for exudative AMD seems to be low under current good medical practice, continuous monthly use of ranibizumab for high-risk patients should be judged carefully.

4617 | Biosimilar formulations of gonadotropins in a central Italian region: Use patterns and time trends

Alessandro Cesare Rosa

Department of Epidemiology, Asl Roma 1, Lazio Region, Rome, Italy

Background: Gonadotropins (Gona) are hormones that play a central role in the follicular growth (and therefore in the production of oocytes) in women but are also useful in male infertility. Gona used for infertility treatment are available as urinary extracts or recombinants. In 2015, the first biosimilar of follitropin alfa (a recombinant Gona) was authorised in Italy.

Objectives: We aimed to evaluate use patterns, temporal and spatial variations of Gona biosimilar formulations in a central Italian region, accounting for about 6 Million residents.

Methods: From administrative healthcare databases of the Lazio region, we extracted drug claims in the years 2015-2018. Gona formulations were grouped into urinary (u-Gona) and recombinant (r-Gona). Special focus was on biosimilar r-Gona. Use patterns were investigated with respect to characteristics of the patients treated, time trends, type of prescribing physician, and differences among local health units.

Results: For the study period, we retrieved 112,090 Gona dispensations for 51,178 patients. The 9,878 r-Gona biosimilar dispensations (8.8% of all claims, of which 99.5% Bemfola®, and 0.5% Ovaleap®), were mostly referred to women, aged 18-45 years, (85.5% of all patients). Median age was 37 years for women, 38 for men. Since its authorisation, biosimilar r-Gona steadily gained market from 2015 (0,4% of claims) to 2017 (22,7%) followed by a decrease in 2018 (9,1%). Biosimilars claims are more frequent in treating men (32,4%) than women (6,4%). Most biosimilar prescriptions were issued by general practitioners (83.9%), followed by specialists (7.1%) and others. Biosimilar use patterns varied between different local health units (IQR 3.4%-9,1%).

Conclusions: In clinical practice, in the Lazio region, r-Gona biosimilar dispensation account for less than 10% and are mostly prescribed by general practitioners and proportionally more used in treating men. Further investigation is under way.

4750 | Dupilumab and the risk of conjunctivitis and serious infection in patients with atopic dermatitis: A propensity score-matched cohort study

Maria Schneeweiss[1], Seoyoung Kim[1], Sebastian Schneeweiss[1] and Joseph Merola[1]

[1]*Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Background: Dupilumab is a human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits signaling of IL-4 and IL-13, and is indicated for use in moderate-severe atopic dermatitis (AD). Dupilumab has been associated with an increased risk of conjunctivitis in trials, yet there is limited real-world data concerning this adverse event.

Objectives: This study compared the 6-month risk of conjunctivitis and serious bacterial and opportunistic infections in patients with AD who initiated dupilumab versus methotrexate (MTX).

Methods: We identified adults and children with AD enrolled in a US commercial health plan who initiated either dupilumab or MTX (i.e., cohort entry), from March 2017 through June 2019. Conjunctivitis, including bacterial and allergic, and serious bacterial and opportunistic infections were identified as study outcomes. Patients were free of any conjunctivitis diagnosis, any autoimmune or chronic

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

inflammatory disease, or other indications for biologic immunomodulating drugs before cohort entry. We computed the 6-month event risks carrying the exposure status at cohort entry forward for the 180 days of follow up. Relative risks of infection and conjunctivitis were computed after 1:1 PS-matching.

Results: Among 1,132,783 patients with AD we identified 2,000 patients who initiated treatment with either dupilumab (n=1,194) or MTX (n=806). PS-matching resulted in 574 pairs of patients who initiated dupilumab and MTX. In comparing patients with AD who initiated dupilumab versus MTX, we found that those who initiated dupilumab had a decreased 6-month risk for serious infections (6.97 vs. 15.68 per 1,000 patients; RR=0.44 [95% CI 0.13-1.44]), and had an increased 6-month risk for any conjunctivitis (76.66 vs. 38.33; RR=2.08 [1.39-3.58]). The 6-month risk of bacterial conjunctivitis requiring antibiotics was RR=1.44 (0.54-3.80), of allergic conjunctivitis was RR=1.51 (0.53-4.26), and of keratoconjunctivitis was RR= 2.85 (1.02-7.95).

Conclusions: In patients with AD who initiated treatment with dupilumab we identified few cases of serious infection showing no indication of an increased 6-month risk with an upper 95% confidence interval of 1.44 when compared to MTX initiators. Dupilumab initiators had twice the risk of developing conjunctivitis compared to MTX consistently across a range of various types of conjunctivitis. This study adds further evidence of no increase in serious bacterial or opportunistic infections and that an increased risk of conjunctivitis needs to be managed in clinical practice.

4807 | Comparability of patients with CIDP using intravenous immunoglobulin in medicaid vs commercial or medicare claims data

J. Bradley Layton[1], Mary E. Ritchey[1], Zhongwen Huang[2] and Colin Anderson-Smits[2]

[1]RTI Health Solutions, Research Triangle Park, NC; [2]Takeda Pharmaceutical Company, Cambridge, MA

Background: Multiple data sources may be required to obtain necessary sample sizes for studies of rare diseases and treatments. While Medicaid, Medicare, and commercial insurance claims data sources are all available in the US, Medicaid programs for patients with low incomes have differences by state in underlying patient case mix, eligibility criteria, and healthcare coverage.

Objectives: To describe the differences in patient characteristics and medication-usage patterns between patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a rare neurological disorder affecting nerve signal transmission, as identified in Medicaid versus Medicare or commercial insurance.

Methods: Patients with diagnoses of CIDP were identified in Medicaid, Medicare supplementary, and commercial insurance data (2008-2018). Those subsequently initiating treatment with intravenous immunoglobulin (IVIg) were identified through procedure and pharmacy dispensing coding. Demographic and clinical characteristics of patients and patterns of use of IVIg were compared between patients identified in Medicaid and those in other insurance.

Results: Out of 32,090 patients with CIDP diagnoses, 12% were identified in Medicaid, and 88% in Medicare or commercial claims. Medicaid patients were younger (mean age 51.7 vs. 57.8) and more likely to be female (59% vs. 47%). Medicaid patients were more likely to have any of several comorbidities, including asthma, arrythmias, chronic obstructive pulmonary disease, heart failure, diabetes mellitus, hepatitis, hypertension, and renal disorders, but were less likely to have electrodiagnostic/nerve conduction testing. Of those with CIDP, 10% of the Medicaid sample and 13% of the others initiated IVIg treatment. 23% of IVIg initiation was identified in pharmacy claims in Medicaid, while only 10% IVIg initiation in other insurance was. The duration of IVIg use was shorter among those with Medicaid (188 vs. 216 days).

Conclusions: The characteristics and treatment patterns of patients with CIDP identified in Medicaid differed from those identified in other data sources. Medicaid may be a valuable source of information on an important population, but the suitability of its use and availability of critical study variables should be carefully considered in context to the research question before inclusion in multi-database studies of rare diseases. Assessment of differences in demographics, comorbidities, and treatment patterns could aid understanding of whether Medicaid patients would be best suited for studies including long-term outcomes.

4820 | Adverse event profiles of therapies that target the calcitonin gene-related peptide (CGRP) pathway, during the first six months after launch: A real-world data analysis using the FDA adverse events reporting system (FAERS)

Stephen D. Silberstein[1], Shoshana Reshef[2], Joshua M. Cohen[2], Sanjay Gandhi[2], Michael Seminerio[2], Verena Ramirez Campos[2], Yoel Kessler[2], Stephen Thompson[2] and Andrew Blumenfeld[3]

[1]Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA; [2]Teva Branded Pharmaceutical Products R&D, Inc., West Chester, PA; [3]Headache Center of Southern California, The Neurology Center, Carlsbad, CA

Background: Since May 2018, three medications that target the CGRP pathway have been FDA approved for preventive treatment of migraine: erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm. Post-marketing data indicate medication safety in a real-world setting.

Objectives: To gain insight into the real-world adverse event (AE) profile of CGRP pathway-targeted migraine preventive treatments.

Methods: This retrospective analysis of data from FAERS, the FDA's database for safety surveillance, evaluated AEs spontaneously reported during the first 6 months post-approval of erenumab, fremanezumab, and galcanezumab using FAERS. We evaluated cases in which the product was classified as the "primary suspect" associated with an AE. Reporting rates (RR) were calculated by dividing number of events in each AE category by estimated number of exposed subjects based on de-identified prescription data (IQVIA database) and multiplied by 1,000 to create a rate per 1,000 exposed.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: The top ten AE RRs per 1,000 were: erenumab: wrong technique (4.97), constipation (4.90), migraine (4.89), accidental product exposure (4.83), drug ineffective (3.68), headache (3.32), injection-site pain (2.94), nausea (2.94), under-dose (2.55), and fatigue (2.33); fremanezumab: headache (1.27), drug ineffective (1.14), migraine (1.01), nausea (0.91), injection-site pain (0.81), pruritus (0.73), injection-site erythema (0.71), injection-site pruritus (0.63), injection-site rash (0.63), injection-site swelling (0.58); galcanezumab: injection-site pain (4.90), under-dose (3.86), headache (3.07), migraine (2.99), drug ineffective (1.69), injection-site erythema (1.58), injection-site swelling (1.25); injection-site pruritus (1.14), nausea (1.09), and product-dose omission (1.09).

Conclusions: Migraine, headache, or drug ineffective AEs were commonly reported for all three products, as were migraine-associated symptoms and injection-site reactions. Constipation ranked second for erenumab but did not make the top ten AEs for fremanezumab or galcanezumab. Cardiovascular events were not ranked in the top ten for any product.

4829 | Identifying immunoglobulin use in claims data with procedure coding and pharmacy dispensing data

Colin Anderson-Smits[1], Bradley Layton[2], Zhongwen Huang[1] and Mary Beth Ritchey[2]

[1]*Takeda Pharmaceuticals, Cambridge, MA;* [2]*RTI Health Solutions, RTP, NC*

Background: Immunoglobulins (Ig) may be administered intravenously (IVIg) or subcutaneously (SCIg), inpatient, at an infusion center or at home, and some Ig may be self-administered. Differences in administration routes, treatment guidelines, and reimbursement policies may result in Ig use recorded as dispensed pharmacy products or procedures in US claims data. Correctly identifying users of Ig treatments is critical for valid generation of real-world evidence for these products.

Objectives: To describe the relative distribution and characteristics of Ig initiators identified via procedure and pharmacy claims.

Methods: Patients with diagnoses of primary immunodeficiency (PID) or chronic inflammatory demyelinating polyneuropathy (CIDP) were identified in US commercial, Medicare, or Medicaid claims data. Patients with PID initiating IVIg or SCIG and patients with CIDP initiating IVIg were identified at the first recorded claim for an Ig product in inpatient or outpatient procedure coding (i.e., HCPCS) or pharmacy dispensing drug claims (i.e., NDC). Characteristics of Ig initiators were described, stratified by the source of the first Ig claim.

Results: For patients with PID initiating Ig (N=17,931), 9% were first identified through pharmacy claims; those identified in pharmacy claims were more likely to have Medicaid insurance than those identified in procedure claims (30% vs. 17%). The characteristics of pharmacy-identified patients differed from procedure-identified patients, with some characteristics higher among those identified in pharmacy claims (e.g. asthma, 55% vs. 40%), but others were higher among procedure-identified patients (e.g. leukemia, 22% vs. 4%). Among those with CIDP (N=3,975), 11% were first identified through pharmacy claims, and they were more likely to have Medicaid (19% vs. 8%) or Medicare (38% vs. 23%) than those identified through procedure claims. Pharmacy-identified patients generally had similar or higher levels of most comorbidities compared to procedure-identified patients. Procedure-identified Ig were more likely to have some markers of health care screening and utilization, such as blood laboratory tests, in both diseases.

Conclusions: While most Ig initiators were identified in procedure claims, pharmacy dispensing claims are an important source of information about Ig use and identifying initiation of Ig products. There may be key differences in patient populations identified by procedure or pharmacy coding reflective of the payer policies or treatment guidelines across disease areas.

4853 | Agreement between electronic health record and medical claims data for defining exposure to infused biologic treatments in inflammatory bowel disease

Carrie Huisingh and Lani R. Wegrzyn

AbbVie, North Chicago, IL

Background: Electronic health record (EHR) databases provide researchers the opportunity to conduct investigations that are not possible in insurance claims databases. For pharmacoepidemiology studies, accurate classification of medication exposure is critical. Several medications for treatment of advanced inflammatory bowel disease, i.e. Crohn's Disease (CD) and Ulcerative Colitis (UC), are administered by intravenous infusion in a healthcare provider's office. It is not clear how well this EHR-based treatment information correlates with medical claims.

Objectives: To evaluate the agreement of medication exposure information in EHR and medical claims for infused biologics in patients with CD or UC.

Methods: We conducted a retrospective study among patients with linked medical claims in the Optum de-identified Integrated Claims-Clinical database. Separately for CD and UC, index was defined as the first medication administration or procedure code for an infused biologic, and patients were required to have continuous medical and pharmacy insurance coverage for 180 days prior to and after index. The agreement between EHR medication administration and procedure data and medical claims data was determined for 3 biologic treatments (Infliximab, Ustekinumab, and Vedolizumab) using the positive predictive value (PPV) calculated in 30-day and 180-day periods. Secondary analyses included using codes for unclassified biologics to identify potential claims and restricting to patients with an encounter with a Gastroenterologist within 180 days after index.

Results: In CD patients, the 30-day period PPV was 86.0% for Infliximab, 53.5% for Ustekinumab, and 83.6% for Vedolizumab. The 180-day period PPV was 91.3% for Infliximab, 86.0% for Ustekinumab, and 86.9% for Vedolizumab. In UC patients, the 30-day PPV was 86.1% for Infliximab and 88.0% for Vedolizumab. The 180-day period PPV was

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

90.4% for Infliximab and 89.8% for Vedolizumab. Identifying Ustekinumab users with unclassified biologics code improved the PPV. Requiring a follow-up visit with a GI physician did not substantially improve medication exposure classification.

Conclusions: There was high agreement between EHR medication administration and procedure data and medical claims data for infused biologics used in the treatment of inflammatory bowel disease. To maximize the validity of classifying medication exposure with EHR data, researchers may consider using longer periods (180 days) and including unclassified biologics codes for newer drugs.

4861 | Profile of patients with rheumatic diseases and treated at a Brazilian Health System Unit in Belo Horizonte City

Natália Brandão, Marina Morgado, Gerusa Araújo, Juliana Alvares-Teodoro, Francisco Acúrcio and Augusto Afonso Guerra
Federal University of Minas Gerais, Belo Horizonte, Brazil

Background: Rheumatic diseases are chronic inflammatory diseases, autoimmune, associated with joint destruction. Biological drugs are often used to treat these diseases.

Objectives: Retrospective analysis of demographic, clinical and drug utilization characteristics of patients diagnosed with rheumatoid arthritis (RA), psoriatic arthritis (PA) or ankylosing spondylitis (AS), undergoing outpatient follow-up and receiving biological drugs by the Brazilian Public Health System (SUS) unit in Belo Horizonte city.

Methods: Cross-sectional study focusing on secondary data of patients attended regularly at the SUS unit through the request for medication completed by the doctor. The categorical variables were described by means of the distribution of frequencies and the continuous variables by means of mean and standard deviation at baseline.

Results: 426 patients were evaluated and 59% used previously biologics. The mean age of 306 RA patients was 56 years and 87.5% were women. The mean disease duration was 34 months. 60% of the patients had affection in more than 10 joints and 76.5% scored 5 or more points in the ACR/EULAR criteria. 51.8% had rheumatoid factor or anti-CCP positive in high titers. 99.7% had rheumatoid vasculitis and 97% rheumatoid lung disease. 95% had high or moderate disease activity, according to the DAS-28. 42% requested tofacitinib, 24% certolizumab pegol and 10% abatacept. The mean age of 65 PA patients was 54 years and 61.5% were women. The mean disease duration was 26 months. All patients had inflammatory joint disease, 89.2% with peripheral involvement, 16.9% enthesitis or dactylitis and 15.4% with axial involvement. 75.4% had current psoriasis, 36.9% psoriatic nail dystrophy, 21.5% current dactylitis and 23.1% radiographic evidence of proliferation bone (CASPAR Classification). Regarding the MDA, 31.3% met 5 or more criteria. 83% requested secuquinumab, 8% golimumab and 5% adalimumab. 65% used previously NSAIDS drugs. The mean age of 58 AS patients was 48 years and 53.4% were women. The mean disease duration was 26 months. 71% had peripheral arthritis and 29% had inflammatory low back pain and enthesitis. As for the ASAS criteria, 98.4% had inflammatory low back pain for at least 3 months, disease onset was up to 45 years and 96.8% had sacroiliitis on imaging tests. 45% requested secuquinumab, 21% golimumab and 19% certolizumab pegol.

Conclusions: The results showed that patients with rheumatic diseases who requested biological drugs in SUS presented high disease activity. This knowledge may support the development of public policies to improve the access of the biological drugs.

5008 | The adherence patterns among patients using infliximab bio-originator and biosimilar

Joseph C. Alanaeme[1], Sarvesh Sujith[1], Jeffrey R. Curtis[1] and Huifeng Yun[1]
[1]*University of Alabama at Birmingham, Birmingham, AL*

Background: Infliximab (INF) biosimilar was approved for multiple indications in U.S. in 2016. Although clinical trials have demonstrated that switching from infliximab bio-originator to its biosimilar is safe with no significant loss of efficacy, there are limited real-world data comparing their utilization and adherence patterns.

Objectives: We evaluated medication adherence among INF biosimilar users and compared them to INF bio-originator users using national administrative data, 2014-2018.

Methods: We established 4 cohorts among patients who had at least one administration or pharmacy claim for INF bio-originator or biosimilar in 2017 Truven Marketscan data, including INF biosimilar naïve users, INF biosimilar prevalent users, INF bio-originator naïve users, and INF bio-originator prevalent users. We evaluate the prior use of INF and other biologics using all available data in 2014-2017 prior to the first INF administration in 2017 (index date). The INF naïve users were defined as no prior use of INF bio-originator or INF biosimilar, whereas prevalent users had any prior use of bio-originator INF but no prior INF biosimilar use. Eligible patients were ≥18 years of age, continuously enrolled with full coverage from 2014 and through follow up. Follow-up started on the index date and ended on the earliest date of death, loss of coverage, or 12/31/2018. For patients who had at least 12 or 18 months of follow-up time, we calculated their proportion of days covered (PDC) at 12 or 18 months. Ongoing analyses are adjusting for important patient characteristics that differ across cohorts.

Results: We identified 96 INF biosimilar naïve users, 223 INF biosimilar prevalent users, 2,149 INF bio-originator naïve users, and 10,970 INF bio-originator prevalent users. The proportion of other biologic use prior to index date and demographic characteristics are similar across different cohorts with mean age of 45 and 60% females. Among patients who had >=12m of follow-up, 43% INF biosimilar naive users, 41.5% INF biosimilar prevalent users, 52% INF bio-originator naïve users and 73% INF bio-originator prevalent users continued to be adherent (>80%) at 12 months. Among patients who had >=18m of follow-up, 48%, 36%, 41%, and 64% user continued to be adherent at 18 months respectively.

Conclusions: The adherence patterns were similar among INF biosimilar naïve, INF biosimilar prevalent, and INF bio-originator naïve users, and the INF bio-originator prevalent users had the highest

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

adherence at 12 or 18 months of follow-up. However, further studies with large sample size are needed to evaluate the adherence and the cost of INF biosimilar users.

5035 | Real-world evidence of the risk of neutropenia among patients treated with filgrastim

Elnara Fazio-Eynullayeva
TriNetX, Inc., Cambridge, MA

Background: As of February 12, 2020, 25 biosimilars referencing nine originator biologics have been approved for use in the United States. Filgrastim is a biologic drug used to treat patients with low neutrophil count. This study builds on previous research in comparing filgrastim originator biologic with stand-alone alternative biologic tbo-filgrastim and biosimilar filgrastim-sndz using real-world data.
Objectives: The aim of this study was to compare the risk of neutropenia in patients on chemotherapy treated with filgrastim, tbo-filgrastim and filgrastim-sndz.
Methods: Chemotherapy-treated patients were identified in a US-based EMR network (>55.8 million patients). Patients with evidence of neutropenia prior to index filgrastim biologic/biosimilar use were excluded. Three separate comparison analyses were conducted: patients treated with filgrastim were compared to patients treated with tbo-filgrastim; those treated with filgrastim were compared with those treated with filgrastim-sndz; and tbo-filgrastim cohort was compared to the filgrastim-sndz cohort. All comparisons were adjusted for baseline confounders using a 1:1 greedy nearest neighbor matching propensity score model. Risk ratios, 95% confidence intervals, and Kaplan-Meier survival curves were calculated. Patient characteristics were defined by ICD, CPT, LOINC, and RxNorm terminology.
Results: The standardized mean difference for all baseline characteristics after propensity score matching was less than 10%. After matching, there were 520 patients in each, filgrastim and filgrastim-sndz cohorts. The risk of neutropenia was higher in filgrastim cohort (N=157) than in filgrastim-sndz cohort (N=91), RR=1.73 [1.37, 2.17]. Differences in the risk of neutropenia between filgrastim and tbo-filgrastim, as well as between filgrastim-sndz and tbo-filgrastim were found to not be statistically significant.
Conclusions: This analysis found that compared with filgrastim-sndz, there was a higher risk in the filgrastim cohort for incidence of neutropenia. No significant differences in the risk of neutropenia were observed in the other two comparisons.

5120 | Seasonal differences in omalizumab utilization among persons with asthma and allergic rhinitis in the United States

Ayobami Akenroye, Kayte Andersen, Corinne Keet, Jodi Segal and Caleb Alexander
Johns Hopkins University, Baltimore, MD

Background: Seasonal variations in asthma morbidity and mortality have been well documented, with disease worsening due to viral respiratory infections in the winter and environmental allergens in the fall. Omalizumab is a monoclonal antibody approved for severe allergic asthma in the case of inadequate control with inhaled corticosteroids. Thus, seasonal variations in asthmatic disease activity may be reflected as treatment escalation to omalizumab.
Objectives: To describe seasonal differences in the initiation, adherence, and persistence to omalizumab in the United States from 2011 to 2017.
Methods: Longitudinal retrospective cohort analysis using the IBM MarketScan® Commercial Claims and Encounters Database. We included patients with concomitant diagnoses of asthma and allergic rhinitis and at least 1 claim for omalizumab between 2011 and 2017, using a 1-year look-back period to ascertain new user status. We used date of dispensation and days of supply to define continuous omalizumab use. Linear regression (adjusted for age, sex, days supply, copay, insurance type & region) was used to compare percent differences in the proportion of days covered (PDC) between seasons with 95% confidence intervals (95% CI). Time to discontinuation, defined as a gap of 180 days or more between claims given the monthly dosing administration, was assessed using hazard ratios (HR) and 95% CI from Cox proportional hazards models, adjusted for the variables listed above.
Results: A total of 7,535 individuals were included, with a mean age of 43 years (standard deviation, SD 15) and 65% were females. A majority of omalizumab initiations (41%) were in the winter, with similar rates for the other seasons (spring 19%, summer 18%, fall 17%). In multivariable analyses, persons who initiated in the winter (-16%, 95% CI -10 to -21%), spring (-16%, 95% CI -10 to -22%) and summer (-12%, 95% CI -6 to -18%) had significantly lower PDC than persons who initiated in the fall. The average duration of use was 2.8 years (1.6 years). Persistence was significantly shorter for prescriptions initiated in the winter (HR=1.74, 95% CI 1.37-2.21) and spring (HR=1.56, 95% CI 1.20-2.01) compared to fall initiations, but not summer (HR=1.27, 95% CI 0.96-1.69).
Conclusions: There is seasonal variation in omalizumab initiation, adherence and persistence, which may reflect confounding by indication rather than true differences in omalizumab effectiveness. Future studies examining adherence to omalizumab and effectiveness should account for possible underlying seasonal differences.

5124 | Use of monoclonal antibodies for asthma in the United States, 2003-2019

Ayobami Akenroye, Jamie Heyward, Corinne Keet and Caleb Alexander
Johns Hopkins University, Baltimore, MD

Background: Little is known about the use of the monoclonal antibodies approved for the treatment of asthma in the US.
Objectives: We quantified trends and patterns of utilization of these biologics in the US.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: We used the IQVIA National Disease and Therapeutic Index™ (NDTI), a nationally representative survey of over 4000 office-based physicians in the US. We focused on ambulatory visits where asthma was diagnosed and treated with one or more of the biologics ("treatment visit").

Results: From 2003 to 2019, annual asthma-related visits plateaued between 12 and 14 million. Biologic treatment visits ranged from 0.4% of 14,167,830 asthma-related visits in 2004, the first full year with a biologic available, to 1.1% of 14,343,305 visits in 2018, the most recent year with complete data [trend, p=0.03]. Omalizumab was the most used biologic, accounting for 53% of the visits in 2018, followed by mepolizumab (26%), benralizumab (21%), and reslizumab (0.7%). Data on dupilumab use is limited given its recent introduction. Of these biologic treatment visits, 58% were female, 48.6% 40-59 years of age, 21% 60-74 years, 17% 20-39, 9% 6-19, and <5% ≥75 years of age. 66.8% were white, 14% black, and 12% Hispanic. These visits were mostly to allergists [55%] and pulmonologists [32%]. Internists, family practitioners, and pediatricians accounted for 9%, 2%, and 0.5% of these visits respectively.

Conclusions: There is an overall increasing trend in the use of biologics for asthma with omalizumab remaining the most commonly prescribed biologic for asthma. Use of mepolizumab and benralizumab is increasing.

5141 | Tumor necrosis factor alpha-inhibitor (TNFα-I) use and hip fracture in United States (US) veterans with rheumatoid arthritis (RA)

Sarah Homann, Carlos Grijalva, S. Bobo Tanner and James Morrow
Vanderbilt University Medical Center, Nashville, TN

Background: Patients with RA have a greater risk of sustaining a hip fracture than those without. Though some studies have reported beneficial effects of TNFα-I on bone health in patients with RA, whether use of TNFα-I decreases the risk of hip fractures remains unclear. Prior work on this subject have included predominantly female populations.

Objectives: To determine whether use of TNFα-I decreases the risk of hip fractures compared with use of non-biologic disease modifying anti-rheumatic drugs (DMARDs) in US Veterans with RA.

Methods: Using national Veterans' Affairs (VA) data linked to Medicare files from 2000-2017, a retrospective cohort of RA patients was assembled. RA was identified using a validated algorithm. Veterans with prior hip fracture, cancer, and serious organ disease identified during the baseline period were excluded. Cohort members were followed until development of exclusion criteria, hip fracture, leaving VA, enrollment in Medicare Advantage or death. Using this cohort, a nested case-control study was implemented with cases of incident hip fractures identified using an adapted validated algorithm. Incidence density sampling was used to select up to 20 at-risk controls per case on the date of the fracture (index date). Controls were matched to cases on age, sex, VA region, and time since cohort entry. Pharmacy data were used to assess DMARD exposure in the two years preceding the index date. Cases and controls were classified into mutually exclusive exposure categories: non-biologic DMARD users (ref.), TNFα-I biologic DMARD users, non-TNFα-I biologic DMARD users, and others. Multiple imputation with chained equations was used to impute missing values. Multivariable conditional logistic regression was used to assess the association between medication exposure and the risk of hip fracture, accounting for covariates.

Results: During follow-up, 496 hip fracture cases and 8917 matched controls were identified. The proportion of male cases was 93%, with median age of 76 years. In multivariable analyses accounting for relevant covariates, hip fracture cases had similar odds of exposure to TNFα-I compared with controls (aOR: 1.08 [95% CI, 0.73 - 1.60]). Factors associated with hip fractures in the multivariable regression included the use of benzodiazepines, opioid analgesics, SSRIs, and inhibitors of bone resorption. Use of thiazide diuretics was associated with a lower risk of fracture.

Conclusions: In this preliminary assessment, use of TNFα-I was not associated with a decreased risk of hip fractures compared with use of non-biologic DMARDs among Veterans with RA.

Disease Epidemiology/Clinical Course -> Cancer

129 | Screening for potential prescription drug effects on prognosis of localized colorectal cancer

Anne Katrine Duun-Henriksen[1], Klaus K. Andersen[1], Irene Petersen[2], Henrik Toft Sørensen[3], Anssi Auvinen[4], Laurel A. Habel[5], Jesper Hallas[6], Anton Pottegård[6], Jiri Bartek[1], Søren Friis[1] and Christian Dehlendorff[1]
[1]Danish Cancer Society Research Centre, Copenhagen, Denmark; [2]University College London, London, United Kingdom; [3]Aarhus University Hospital, Aarhus, Denmark; [4]University of Tampere, Tampere, Finland; [5]Kaiser Permanente, Oakland, CA; [6]University of Southern Denmark, Odense, Denmark

Background: Identification of harmful or beneficial effects of drugs on cancer prognosis has inspired efforts in drug safety and drug repurposing for cancer treatment. Large registries are excellent data resources for screening for potential candidate drugs.

Objectives: In this study, we present a framework for screening the potential effects of prescription drugs on cancer prognosis based on the Danish nationwide health registries, illustrated by localized colorectal cancer (CRC) patients.

Methods: We used the National Cancer Registry to identify all one-year survivors of localized CRC in the period 2002-2015 and retrieved their prescription history from the Danish Prescription Registry. We followed the patients from one year after diagnosis up to 5 years after diagnosis. The framework consists of two estimation steps and three evaluation criteria for each unique drug class (4^{th} ATC level). First, inverse probability (IP)-weighted hazard ratios (HRs) for overall and cancer-specific death from Cox models were used to compare drug users vs. nonusers. Stabilized IP weights were estimated from a

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

logistic regression model with sex, age at diagnosis, period of diagnosis, marital status, income, and cancer treatment included as covariates. Secondly, five-year survival probabilities for users and nonusers were estimated using the IP-weighted Kaplan-Meier (KM) estimator. For each drug class, use was defined as redeeming at least one prescription within the first year after diagnosis. Drug classes with less than 100 users were not considered. For each drug class, the analyses were restricted to individuals with no prescriptions within the last year prior to diagnosis. Drug classes fulfilling all of the following three criteria were defined as potential signals: Criteria 1: The HR for overall death was >1.5 or <0.67 or the confidence interval did not overlap 0.83-1.2. Criteria 2: The HR for cancer-specific death was as least the magnitude as the HR for overall death. Criteria 3: The IP-weighted KM five-year survival estimates for users and nonusers was statistically significantly different at a 5% significance level.

Results: In total, 15,274 one-year survivors of CRC filled prescriptions of 941 unique drugs in 412 unique drug classes during the first year after cancer diagnosis. Out of the 412 drug classes, 94 were eligible for screening. From the evaluation, we identified seven drug classes with a potential effect on the prognosis of one-year survivors of CRC.

Conclusions: Applied on localized CRC patients, our proposed screening framework identified seven potential candidates among 94 drug classes for further investigation.

2371 | Venous thromboembolism and risk of cancer in users of low-dose aspirin: A Danish population-based cohort study

Frederikke Schønfeldt Troelsen[1], David Nagy[1], Nils Skajaa[1], Dóra Körmendiné Farkas[1], Rune Erichsen[1,2] and Henrik Toft Sørensen[1]
[1]Aarhus University Hospital, Aarhus N, Denmark; [2]Randers Regional Hospital, Randers, Denmark

Background: Long-term use of low-dose aspirin has been associated with a reduced risk of several cancers. Venous thromboembolism (VTE) is a marker of increased cancer risk; however, it remains unknown whether VTE is a marker of occult cancer in users of low-dose aspirin.

Objectives: To investigate the risk of cancer subsequent to VTE among users of low-dose aspirin.

Methods: We performed a population-based cohort study in Denmark, linking prospectively collected, individual-level data from existing Danish health registries during 2006-2017. We identified all patients with a first-time hospital-based diagnosis of VTE who also redeemed a prescription for low-dose aspirin within 90 days prior to the date of their first-time VTE. We defined new use of aspirin as first-time prescription within one year prior to the VTE diagnosis and current use as first-time prescription more than one year prior to the VTE diagnosis. We computed absolute risks of cancer, treating death as a competing risk, and age-, sex-, and calendar-period standardized incidence ratios (SIRs) by comparing the observed cancer incidence among aspirin users with the expected risk of cancer based on national cancer incidence during the study period.

Results: We followed 8,891 users of aspirin with VTE for a median of 2,5 years (interquartile range (IQR): 0.6-5.3 years). Current users comprised 87% of the study population. The median age at VTE diagnosis was 77 years (IQR: 68-84 years) for current and 68 years (IQR: 58-78) for new users, respectively. We observed 1,159 cancers among current users of aspirin. The one-year absolute risk of cancer was 7.0% (95% confidence interval [CI]: 6.5-7.6) with a corresponding SIR of 3.0 (95% CI: 2.8-3.3). The SIR decreased to 1.1 (95% CI: 1.0-1.2) during the subsequent years of follow-up. We observed 182 cancers among new aspirin users yielding an absolute risk of 6.1% (95% CI: 4.8-7.6) during the first year of follow-up. The SIRs were 3.4 (95% CI: 2.6-4.3) and 1.2 (95% CI: 1.0-1.5) after one and more than one year of follow-up, respectively.

Conclusions: VTE might be a harbinger of cancer even in users of low-dose aspirin regardless of treatment duration.

2376 | Antidepressant dispensing among women with breast cancer, United States, 2001-2018

Jihye Park, Sara Dejene, Sophie E. Mayer, Alan Kinlaw, Hazel B. Nichols, Michele Jonsson-Funk, Virginia Pate, Eliza M. Park, Katherine E. Reeder-Hayes and Jennifer L. Lund
University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Breast cancer is the most common cancer among women in the US. In women with early breast cancer, prevalence of clinically significant depression or anxiety symptoms is twice as many than seen in the general female population, and antidepressant (AD) use is common in this population.

Objectives: To provide an updated summary of patterns of AD dispensing among women with breast cancer diagnosis using a sample of US commercial health insurance claims data, 2001-2018.

Methods: Using the MarketScan claims databases from 2001 to 2018, we identified women aged 18-64 with at least one breast cancer diagnosis code. Women were eligible if they had at least one-year of continuous enrollment pre- and post-breast cancer diagnosis date (index date). A woman was classified as an AD user if she filled at least one prescription at any point within one year of the index date. Descriptive statistics were used to summarize the distribution and trend of AD dispensing. The prevalence of psychiatric diagnosis was determined using the diagnosis codes of depression, anxiety disorder, and adjustment disorder.

Results: Overall, 176,867 women with a diagnosis of breast cancer with a minimum one-year post-diagnosis were identified (median=2.9, IQR=1.8-3.0 years). During the first year after breast cancer diagnosis, 58,205 women (32.9%) had at least one prescription fill for an AD (median time to first fill=45 [IQR=17-121] days). While there was some fluctuation, an overall decrease from 33.8% to 31.1% was observed in the proportion of one-year post-diagnosis AD users between 2001 and 2009, whereas there was a steady increase between 2010 and 2018 from 32.0% to 33.4%. Of all ADs, selective serotonin reuptake inhibitors (SSRIs) were the most common class

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

that was first filled after diagnosis date (49.1%), followed by serotonin and norepinephrine reuptake inhibitors (SNRIs; 26.6%), and tricyclic antidepressants (6.9%). When assessing the trend of first fill after diagnosis by drug class among AD users, there was an observed decline in SSRI prescription fills from 51.7% to 46.3%, whereas an observed increase in SNRI prescription fills from 18.5% to 37.0%. Among all women in the cohort, 47,021 (26.6%) had at least one psychiatric diagnosis at any point prior to and during the first year after index date.

Conclusions: In a population of commercially-insured women with breast cancer diagnosis, nearly 33% had at least one prescription fill for an AD during one-year post-diagnosis. Understanding patterns of AD discontinuation and co-prescription with cancer therapy can inform pharmacologic management of depression and anxiety disorders in women with breast cancer.

2378 | Deriving the European Leukemia Net (ELN) risk categorisation in acute myeloid leukemia (AML) patients in a real-world data source

Tao Xu[1], Ana Ferro[2], Felipe Castro[1], Anne-Marie Meyer[1], Bruno Medeiros[3], Tarec Christoffer El Galaly[1] and Evelyn M. Flahavan[2]
[1]Hoffmann-La Roche, Basel, Switzerland; [2]Roche Products Limited, Welwyn Garden City, United Kingdom; [3]Genentec Inc., South San Francisco, CA

Background: ELN risk categorization is key for diagnosis and management of AML. It is based on cytogenetics in combination with specific recurrent molecular mutations. However, the assignment of patients to ELN risk groups using real-world data (RWD) can be limited by data availability and timing of test results.

Objectives: 1) To assess availability of ELN data elements captured in routine clinical practice in an electronic health record (EHR) database, 2) to derive a modified ELN stratification in AML patients based on minimum available variables and 3) describe overall survival (OS) by assigned risk group.

Methods: This retrospective cohort study included patients from the Flatiron Health EHR-derived de-identified database, diagnosed with AML between 2014 and 2019 in the Flatiron Health network which is predominantly community oncology clinics. The database contains demographic and clinical data curated via technology-enabled abstraction. Cytogenetic and molecular testing results were abstracted from unstructured data. We implemented an algorithm based on the 2017 ELN definition, while accounting for data completeness. Median OS (mOS) from the time of 1L treatment (tx) was evaluated across risk groups.

Results: Of 815 AML patients, 700 patients had 1st line (1L) tx information available. Of these, 589 had ELN markers tested pre-1L tx. Cytogenetic markers such as t(8;21), were tested in 552 (78.9%) of the patients pre-1L tx. Molecular markers, such as RUNX1 or TP53, were more commonly tested in recent years e.g. TP53 was tested in 7.2% of the patients in 2014 and 38.6% in 2019. Overall, the test prevalence was <50% for these markers. Cytogenetic tests still dominated the genetic profiling techniques used (~ 80%), however, increased use of next generation sequencing (NGS) was observed: 7.2% in 2014, 50% in 2019.

The algorithm identified AML patients with favorable N=94, mOS 35.6 months (95% CI 26.9, NA), intermediate N=225, mOS 12.5 (95% CI 10.9, 18.4) and adverse N=179, mOS 9.1 (95% CI 7.9, 10.5) risk. Ninety-one patients had insufficient markers for risk categorization and were assigned to "unknown" with mOS 13.9 months (95% CI 12.2, NA), and had slightly better mOS than the patients with no ELN markers tested N=111, mOS 10.2 months (95% CI 5.8, 18.2). Results were robust when restricted to patients receiving intensive tx.

Conclusions: Increased use of NGS testing was observed in patients with AML. EHR-derived data can be used to define risk groups based on the 2017 ELN criteria. We demonstrated the stratification of patients and outcomes with the derived ELN algorithm.

2425 | Serum lipid trajectories in the years before a lymphoma diagnosis

Joan Fortuny[1], Estel Plana[1] and James A. Kaye[2]
[1]RTI-Health Solutions, Barcelona, Spain; [2]RTI-Health Solutions, Waltham, MA

Background: Serum cholesterol levels are known to be low in patients newly diagnosed with a lymphoma. Only one study has examined the trajectory of cholesterol levels in the years before a lymphoma diagnosis.

Objectives: To describe the trajectories of lipid serum levels (total, low and high-density lipoprotein cholesterol and triglycerides) in the years before a diagnosis of lymphoma in a European population.

Methods: We conducted a case-control study on patients with a lymphoma diagnosed between 2000 and 2017. Up to 5 noncancer controls per case were matched on practice, sex, calendar year, and age at lymphoma diagnosis date or an equivalent date among the controls (index date). Study participants were aged ≥ 40 years at index date; had no evidence of another cancer, HIV infection, or organ transplantation before or on the index date; and had ≥ 1 cholesterol measurement before the index date and before the first prescription of a hypolipidemic drug. General practitioner and hospital data from the Clinical Practice Research Datalink in the United Kingdom were used. Multilevel, multivariable linear longitudinal models were fit to examine the trajectories of serum lipid levels in the years before the index date with time since index date, case status, and confounders in the model.

Results: During the study period, 3,161,492 patients had a valid cholesterol measurement. Among these, 11,969 cases of non-Hodgkin lymphoma and 473 of Hodgkin lymphoma met the study's inclusion and exclusion criteria. Controls were selected for non-Hodgkin lymphoma and Hodgkin lymphoma cases (59,537 and 2,357, respectively). The most common subtypes of lymphoma were plasma cell neoplasm, chronic lymphocytic leukemia, and diffuse large B cell lymphoma. For all lymphoma types, crude mean cholesterol levels in the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

years before index date was lower in cases than in controls. For most lymphoma subtypes, the adjusted cholesterol levels showed a more pronounced decrease in the 4 years before diagnosis. On the other hand, triglycerides levels were not clearly related to case status. Results remained similar when restricting to patients who had never used any hypolipidemic drug and had ≥ 1 measure of cholesterol within 1 year before index date.

Conclusions: This research is the first to replicate a similar study conducted in the United States, while more thoroughly adjusting for potential confounders. The different behavior of cholesterol and triglycerides, described here for the first time, offers insight into the role of lipids in lymphomagenesis. The study suggests the potential role of cholesterol as a biomarker for lymphoma in the years prior to its diagnosis.

2452 | End-of-life anticancer treatment: A nationwide registry-based study

Thea O. Mattsson[1], Anton Pottegård[2], Trine L. Jørgensen[1], Anders Green[1,2] and Mette Bliddal[1,2]

[1]*Odense University Hospital, Odense, Denmark*; [2]*University of Southern Denmark, Odense, Denmark*

Background: Anticancer treatments near the end of a patient's life should generally be avoided, as it leaves the patient with no significant anticancer effect but increases the risk of severe side effects. Reports of the frequency of end-of-life treatment including chemotherapy vary markedly.

Objectives: To describe the magnitude of all anticancer end-of-life treatment in Denmark and to identify subpopulations of patients more likely to receive anticancer treatment at the end of their lives.

Methods: Using the Danish national health registers, we performed a nationwide cohort study identifying all deceased cancer patients (≥18 year of age) during 2010-2015 with 1) a diagnosis of a solid tumor defined by ICD10 codes, 2) a clinical oncology contact within 12 months prior to death, and 3) and cancer listed as their primary cause of death. Use of any anticancer treatment in the last 30 days of life was categorised as end-of-life treatment. We used logistic regression models to estimate odds ratios (OR) with 95% confidence intervals (CI) for receiving end-of-life treatment according to sex, age group, cancer group, Charlson Comorbidity Index (CCI), and time since diagnosis.

Results: We identified 42,277 patients (mean age 70 years), of whom 15.9% received end-of-life anticancer treatment. The probability of receiving end-of-life treatment did not change over the study period (p-value 0.09). Chemotherapy alone was the most frequent treatment accounting for 78% of all end-of-life treatments in 2010 decreasing to 71% in 2015. In contrast, immunotherapy and hormone/anti hormone both used as single and combination therapy increased during the study period. Patient dying with breast cancer had the highest frequency of end-of-life treatment (23%), followed malignant melanoma (21%) and prostate cancer (18%). Protective factors for end-of-life treatment were female sex (OR 0.91, 95% CI 0.86-0.97), older age (OR 90+ years 0.10, 95% CI 0.07-0.16 and 75-89 years 0.32, 95% CI 0.27-0.38 compared to 18-44 years), high comorbidity according to CCI (OR CCI 3+ 0.82, 95% CI 0.76-0.88 compared to 0), and being diagnosed >6 months prior to death (OR diagnosed 1-5 years prior to death 0.53, 95% CI 0.50-0.57).

Conclusions: In this nationwide Danish sample of cancer deaths, we found a stable overall rate at 15.9% of receiving anticancer treatment one month prior to death. During the period, a decreasing use of chemotherapy was out-balanced with an increasing use of immunotherapies and targeted treatments. Although, some end-of-life treatment is unavoidable, further research is needed to assess if the frequency of treatment during this period of life reflects inappropriate use.

2469 | Biliary tract cancer (BTC) epidemiology in the United States

Huifen Wang, Binbing Yu and Katherine Baria

AstraZeneca Pharmaceuticals, Gaithersburg, MD

Background: BTC is a rare diagnosis in the US (~8000 people annually) but represents a high disease burden due to late diagnosis, poor prognosis, and limited treatment options. Monitoring the epidemiology of BTC will inform public health management and development of clinical programs and research.

Objectives: Evaluation of BTC incidence, prevalence, mortality and survival rates (SR) using the latest data from SEER and NPCR databases.

Methods: Data (2001-2015) were assessed by age, gender, race/ethnicity (White [W]; White, Hispanics [H]; Black [B]; Asian/Pacific Islander [A/PI]; American Indian/Alaska Native [AI/AN]); and anatomic site (extrahepatic cholangiocarcinoma [ECC], intrahepatic cholangiocarcinoma [ICC], gall bladder cancer [GBC], and ampulla of Vater cancer [AVC]). Incidence was reported as age-standardized rate (ASR; per 100,000 person-yrs) using the 2000 US standard population. Estimates of annual percent changes (APC) were calculated using the weighted least squares method.

Results: ASR for BTC in the US was 5.04. Incidence was slightly higher in males vs females (M, ASR = 5.31; F, ASR = 4.85), and was consistent across most subtypes; although females had a higher incidence of GBC (ASR = 1.92; M, ASR = 1.14). Using incidence of W ethnicity as a reference value (ASR = 4.64), H and A/PI have higher incidence rates (incidence rate ratio = 1.65 and 1.45, respectively). During the survey period, total incidence of BTC increased significantly (APC = 1.76). The highest increase was reported for ICC (APC = 6.65). Overall mortality ASR for patients (pts) with BTC was 3.40. H, A/PI, and AI/AN had higher mortality rates (mortality rate ratio = 1.36, 1.22, and 1.32, respectively) when using W as reference (ASR = 3.25). The 5-yr SR for BTC is 15.2%; all subtypes had a consistent rate (GBC = 18%; ICC = 8.5%; ECC = 9.1%), except AVC (34.5%). SRs among ethnic groups were also largely consistent with the overall, with B having the lowest SR (13.8%) and H the highest (16.6%). While the 5-yr SR is low for BTC overall, it is extremely low for pts with

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

distant disease (3.0%), compared with regional (19.1%) or localized disease (31.5%). The 10-yr prevalence for BTC is 10.8 per 100,000.

Conclusions: Incidence of BTC, particularly ICC, has increased over the last decade and the 5-yr SR for BTC remains low. Discrepancies among race/ethnicity groups may reflect socio-economic and health care access differences. These data underscore the serious unmet need among pts with BTC. Public health efforts should be applied to raising awareness of the growing BTC population and integrating novel therapy options for BTC pts.

2572 | Risk and prognosis of cancer after acute kidney injury

Christian Fynbo Christiansen[1], Dóra K. Farkas[1], Jon P. Fryzek[1,2], Paola Romagnani[3], Mette Nørgaard[1], Kenneth J. Rothman[4,5] and Henrik Toft Sørensen[1]

[1]Aarhus University Hospital, Aarhus N, Denmark; [2]EpidStrategies, John Hopkins Campus, Rockville, MD; [3]Nephrology and Dialysis Unit, Meyer Children's University Hospital, Florence, Italy; [4]RTI Health Solutions, Research Triangle Park, NC; [5]Boston University, Boston, MA

Background: Acute kidney injury (AKI) is a common adverse drug reaction in cancer patients, but case-reports suggest that it may also be the first symptom of occult cancers and may worsen the prognosis of cancer.

Objectives: To examine the risk and prognosis of cancer following AKI.

Methods: We conducted this nationwide cohort-study in Denmark (population 5.6 million) using population-based medical databases. We identified all patients with hospital-diagnosed AKI between 1995 and 2017. We obtained data on any subsequent incident cancer (except non-melanoma skin cancer) and cancer stage. We quantified the 1-year and 1-5-year risk of cancer after AKI using the cumulative incidence method accounting for death as a competing risk. Standardized incidence ratios (SIRs) were computed as the observed number of cancers during the follow-up time divided by the expected number based on national cancer incidence rates by age, sex and calendar year. We computed five-year survival for patients diagnosed with solid and hematological cancer within one year after AKI using the Kaplan-Meier method and compared this with a cancer comparison cohort matched (1:5) on cancer site, age, sex, and year of cancer diagnosis. The 5-year hazard ratios (HR) of death with 95% confidence interval (95% CI) were computed using Cox regression analysis adjusted for age, sex, calendar year, Charlson Comorbidity Index Score, and cancer stage in solid cancers.

Results: We identified 29,977 patients with AKI. Among these, 1303 were diagnosed with cancer within the first year [1-year risk 4.4% (95% CI: 4.2—4.7) and SIR 4.6 (95% CI: 4.4—4.9)] and 827 were diagnosed with cancer 1-5 years after first AKI diagnosis [1-5 year risk 6.7% (95% CI: 6.3—7.2) and SIR 1.3 (95% CI: 1.2—1.4)]. The 1-year SIRs were highest for multiple myeloma, liver cancer, urological cancers, and cancer of the uterine cervix. The prevalence of distant metastases in solid cancer diagnosed within one year after AKI was similar in patients with and without a previous history of AKI (27% vs. 24%). The 5-year survival was 17% for patients with AKI and solid cancer and 39% in the corresponding comparison cohort (adjusted HR = 2.4, 95% CI: 2.1—2.8). The 5-year survival was 29% for patients with AKI and hematological cancer and 48% in the corresponding comparison cohort (adjusted HR = 2.8, 95% CI: 2.3—3.3).

Conclusions: Hospital-diagnosed AKI appeared to be a marker of occult cancer, but is also associated with an increased cancer rate beyond the first year, and signals a poor prognosis.

2594 | Methodologic considerations for evaluating adherence to oral oncologic therapy in a high mortality population

Danielle Chun[1], Blánaid Hicks[2], Sharon Peacock-Hinton[1], Hung-Jui Tan[3], Michele Jonsson-Funk[1], Alex Keil[1], Til Stürmer[1] and Jennifer Lund[1]

[1]Gillings School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Queen's University Belfast, Belfast, Ireland; [3]School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Continuous and on-time medication use is critical to for drug effectiveness and improving patient outcomes. However, key methodological decisions must be made when designing and analyzing studies of medication adherence and persistence in populations with a high risk of short-term mortality, such as the setting of metastatic cancer.

Objectives: To compare different measures of and approaches to quantifying adherence and persistence to oncologic therapy in a high mortality population using a motivating example of oral targeted therapy (TT) in patients diagnosed with metastatic renal cell carcinoma (mRCC).

Methods: Patients aged ≥66 years old with a primary diagnosis of mRCC who initiated TT within 4 months of their diagnosis were identified in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database from 2007-2015. We estimated 6-month adherence to oral TTs using an 80% threshold for proportion of days covered, including and excluding patients who died within 6 months. We then estimated the proportion of patients who were persistent (e.g., continuous TT users) at 6 months: (1) censoring patients at death and (2) treating death as a competing risk using nonparametric cumulative incidence functions. A gap of up to 30 days between TT fills was allowed.

Results: Among 507 mRCC patients initiating an oral TT (sunitinib:63%, pazopanib: 26%, sorafenib:10%), 32% died within 6 months. After excluding those who died, the proportion of adherent patients was substantially higher (38%) than when these patients were included but assigned zero days covered after death (26%). The proportion of patients who were persistent at 6 months was also substantially higher when censoring patients at death at 82% (95% confidence interval (CI): 78, 85%) compared with treating death as a competing risk at 50% (95% CI: 46, 54%).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Different approaches to the treatment of death result in substantially different estimates of oral oncologic adherence and persistence in high-mortality populations. This may have potential for bias when making comparisons in this setting. Because short-term mortality is so common in the metastatic cancer setting, studies of oncologic therapy adherence and persistence should explicitly report the proportion of patients who die over time and use appropriate methods to account for this competing risk.

2648 | The risk of late breast cancer recurrence in Denmark during 17 years of follow-up

Rikke Nørgaard Pedersen[1], Buket Öztürk[1], Lene Mellemkjær[2], Søren Friis[2], Bent Ejlertsen[3], Timothy L. Lash[4], Mette Nørgaard[1] and Deirdre Cronin-Fenton[1]

[1]Aarhus University, Aarhus, Denmark; [2]Danish Cancer Society Research Center, Copenhagen, Denmark; [3]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [4]Rollins School of Public Health, Emory University, Atlanta, GA

Background: Breast cancer (BC) may recur many years after primary diagnosis. Therefore, it is necessary to extend the focus to identify patients at risk of late breast cancer recurrence (BCR) (>= 10 years after primary surgery).

Objectives: We investigated the incidence of late BCR and identified potential associations between clinico-pathological factors at baseline and late BCR.

Methods: Using the Danish Breast Cancer Group's (DBCG) database we identified all women with incident stage I-III operable BC diagnosed during 1987-2002, who were alive and without a recurrence or new primary cancer 10 years after diagnosis. We derived an algorithm to identify late BCR using Danish population-based registries. Follow-up began 10 years after primary surgery date and continued until late BCR, death, emigration, second cancer or 31/12/2013. Crude incidence rates (IRs) per 1,000 person-years (PY) and cumulative incidence proportions (CIPs) for late BCR were calculated by patient- and tumor characteristics at baseline. Cox regression models were used to calculate hazard ratios (HRs), accounting for competing risks. The HRs were adjusted for tumor- and patient characteristics.

Results: 18,117 women of 31,528 (57%) reached year 10 without BC recurrence, a contralateral breast cancer or other primary cancer, and were followed for a total of 106,602 PY with a median follow-up of 4.9 years (IQR; 2.4-8.7). Of these 10-year survivors, 1,763 developed late BCR corresponding to an IR of 16.5 (95% CI, 15.8-17.3) per 1,000 PY and a CIP of 15% maximum 27 years after primary diagnosis. The 10-15 years IR was 19.6 (95% CI, 18.6-20.7) per 1,000 PY, the 15-20 years IR was 11.8 (95% CI, 10.6-10.1) per 1,000 PY and the IR 20 years or more after primary surgery was 9.8 (95% CI, 8.0-12.0) per 1,000 PY. CIP was higher among patients with estrogen receptor $(ER)^+$ tumors, stage III disease and high nodal status. We found an adjusted HR of 3.0 (95% CI, 2.47-3.55) for patients with 4 or more positive lymph nodes versus patients with no lymph node involvement, an adjusted HR of 1.85 (95% CI, 1.59-2.15) for patients with stage III disease versus stage I disease and an adjusted HR of 0.57 (95% CI, 0.45-0.72) for patients with an ER^- tumor versus patients with an ER^+ tumor.

Conclusions: Conclusion: Our findings suggest that women with breast cancer can remain disease-free for at least ten years, but recurrences continue to occur from 10 to 27 years after primary diagnosis. Baseline tumor characteristics such as lymph node status, stage, and ER receptor status seems to be associated with late breast cancer recurrence.

2653 | Improving predictive ability of survival models: Comparison of multiple state of the art models

Hugo Loureiro[1,2], Tim Becker[1], Anna Bauer-Mehren[1], Narges Ahmidi[2] and Janick Weberpals[1]

[1]Roche Innovation Center Munich (RICM), Penzberg, Germany; [2]HelmholtzZentrum München, Neuherberg, Germany

Background: More complex statistical methods are being suggested to increase the predictive power of survival models when analyzing electronic health record (EHR)-derived datasets containing a massive number of patients and covariates.

Objectives: To determine if more complex survival analysis algorithms offer a gain in predictive ability over classical statistical methods when modelling oncological prognostic scores.

Methods: In this study, we used data from two datasets: Flatiron Health (FH) EHR-derived de-identified database for training and validation and OAK III clinical trial for validation. From FH we included 99,249 first-line treated patients with any cancer type. This cohort was split into a 90% training dataset and 10% validation dataset, respectively. The FH database comprises patient-level structured and unstructured data collected from more than 280 oncology clinics in the USA. With a new-user design, we defined overall survival as the time starting from the day of the first line treatment as index date until death due to any reason or censoring. A total of 26 covariates were measured in the 90 days before the index date. If there were multiple measurements available, the last observed value was chosen. To further validate our findings, we used data derived from the OAK (phase) III study. It is composed of 1187 patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) and compares the efficacy and safety of atezolizumab versus docetaxel. The models compared in this analysis included a conventional Cox model (CM), as well as Survival Forests (SF), Gradient Boosting (GB) and a neural network-based DeepSurv (DS) algorithm as the more complex models. The c-index was used as the performance metric to compare different models.

Results: Overall, the median survival across all patients was 581 days (95% CI 574-588). Within the FH database, the more complex models SF and GB (both c-index 0.722) and DS (c-index 0.720) seemed to perform marginally better than CM (c-index 0.695). However, when validating the models using the OAK III dataset, the superior

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

performance of SF, GB and DS disappeared and the predictive ability across all methods was comparable with c-indexes as high as 0.677 (SF), 0.6696 (GB), 0.676 (CM) and 0.675 (DS), respectively.

Conclusions: The more complex models are able to capture non-linearities and variable interactions that CM, due to its linear nature cannot. However, this did not lead to an increased predictive ability of the prognosis score across datasets.

3711 | Glucocorticoid use and breast cancer risk in a prospective cohort study of postmenopausal women

Manon Cairat[1], Marie Al Rahmoun[2], Marc Gunter[1], Gianluca Severi[2], Dossus Laure[1] and Agnes Fournier[2]

[1]International Agency for Research on Cancer, Lyon, France; [2]Centre de Recherche en Epidémiologie et Santé des Populations (CESP), équipe "Exposome, Hérédité, Cancer et Santé", Inserm UMR1018, Facultés de Médecine, Université Paris-Saclay, Université Paris-Sud, Gustave Roussy, Villejuif, France

Background: Trough their anti-inflammatory properties, glucocorticoids are hypothesized to prevent breast cancer. However, glucocorticoids are known to decrease glucose tolerance and to interact with the oestrogen pathways, two mechanisms involved in breast cancer development. Experimental data suggested that glucocorticoids could play a complex/dual role in breast cancer initiation and progression but epidemiological evidence are scare regarding the associations between glucocorticoid use and breast cancer risk.

Objectives: We investigated the association between glucocorticoid use and breast cancer incidence, overall and by subtypes, in the French E3N prospective cohort.

Methods: E3N includes 98,995 French women born between 1925 and 1950 and insured by a health insurance plan that covers mostly teachers. Information on lifestyle, anthropometric and reproductive factors, and medical history were collected biennially by self-questionnaires and matched with data from a drug reimbursement database pertaining to years 2004-2014. Women with at least two reimbursements in any 3-month period since 2004 were defined as ever exposed to glucocorticoids. Considering exposure as time-varying, multivariable Cox regression models were used to estimate hazard ratios (HRs) for the association of glucocorticoid use with breast cancer risk, overall and by breast cancer subtypes.

Results: In the current analysis, 62,390 postmenopausal women were followed between 2004 and 2014 (9 years on average, starting at a mean age of 63 years; 2,887 breast cancers). Of them, 28% had been exposed to glucocorticoids during follow-up. In multivariable models, there was no statistically significant association between ever use of glucocorticoids and breast cancer risk overall [HR= 0.96 (0.90 - 1.06)]. However, we found a statistically significant heterogeneity according to breast cancer subtypes suggesting an increased risk of *in situ* breast cancer and a decreased risk of invasive breast cancer [$HR_{in\ situ}$= 1.32 (1.00 - 1.75), $HR_{invasive}$=0.87 (0.77 - 0.98), $P_{heterogeneity}$=0.01] associated with glucocorticoid ever use.

Conclusions: Glucocorticoid use was associated with an increased *in situ* breast cancer risk and a decreased invasive breast cancer risk in this large, prospective cohort of postmenopausal women with 10 years of exposure information. Associations according glucocorticoid types, main breast cancer risk factors as well as potential confounding effect by other drugs/comorbidities will be explored and presented at the conference.

3727 | A US multicenter chart review study of patients with metastatic pancreatic ductal adenocarcinoma receiving liposomal irinotecan after gemcitabine-based therapy

Kenneth H. Yu[1], Andrew Hendifar[2], Olatunji Alese[3], Amber Draper[3], Maen Abdelrahim[4], Ethan Burns[4], Gazala Khan[5], Paul Cockrum[6], Rachel Bhak[7], Maral DerSarkissian[7], Catherine Nguyen[7], Mei S. Duh[7] and Nathan Bahary[8]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Cedars-Sinai Medical Center, Los Angeles, CA; [3]Emory Winship Cancer Institute, Atlanta, GA; [4]Houston Methodist Cancer Center, Houston, TX; [5]Henry Ford Cancer Institute, Detroit, MI; [6]Ipsen Biopharmaceuticals, Inc., Cambridge, MA; [7]Analysis Group, Boston, MA; [8]University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Real-world data allows healthcare decision-makers to assess and manage therapeutic and economic options for patients, including those who would and would not have met eligibility criteria for randomized control trials (RCT) and are instead managed under usual care.

Objectives: This retrospective multi-academic center chart review study describes real-world characteristics and outcomes of US patients receiving liposomal irinotecan for the management of metastatic pancreatic ductal adenocarcinoma (mPDAC).

Methods: Patients with mPDAC treated with liposomal irinotecan were eligible. Initiation of liposomal irinotecan defined index date; covariates assessed included clinical characteristics and treatment patterns; real-world overall survival (rwOS) was assessed via Kaplan-Meier methodology. The target enrollment is 300 patients. The study centers included were Memorial Sloan Kettering Cancer Center, Cedars-Sinai Medical Center, Emory Winship Cancer Institute, Houston Methodist Cancer Center, Henry Ford Cancer Institute, and University of Pittsburgh Medical Center.

Results: Data on 26 patients were available for initial analyses. Mean age was 68 years; 58% were female and 65% Caucasian. 54% of patients had stage IV disease at first diagnosis, and 17%, 65%, and 17% had index ECOG score of 0, 1, and 2, respectively. Common genetic mutations include KRAS (40%) and TP53 (40%). Prior to liposomal irinotecan, treatments received for metastatic disease include gemcitabine+nab-paclitaxel (77%) and fluorouracil (5-FU)/leucovorin (LV)+irinotecan+oxaliplatin (19%). Patients had received 0 (12%), 1 (23%), and ≥2 (65%) lines of therapy in the metastatic setting prior to liposomal irinotecan. Mean duration of liposomal irinotecan use was 3.0 months; liposomal irinotecan was mostly received with 5-FU

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(23%) or 5-FU/LV (69%). Median rwOS was 4.9 months (95% CI: 3.0, 6.3).

Conclusions: Real-world data of the first 26 patients in this study show patients treated with liposomal irinotecan are older, sicker, and have had more lines of therapy than previously reported in RCT data.

3918 | Declines in health related quality of life among older patients with hematologic malignancies

Ashwini Zolekar[1], Nadia A. Nabulsi[1], Alemseged A. Asfaw[1], Jifang Zhou[1], Karen Sweiss[1,2], Pritesh R. Patel[2,3], Brian C.-H. Chiu[4], Edith A. Nutescu[1] and Gregory S. Calip[1,2]

[1]University of Illinois at Chicago College of Pharmacy, Chicago, IL; [2]University of Illinois Cancer Center, Chicago, IL; [3]University of Illinois at Chicago, Chicago, IL; [4]University of Chicago, Chicago, IL

Background: Although advances in novel therapy and stem cell transplantation have increased survival in patients with hematologic malignancies (HM), less evidence exists on the subsequent impacts of HM on HRQOL.

Objectives: The aim of this study was to evaluate changes in HRQOL following diagnosis of HM in a cohort of older Medicare beneficiaries.

Methods: This was a retrospective study utilizing the Surveillance, Epidemiology and End Results Medicare Health Outcomes Survey Data Resource. We included patients ages ≥65 years diagnosed with first primary leukemia, lymphoma or multiple myeloma between 1998 and 2014 who completed at least one survey within two years pre- and post-diagnosis. HRQOL was measured using the Short Form Health Survey (SF-36) composite scores with a minimum clinically important difference of 2 points. We also measured self-reported general health, depressive symptoms, and the deficit-accumulation frailty index before and after HM diagnosis. Patients with HM were compared to up to four patients without cancer with exact matching on age, sex, race, marital status, smoking status, education, comorbid conditions, proxy response and calendar time of HM diagnosis. Comparisons of means were performed between groups using ANOVA with adjustment for survey type.

Results: Among 401 patients with HM, mean (SD) age of diagnosis was 75.98 (6.2) years and 26% were diagnosed with leukemia, 57% with lymphoma, and 17% with multiple myeloma. No significant differences in HRQOL, self-reported health, depressive symptoms, or frailty were observed between patients with HM and their non-cancer matches (n=1578) before diagnosis. Substantial declines in HRQOL were observed across all types of HM after cancer diagnosis. Mean decreases in SF-36 scores among patients with HM (physical component score [PCS] -7.1, 95% CI -8.8, -5.5; mental component score [MCS] -3.4, 95% CI -4.9, -1.8) were greater in magnitude compared to declines in matched non-cancer patients (PCS -1.6, 95% CI -2.4, -0.7; MCS -0.6, 95% CI -1.3, 0.1). During follow-up, patients with HM also had higher rates of low self-reported health (46% vs. 27%), depressive symptoms (34% vs. 25%) and frailty (32% vs. 25%).

Conclusions: Our study found decreases in HRQOL measures among older patients with HM that were more than three-fold higher than the minimum clinically important differences in the general population and twice that reported in older patients with common solid tumors. Prospective studies and clinical trials in patients with HM should include measures that assess whether life-prolonging, novel therapies are also effective in preserving HRQOL.

3993 | Risks of squamous cell carcinoma of the lip and cutaneous melanoma in older Australians using hydrochlorothiazide (HCTZ)

Benjamin Daniels[1], Sallie-Anne Pearson[1], Claire M. Vajdic[1], Anton Pottegard[2], Nicholas A. Buckley[3], Nicholas A. Buckley[3] and Helga Zoega[1]

[1]University of New South Wales, Sydney, Australia; [2]University of Southern Denmark, Denmark, Odense, Denmark; [3]University of Sydney, Sydney, Australia

Background: HCTZ is first-line treatment for hypertension and among the most commonly used medicines in Australia. Recent evidence suggests increased risks of skin cancer, in particular squamous cell carcinoma (SCC), in association with HCTZ use.

Objectives: To determine the risk of SCC of the lip and melanoma among people prescribed HCTZ in Australia.

Methods: We conducted a case-control study nested within a population of veterans residing in New South Wales from 2004 through 2015, using data from the Australian Department of Veteran's Affairs linked with cancer registrations, hospitalisation and prescription dispensings. Among veterans 65 years and older, we identified incident cases of SCC of the lip (lip cancer) and of cutaneous melanoma (malignant melanoma), each matched by sex and age with up to 20 controls through risk-set sampling. We ascertained HCTZ use from dispensing data and classified use according to ever/never use and cumulative use. We estimated odds ratios (ORs) associating HCTZ use with lip cancer and malignant melanoma using conditional logistic regression, adjusting for predefined confounders obtained from dispensing and hospitalisation data. To assess potential confounding by indication, we repeated the analysis for other antihypertensives including furosemide, ACE inhibitors, ATII antagonists, calcium channel blockers (CCBs), and indapamide.

Results: For lip cancer (45 cases; median age 79 years; 56% male) ever-use of HCTZ yielded an OR of 2.6 (95%CI: 1.4 - 5.0) and high HCTZ use (≥25,000mg) an OR of 4.7 (95%CI: 1.61 - 13.7). For malignant melanoma (659 cases; median age 81 years; 67% male) ever-use of HCTZ resulted in an OR of 1.2 (95%CI 1.0 - 1.5) and high HCTZ use in an OR of 1.2 (95%CI: 0.8 - 1.8). For melanoma subtypes, we observed elevated ORs for superficial spreading melanoma (OR: 1.6; 95%CI: 1.2 - 2.2) with ever-use and for lentigo melanoma (OR: 2.1; 95%CI: 1.0 - 4.5) with high use of HCTZ. We found no association with nodular melanoma. We did not observe associations between

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

either cancer type and the use of furosemide, ACE inhibitors, ATII antagonists, CCBs, or indapamide.

Conclusions: Our study provides further evidence that the photosensitising properties of HCTZ may promote SCC carcinogenesis, and possibly melanoma, in susceptible sun-exposed tissues. Our findings are the first from the Australian population—already at elevated risk of developing skin cancer—and add to the growing body of data supporting the need for skin cancer prevention advice and behaviours, and potentially heightened surveillance, for individuals prescribed this medication.

4067 | Mortality after late breast cancer recurrence in Denmark

Rikke Pedersen[1], Lene Mellemkjær[2], Søren Friis[2], Bent Ejlertsen[3], Mette Nørgaard[1] and Deirdre Cronin-Fenton[1]

[1]Aarhus University, Aarhus, Denmark; [2]Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark; [3]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Background: Data on mortality after late breast cancer recurrence (BCR) (≥10 years after primary diagnosis) is sparse. The few existing studies have focused on incidence and risk factors for late BCR while data on the outcome of late BCR is lacking.

Objectives: To investigate survival after late BCR focusing on potential prognostic factors, such as localization of late BCR and characteristics of the primary tumor.

Methods: From the Danish Breast Cancer Group database, we assembled a cohort of 31,528 women with incident operable stage I-III breast cancer (BC) diagnosed during 1987-2002. Among 18,117 women who were alive, without BCR or new primary cancer 10 years after diagnosis, 1,763 developed late BCR. We followed these patients from the date of late BCR to date of death (due to BC or other causes), emigration or December 31, 2018. We calculated the cumulative incidence proportions (CIPs) of BC death overall, by localization of the late BCR, and by characteristics of the primary tumor. We computed mortality rates (MRs) per 1000 person-years (PY) stratified by follow-up time. We used Cox regression to compute hazard ratios (HRs) and 95% confidence intervals (95%CI), adjusting for confounders and accounting for competing risks.

Results: The 1,763 patients generated 106,602 PY of follow-up. Median follow up was 5.6 years (IQR; 2.4-8.6). In total, 818 women died from BC and 303 died from other causes. The 2-year CIP of BC death was 17%, 5-year CIP 34%, 10-year CIP 47%, and 20-year CIP 55%. The CIP of dying from other causes was 25% 20 years after late BCR. The 20-year CIP of BC death was 79% in patients diagnosed with distant late BCR, 14% in patients diagnosed with locoregional late BCR, and 42% in patients with both locoregional and distant spread at diagnosis of late BCR. Patients with stage III disease and ≥4 involved lymph nodes at primary tumor diagnosis had higher CIPs of BC death after late BCR. The MR 5 years after late BCR was 91.0 (95%CI=90.6-113.3) per 1000 PY, 62.8 (95%CI=54.5-72.4) per 1000 PY from year 5-10, and 29.6 (95%CI=20.9-41.8) per 1000 PY from year 10-20. The HR for BC death was 6.1 (95%CI=4.7-8.0) per 1000 PY for patients with distant late BCR and 2.8 (95%CI=1.9-4.2) per 1000 PY for patients with both distant and locoregional spread at diagnosis of late BCR compared with those with locoregional late BCR. Tumor characteristics at primary BC diagnosis were not associated with BC mortality in patients with late BCR.

Conclusions: Mortality after late BCR is high especially among patients diagnosed with distant late BCR. The MR is highest in the first 5 years after late BCR, but BC deaths continue to occur during follow-up.

4102 | Adverse mental health outcomes in women with a history of breast cancer: A matched population-based cohort study in the United Kingdom (1988-2018)

Helena Carreira[1], Rachael Williams[2], Garth Funston[3], Susannah Stanway[4] and Krishnan Bhaskaran[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]Clinical Practice Research Datalink, London, United Kingdom; [3]Univeristy of Cambridge, Cambridge, United Kingdom; [4]The Royal Marsden NHS Foundation Trust, London, United Kingdom

Background: Treatments for breast cancer are highly effective, but carry the risk of several short- and long-term side effects that may negatively affect patients' mental health.

Objectives: To estimate the risk of anxiety and depression (primary outcomes), and seven secondary mental health-related outcomes, in breast cancer survivors compared to women with no prior cancer.

Methods: This was a matched population-based cohort study. The exposed cohort included all adult women diagnosed with an incident breast cancer between 1988 and 2018 in the Clinical Practice Research Datalink (CPRD) GOLD primary care database; women with history of other cancers were excluded. The unexposed cohort comprised a random selection of women with no cancer history, matched to exposed women on age and primary care practice. Median follow-up was 4.5 years in the exposed group and 5.2 years in the comparison group. The outcome measures were relative risks of the primary and secondary outcomes, calculated using Cox proportional hazards models, adjusting for confounders.

Results: 57,571 women diagnosed with breast cancer (mean age 62.3 ± 13.9 years) and 230,067 women with no previous cancer were included. Breast cancer survivorship was positively associated with the primary outcomes of anxiety (adjusted hazards ratio=1.33; 95%CI: 1.29-1.36), and depression (1.35; 1.32-1.38), and the secondary outcomes of fatigue (1.28; 1.25-1.31), pain (1.22; 1.20-1.24), sexual dysfunction (1.27; 1.17-1.38), sleep disorder (1.68; 1.63-1.73) and being prescribed opioid analgesics (1.86; 1.83-1.90), but there was no evidence of an association with cognitive dysfunction (1.00; 0.97-1.04) or fatal and non-fatal self-harm (1.15; 0.97-1.36). Hazard ratios for anxiety and depression reduced over time ($p < 0.001$) but raised risks persisted for two and four years, respectively, after cancer diagnosis. For the secondary outcomes, increased levels of pain and sleep disorder persisted for at least 10 years. Younger age was associated with

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

larger increases in the risks of depression, cognitive dysfunction, pain, opioid analgesic use and sleep disorders (p-interaction < 0.001 in each case).

Conclusions: Breast cancer survivorship is associated with raised risks of anxiety and depression, as well as other adverse mental health-related outcomes, persisting well into the survivorship period. Future research should investigate the role of direct toxicities of anti-cancer treatments versus other psychosocial impacts of cancer in driving these risks.

4165 | Epidemiology of HER2+ metastatic breast cancer in Germany and France in 2019

Kendra DeBusk[1], Naomi R.M. Schwartz[2], Susan Dennett[3], Nicolas Lindegger[4] and Sonia Pulgar[1]

[1]Seattle Genetics, Bothell, WA; [2]University of Washington, Seattle, WA; [3]Strategic Health Outcomes, Inc., Carmel, IN; [4]SeaGen International GmbH, Zug, Switzerland

Background: The real-world incidence of HER2+ metastatic breast cancer (MBC) in Europe is not well-established. Population-based registries in some countries capture incident *de novo* MBC, but these data may underestimate the incidence because they do not capture new cases of MBC that result from progression of early breast cancer (EBC) after neoadjuvant/adjuvant treatment. Accurate estimates of MBC incidence are important for researchers and policy makers who use these data for healthcare decision-making.

Objectives: To estimate the incidence of HER2+ MBC in Germany and France in 2019.

Methods: Patient flow models for 2019 were developed using data from a targeted literature review and the International Agency on Cancer GLOBOCAN database, which provides estimates of cancer in multiple countries, as well as the most robust data from the literature for each country. We extracted estimates of breast cancer incidence for Germany and France from GLOBOCAN. Estimates of *de novo* MBC incidence, frequency of HER2+ disease, and 5-year progression rates from EBC to MBC for these countries were obtained from population-based, observational studies published since 2010. Studies were assessed for quality based on inclusion/exclusion criteria, sample size/data source, time period, and methodology.

Results: Estimates from the patient flow models show that in Germany, an estimated 71,888 patients had incident breast cancer (GLOBOCAN); 4,601 (6.4%) had *de novo* MBC, of whom 828 (18.0%) were HER2+. Of patients with incident EBC (n=67,287), 8,142 (12.1%) were HER2+ and 1,083 patients (13.3%) progressed to HER2 + MBC. In total, an estimated 1,911 patients were newly diagnosed with or progressed to HER2+ metastatic disease in Germany in 2019. In France, 56,162 patients had incident breast cancer (GLOBOCAN); 3,201 (5.7%) had de novo MBC, of whom 650 (20.3%) were HER2+. Of patients with incident EBC (n=52,961), 8,474 (16.0%) were HER2+ and 1,059 progressed to HER2+ MBC (12.5%). In total, an estimated 1,709 patients were newly diagnosed with or progressed to HER2+ metastatic disease in France in 2019.

Conclusions: These estimates provide important insight into the burden of HER2+ MBC in Germany and France in 2019. The inclusion of incident HER2+ MBC that results from the progression of EBC in the models provides more robust estimates of HER2+ MBC incidence than are currently available for these countries. Future research to incorporate patient survival in the models could extend these estimates to HER2+ MBC prevalence.

4175 | Association of calcium channel blocker subtypes and prostate cancer related mortality

Kevin Yan[1,2], Kathy Li[1,2], Mahyar Etminan[1], HJ Gober[1,2] and Bruce Carleton[1,2]

[1]University of British Columbia, Vancouver, BC, Canada; [2]BC Children's Hospital Research Institute, Vancouver, BC, Canada

Background: In Canada, prostate cancer (PC) is the most common cancer diagnosis in men. There is limited evidence on CCB use and PC outcomes.

Objectives: In this epidemiologic study we examined different subclasses of calcium channel blockers (CCB) and their association with PC-related mortality.

Methods: An observational active-comparator study was conducted to examine the association between CCB subtypes and PC-related mortality. The data was obtained from the BC Cancer Agency Registry and all newly diagnosed stage 1 or stage 2 PC patients between 1996 to 2010 were included. Four groups of patients were compared: 1) non CCB users; 2) pure dihydropyridine (DHP) CCBs users (amlodipine, nifedipine); 3) pure diltiazem (DILT) users; and 4) pure verapamil (VERAP) users. Non-CCB users must have used an angiotensin converting enzyme inhibitor (ACEi). Individuals were followed from the index date and to either of the following, 1) mortality date, 2) time of switch between ACE-Is and CCBs, 3) last health service record date, 4) end of study follow up period (12/31/2010), whichever came first. We defined exposure to CCBs and ACEis as having received at least 2 prescriptions in six months prior to one year of the index date. Comorbid conditions were accounted for using the Charlson Comorbidity Index and covariates were adjusted using a multivariable cox regression. To control for PC latency and to prevent reverse causality bias, deaths within the first year of follow-up were excluded from the analysis. Fine and Gray's extension of Cox regression was used to model the multiple failure events data associated with different causes of mortality, to address competing risk bias.

Results: A total of 7,056 patients were included in the study: 1,467 in the DHP cohort; 794 in the DILT cohort; 251 in the VERAP cohort; and 4,544 in the non-CCB cohort. Patient ages were relatively equally distributed across all groups. The adjusted multivariable analysis favoured DILT demonstrating a significant decreased risk of experiencing PC-related mortality compared to non-CCB users (HR: 0.69, 95% CI: 0.54-0.89, p=0.0039). There was no association in both the DHP (HR: 1.08, 95% CI: 0.90-1.29, p=0.4237) and VERAP (HR: 0.85, 95% CI: 0.57-1.23, p=0.3633) groups compared to non-CCB users.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: This preliminary population study shows an association between DILT and PC-related mortality. Limitations include the absence of assessing duration of CCB use prior to and post-diagnosis of PC. However, we are in the process of replicating our findings using PC data from a different cancer institute and will include duration of CCB use in our future analysis.

4183 | Comparative risks of cardiotoxicity following initiation of checkpoint inhibitors, BRAF/MEK inhibitors, and interferon alpha in patients with metastatic melanoma

Benjamin Bates, Poonam Gandhi and Soko Setoguchi
Rutgers, New Brunswick, NJ

Background: Checkpoint inhibitors (CPi) activate anti-tumor T cells and have demonstrated improvement in overall survival for patients with metastatic melanoma. Severe cardiotoxicity has been reported, but little is known concerning comparative risks of cardiotoxicity among available treatments for metastatic melanoma.

Objectives: To compare risks of cardiac events in melanoma patients who initiated CPi, BRAF/MEK inhibitors (BMi), or interferon alpha-2b (IFN).

Methods: We identified patients with ≥1 diagnosis of melanoma followed by an initiation of a therapy used for metastatic melanoma, i.e., CPi, BMi, and IFN in MarketScan commercial and Medicare databases (2011-2017). The primary outcome was a composite of all cardiac events including myocardial infarction, heart failure and other cardiovascular hospitalizations. The secondary outcome was a composite of immune-related cardiac events, including myocarditis/pericarditis, takotsubo cardiomyopathy, ventricular arrhythmia, and heart block with pacemaker placement. We described patient characteristics and calculated incidence rates (IRs) of outcomes and their 95% confidence intervals (CIs). We used Cox regression to estimate hazard ratios (HRs) and their 95% CIs after adjusting for potential confounding using propensity score (PS).

Results: We identified 15,693 melanoma patients initiating CPi (65%), BMi (2%), or IFN (33%). CPi users on average were slightly older (age 62) compared to IFN (age 60) and BMi (age 54); IFN had higher proportion of males (68%) than CPi (58%) or BMi (54%). During 6,654 person-years on therapy, we observed an IR of 288, 136, and 447 per 1000 person-years in CPi, BMi, and IFN, respectfully. For all cardiac events comparing CPi to BMi, the risks were similar (adjusted HR 1.1 [95% CI: 0.7-1.8]). However, CPi users had significantly lower risk compared to IFN users (adjusted HR 0.6 [95% CI: 0.5-0.7]). Secondary analysis comparing the risk of immune related cardiotoxicity in CPi vs IFN demonstrated a significant reduction in the risk (adjusted HR 0.3 [95% CI: 0.3-0.4]).

Conclusions: In real-world melanoma patients, we found CPi did not increase the risk of cardiac events compared to BMi or IFN. IFN, in fact, demonstrated higher risk of overall cardiac events and immune-related cardiac events compared to CPi, consistent with FDA boxed warning for IFN causing life-threatening autoimmune diseases. More studies with larger sample size and better identification of melanoma characteristics is needed to better quantify the comparative risk of CPi cardiotoxicity.

4199 | Thiamine deficiency as a misdiagnosed and unrecognized cause of delirium in referred patients with cancer

Hideki Onishi[1], Izumi Sato[2] and Mayumi Ishida[1]
[1]*Saitama Medical University International Medical Center, Hidaka, Japan;* [2]*Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan*

Background: Thiamine deficiency (TD) may increase the risk of delirium among patients with cancer. However, the TD is unrecognized or overlooked because of symptomless or unspecific symptoms, and that may lead to severe brain damage. Previous studies did not revile the prevalence of TD among cancer patients with delirium.

Objectives: To investigate the percentage of TD and the patients' background characteristics among patients with cancer who were referred to the department of psycho-oncology for developing delirium from oncologists in the cancer center of the university hospital.

Methods: We conducted a cross-sectional study to describe the prevalence of TD and the patients' characteristics using electrical medical records in the cancer center on University hospital, including patients with cancer aged 18 years or older who were referred for the incidence of delirium to the psycho-oncologist from October 2014 to March 2018. We collected patients' backgrounds (e.g., age, gender), and cancer-related data (primary site of cancer, performance status, treatment within two months before the blood sampling), and results of blood test (vitamin B1, albumin, and lactate dehydrogenase). We calculated descriptive statistics to summarize them, the prevalence of TD, and the percentage of undiagnosed TD. Then we performed multivariable logistic regression analysis to investigate the association between thiamin deficiency and socio-demographics, cancer-related states, and blood tests.

Results: We identified 71 patients diagnosed with delirium by psycho-oncologist (mean age 69.6 years old; 66% male). TD was found in 45% of the patients. Of these patients with TD, 60% were misdiagnosed and unrecognized by the oncologists at the time of consultation. Patients with TD were more likely to be diagnosed with gastroenterological cancer, had lower albumin levels, lower BMI, and received chemotherapy. We found the association between chemotherapy and TD (adjusted OR, 1.98; 95%CI [1.04-3.77]).

Conclusions: We found 45% of TD in patients with cancer developing delirium who were referred to psycho-oncologist in the cancer center of the University hospital. Although TD was not rare, more than half of these patients were unrecognized by the TD by oncologists at a consultation. Oncologists should be more careful about detecting TD when patients with cancer develop delirium.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4205 | Risk of malignancy in rheumatoid arthritis patient and association with biologic DMARDs using national health insurance service claim database

Sang Oh Kang, Kyung Hyun Min, Harim Yeon and Kyungeun Lee
Chung-Buk National University College of Pharmacy, Cheong-ju, Republic of Korea

Background: Since the development of biologic disease-modifying anti-rheumatic drugs (bDMARDs), treatment outcome for rheumatoid arthritis (RA) has been improved in the aspect of effectiveness. But, in regard to safety, concerns about malignancy risk has been raised.
Objectives: The aim of this study was to investigate the risk of malignancy in RA patients especially in bDMARDs users.
Methods: A retrospective cohort study was conducted using the customized RA cohort database from Korean National Health Insurance database. From 2002 to 2017, A total of 928,200 patients were included in the database and 232,050 were identified as RA patients. In a disease association analysis, RA patients treated with conventional synthetic DMARDs (csDMARD) were enrolled as the case group. Patients who had never been diagnosed RA nor prescribed DMARDs were classified as the control group. We examined the association of RA with malignancy by comparing the incidence of malignancy in both groups. In an analysis between malignancy and bDMARDs, bDMARDs users were defined by patients who were prescribed more than three times within 6 months from the first prescription and non-bDMARDs group was patients who had never been prescribed bDMARDs. The outcome of this study was malignancy occurrence during drug exposure or within 90 days after last drug prescription. We compared the malignancy incidence using incidence rate ratio (IRRs) after adjustment for age, gender and Charlson comorbidities index.
Results: After exclusion, 900,283 patients were included in this study. In a disease association analysis, 227,764 were in RA group and 672,519 were in control group. In RA group, during 1,732,896 person-years (PY) of follow up, 41,486 malignancies were detected (2394/100,000 PY). In non-RA group, IR was 114,630/4,527,648 PY (2532/100,000 PY). IRR between RA group and non-RA group was 0.946 (95% CI 0.943-0.948, $p<0.05$). In the analysis between malignancy and bDMARDs, there were 10,099 patients using bDMARDs and 151,570 patients without bDMARDs in non-bDMARDs group (who were prescribed csDMARDs more than three times). IR was 647/2132 PY (1657/100,000 PY) for bDMARD user and 16,393/84068 PY (2250/100,000 PY) for bDMARD non-user, resulting IRR of 0.736 between bDMARD users and non-bDMARD users (95% CI 0.734-0.739, $p<0.05$).
Conclusions: The incidence of malignancies was lower in RA group when compared with non-RA patients. The overall risk of malignancies was decreased in bDMARD user as compared with non-bDMARD user.

4213 | Disease characteristics, treatment and clinical outcomes of patients with B-cell non-Hodgkin lymphoma: A retrospective study in Taiwan

Sung-Nan Pei[1], Hong Qiu[2], Lee Anne Rothwell[3] and Yanfang Liu[4]
[1]Division of Hematology/Oncology, Chia-Yi Chang Gung Memorial Hospital, Division of Hema-Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, and Chang Gung University College Medicine, Chia-Yi, Taiwan; [2]Global Epidemiology, Janssen Research & Development, Titusville, NJ; [3]Janssen Medical Affairs, Macquarie Park, Australia; [4]Global Epidemiology, Janssen Research & Development, Singapore, Singapore

Background: Despite improved survival associated with the use of rituximab in standard chemotherapy regimens for B-cell Non-Hodgkin lymphoma (BNHL), survival remains poor. Understanding the current disease journey will facilitate evaluations of effectiveness of new therapies that may enter the market in coming years.
Objectives: To evaluate the clinical characteristics, treatment, outcomes and survival among patients with BNHL (subtypes DLCBL, FL, CLL/SLL, MZL, MCL, WM).
Methods: We conducted a retrospective cohort study using electronic medical records from Kaohsiung Chang Gung Memorial Hospital, a regional tertiary hospital in southern Taiwan, from 01 January 2008 to 31 December 2017. All adult patients with a new diagnosis of BNHL (ICD-O 9680/3, 9823/3, 9673/3, 9690/3, 9699/3, 9761/3) from January 01, 2008 until December 31, 2013 were included and followed until 31 December 2017. Patients with a previous malignancy were excluded. Deaths were captured from the hospital database and correlated with the National Death Registry. Event-free survival (EFS) and overall survival (OS) were calculated using Kaplan-Meier methods.
Results: 441 patients were newly diagnosed with BNHL between 2008-2013; 54.6% were diagnosed with DLBCL, 15.2% with FL, 13.8% with MZL, 10.7% with CLL/SLL, 3.4% with WM, and 2.3% with MCL. More than 50% of patients were diagnosed with Stage III or IV disease, except for MZL (16.4%). At diagnosis, 19.5% of patients with DLBCL were positive for hepatitis B surface antigen and 15.8% were positive for hepatitis C virus. Active treatment was administered to 397 patients (81.7%). Complete and partial response rates after first line treatment were 57.6% and 18.3% for DLBCL, 54.0% and 33.3% for FL, 57.9% and 28.1% for MZL, and 30.0% and 30.0% for MCL. Partial response rate was 42.9% for WM. The relapse rate after first line treatment was highest in MCL (20%) and lowest in MZL (8.8%). 5-year OS was 86.7% for MZL, 76.2% for FL, 71.0% for CLL/SLL, 58.3% for WM, 52.7% for DLBCL, and 20.0% for MCL. OS was significantly reduced in patients with an early disease flare (relapse <6 months after commencing chemotherapy) compared with disease flares after 6 months (median OS 0.75 yrs versus 4.47 yrs, $p=0.037$). 2-year EFS was 49.1% for DLBCL, 63% for FL, 62% for MZL, 10% for MCL, 0% for WM.
Conclusions: More than half of BNHL patients presenting to this tertiary hospital in Taiwan had advanced disease at diagnosis. More than 75% with DLCBL, FL or MZL responded to conventional chemotherapy but response rates in WM and MCL were low. New treatments are needed to improve the outcome of BNHL.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4223 | Novel use of the England National Cancer Registry to describe treatment patterns and disease outcomes in patients with advanced or metastatic cancer

Francois-Xavier Lamy[1], Craig Knott[2,3], James Harnett[4], Amerah Armin[5], Leo Russo[6], Emmanuelle Boutmy[1] and Patrice Verpillat[1]
[1]*Merck KGaA, Darmstadt, Germany;* [2]*HealthDataInsight CIC, Cambridge, United Kingdom;* [3]*Public Health England, Cambridge, United Kingdom;* [4]*Pfizer Inc., New York, NY;* [5]*Merck Serono Ltd, Feltham, United Kingdom;* [6]*Pfizer Inc., Collegeville, PA*

Background: The recent approvals of immuno-oncology (IO) treatments for several types of cancer is expected to substantially impact the standard of care and clinical outcomes. Real-world data (RWD) on the treatments and outcomes for patients with advanced or metastatic cancer would provide relevant supplementary evidence to clinical trial results.
Objectives: To set up and describe 4 open-ended cohorts of patients diagnosed in England with advanced or metastatic cancer where IOs were recently approved: Merkel cell carcinoma (MCC), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) and urothelial carcinoma (UC). We report here the first results for these cohorts.
Methods: The cohorts were identified using the National Cancer Registration and Analysis Service (NCRAS) in England. In addition, patient-level linkage was used to extract comprehensive national data on the disease (national cancer registry), inpatient, outpatient and emergency admissions and diagnoses (Hospital Episode Statistics), anticancer radiotherapy (National Radiotherapy Dataset), systemic anticancer treatments (Systemic AntiCancer Therapy database), and mortality (Office for National Statistics). Adult patients were included following diagnosis date (index date) of stage III or IV MCC, NSCLC, RCC or UC between January 2013 and June 2017 for the first data cut-off. Patients identified through death certificates only, or those receiving systemic therapy via the cancer drug fund were not included. The follow-up period ran from index date to the earliest of death, loss to follow-up or end of study period (March 2018). Overall survival (OS) was estimated by Kaplan-Meier from index date to death, censoring at loss to follow-up or end of study period.
Results: A total of 392 MCC (of which 32.7% were stage IV at diagnosis), 67,148 NSCLC (68.4% stage IV), 14,629 RCC (57.5% stage IV) and 10,510 UC (68.1% stage IV) patients were included in each corresponding cohort. Systemic treatments were reported for 18.4% of MCC, 42.1% of NSCLC, 24.3% of RCC and 26.6% of UC patients. Use of IO was reported in all cohorts but limited (<10%). Median OS from diagnosis ranged from 6.0 months in the NSCLC cohort to 21.6 months in the RCC cohort.
Conclusions: Robust RWD relying on secondary use of data can provide relevant supplementary information to clinical trials on the rapidly evolving anticancer treatment landscape and disease outcomes following the advent of IO therapy. Furthermore, the open-ended nature of these cohorts will offer the opportunity to describe these changes over time at future data releases.

4253 | Parity, use of statins and breast cancer risk in a Danish population-based cohort

Agnès Fournier[1], Aurélie Mailhac[2], Bianka Darvalics[2], Henrik T. Sørensen[2], Marc J. Gunter[3] and Deirdre Cronin-Fenton[2]
[1]*Université Paris-Saclay, UVSQ, Inserm, Paris, France;* [2]*Aarhus University, Aarhus N, Denmark;* [3]*International Agency for Research on Cancer, Lyon, France*

Background: While statin use is associated with better disease-free survival after breast cancer (BC) diagnosis, these widely used lipid-lowering drugs have shown inconsistent associations with primary BC incidence. Previously, in a French cohort study of postmenopausal women aged an average of 63 years old at baseline, statin use was found to be associated with decreased BC risk (-20%) only among women with at least 3 full-term pregnancies. Whether such an interaction is observable in other cohorts is not known.
Objectives: To assess the association between statin use and BC incidence according to parity using data from a Danish nationwide cohort.
Methods: Our source population was all female residents of Denmark born 1955-1960. Information on the number of full-term pregnancies was ascertained from the Danish Medical Birth Register established in 1973 and was hence considered complete for women born from 1955. In our analysis, we included women aged at least 45 years old in 2000-2005, our enrollment period, i.e. born until 1960. They were followed for invasive BC incidence from age 45 through December 2014. Exposure was defined as at least one statin prescription identified since 1995 from the Danish National Prescription Registry. Deaths and cancers were ascertained using the Danish Civil Registration System and the Cancer Registry. We fitted Cox regression models to compute hazard ratios (HR) between statin exposure, treated as a time-varying lagged variable, and incident invasive BC risk. We adjusted our models for age (time scale), Charlson comorbidity index and prescriptions for hormone replacement therapy, oral contraceptives, antihypertensive drugs, hypolipidemic drugs other than statins, antidiabetics, low-dose aspirin and bisphosphonates.
Results: A total of 198,539 women without cancer before the age of 45 years were followed for a median of 11.8 years, during which 5421 invasive BCs occurred. At the end of follow-up, 17% had been ever exposed to statins. Statin use was not associated with BC incidence, neither among all women combined (HR = 0.94, 95% CI = 0.84-1.06) nor by any parity strata: the HRs were 0.78 (0.58-1.06), 1.08 (0.84-1.39), 0.91 (0.76-1.10), and 1.01 (0.78-1.32) among women with 0, 1, 2, and 3+ full-term pregnancies, respectively (p homogeneity = 0.59).
Conclusions: In this cohort of women followed from age 45 up until 60 years old, there was little evidence of an association between exposure to statins and invasive BC risk, neither overall nor by parity strata. Whether associations would differ in older women should be explored in future studies.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4298 | Evaluation of electronic health record (EHR) data of patients with acute myeloid leukaemia (AML) for real-world data analyses

Charlotta Früchtenicht[1], Evelyn M. Flahavan[2], Tao Xu[1], Tarec Christoffer El-Galaly[1], Jessica Davies[2], Craig Gower-Page[2] and Anne-Marie Meyer[1,3]

[1]F. Hoffmann-La Roche Ltd., Basel, Switzerland; [2]Roche Products Limited, Welwyn Garden City, United Kingdom; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Care pathways in aggressive diseases like AML are complex and occur in multiple clinical settings which are not typically captured by a single EHR. Understanding this complexity is critical to capturing treatments and outcomes in real world patients and identifying sources of bias to address in the study design.

Objectives: To assess the completeness of patient data captured from AML patients in oncology clinic EHRs and quantify the potential biases that impact study design.

Methods: De-identified patient-level data was obtained from Flatiron Health's (FIH) database (December 2019 release), including patients diagnosed with AML (excluding acute promyelocytic leukemia) between 01/2014 and 11/2019 with at least two distinct clinic visits on or after January 1, 2014. Patient information was aggregated from either structured data collected within the FIH network EHR or abstracted from unstructured information in the EHR by an expert reviewer. We combined structured and abstracted data to describe treatment and outcomes observed within and outside of the clinic network. Gaps in care were identified by absence of activity data from any source.

Results: The source cohort consisted of 815 patients of which 809 (99.2%) had structured clinical activity after abstracted diagnosis (Dx) date. Gaps in patient care are rare in AML, however, 136 patients (17%) showed at least one activity gap of more than three months in the first year post-Dx.

Structured Tx data was available post-Dx for 590 patients, however Tx for an additional 145 patients was captured from abstracted data (oral or intravenous (IV)), increasing the treated cohort to n=735. Of these, 700 (95%) could be assigned a first line (1L) Tx regimen. The vast majority (n=617, 88%) received antineoplastic Tx within 31 days after AML Dx.

One-third of the patients did not have structured data concurrently with their abstracted Dx date and were likely diagnosed outside the network. Furthermore, among the 1L treated patients, 212 (31%) of patients had evidence of 1L Tx likely outside the network based on evidence of Tx abstracted from unstructured data and no structured drug administrations during 1L in the network.

Conclusions: This analysis demonstrates the complexity of capturing Tx and outcome information in a disease where care may occur at multiple sites of care. Users must be knowledgeable about treatment pathways and vigilant about potential biases from missing data. Though, careful curation of EHR data shows that it is possible to recover substantial exposure information through the abstraction of data captured outside the structured EMR.

4397 | Incidence, prevalence, and survival in patients with metastatic non-small cell lung cancer in the United States (US)

Engels Chou, Alyssa B. Klein, Ion Cotarla and Brian Seal

AstraZeneca, Gaithersburg, MD

Background: Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancers (LC). At the time of diagnosis, 70% of NSCLC patients already have locally advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage (30-55%) of early stage NSCLC patients who have undergone surgery subsequently develop distant metastases and die as a result of their lung cancer.

Objectives: To calculate the most recent epidemiology estimates of metastatic NSCLC (mNSCLC) in the US.

Methods: Patients diagnosed with NSCLC were identified from National Cancer Institute (NCI)'s Surveillance, Epidemiology, and End Results (SEER) and Centers for Disease Control and Prevention (CDC)'s National Program of Cancer Registries (NPCR) merged databases, as well as SEER-18 (data cut up to Dec 2016, staging available up to 2015). NPCR-SEER was used to calculate national age-adjusted incidence of NSCLC, while SEER18 was used to calculate age-adjusted incidence and prevalence, as well as survival by age group.

Results: In NPCR-SEER, NSCLC incident cases (N=161,273) accounted for 83.4% of all LC in 2016, and the incidence rate decreased from 45 per 100,000 in 2012 to 41.4 per 100,000 in 2016; Of these NSCLC patients, 68.2% were aged ≥65 years with a 16-fold incidence rate higher than that in <65 years (232.2 per 100,000 vs. 13.8 per 100,000). In SEER18, similar decreasing incidence rate of NSCLC was observed: 41.7 per 100,00 in 2012 decreased to 38 per 100,000 in 2016. In the most recent 5-year data, NSCLC incident cases accounted for 84.6% of all LC, and 49.2-51.9% of these cases were metastatic before adjusting for age. The incidence of mNSCLC in 2015 was 17.1 per 100,000, accounting for 37.2% of LC, or 44.3% of NSCLC after adjusting for age. The prevalence of NSCLC was 104.7 per 100,000 when extrapolated to the national level (prevalence was 500.4 per 100,000 for ages ≥65 years and 34.6 per 100,000 for <65 years). Of mNSCLC patients, 65.4% were aged ≥65 years with 16.3% being squamous, 68.8% adenocarcinoma, and 6.8% with non-small cell carcinoma; in patients <65 years, 21.4% were squamous, 64.5% adenocarcinoma, and 7.7% with non-small cell carcinoma. Survival for mNSCLC was low: 1-, 2-, 3-, 4-, and 5-year survival were 30%, 15.1%, 9.2%, 6.4%, and 4.8%, respectively. The 5-year survival was only 4% for patients ≥65 years (6.1% for <65 years), and 3.8% for males (6% for females).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Almost half of NSCLC incident cases were metastatic. About half of the prevalent mNSCLC patients were progressed from earlier stages. The 5-year survival rate was lower than 5% for mNSCLC patients.

4419 | KADor: A French retrospective study describing the therapeutic management of patients who received Herceptin® based neoadjuvant treatment for HER2+ early breast cancer (eBC)

Paul Cottu[1], David Perol[2], Olivier Tredan[2], Alain Livartowski[1], Melina Gilberg[3], Rim Ghorbal[3], Julien Dupin[3] and Cathy Maillard[4]
[1]*Institut Curie, Paris, France;* [2]*Centre Leon Berard, Lyon, France;* [3]*Roche SAS, Boulogne-Billancourt, France;* [4]*IQVIA, Paris la Defense, France*

Background: The results from the KATHERINE trial showed an improvement in invasive Disease-Free Survival (iDFS) associated with Kadcyla® administered as adjuvant therapy compared to Herceptin® in patients with HER2+ eBC who had residual invasive disease in the breast or axillary lymph nodes (incomplete pathological response, non-pCR) following conventional neoadjuvant therapy. These results led to the development of the observational study KADor to obtain French data on these patients' characteristics and therapeutic management.
Objectives: The main objective of this study was to describe the therapeutic management, between 2014 and 2018, of patients with HER2 + eBC who initiated neoadjuvant therapy in 2014. The estimation of the proportion of non-pCR patients and the iDFS were assessed as secondary objectives.
Methods: This was an observational, retrospective and multicenter study involving French HER2+ eBC patients who had initiated a Herceptin® based neoadjuvant treatment during 2014 followed by a surgery. A registry based medical records was first set up to capture the entire flow of patients managed in participating sites, then a follow-up cohort including patients treated with a Herceptin® based adjuvant therapy was created. A weighting was applied to control sites representativeness at the national level.
Results: Of the 460 French hospital sites (public/private) contacted, 57 participated in the study. The populations in the registry and the cohort were 306 and 301 patients respectively. The mean age of the patients included in the cohort was 52 years (±12.6). According to T (tumor size) and N (lymph nodes) staging of the primary tumor at diagnosis, the majority of patients were T2N0 (22.9%), T2N1 (22.2%) and T3N1 (13.3%). Nearly 60% of patients presented hormone receptors. More than half (57.1%) of the patients were non-pCR. The mean number of Herceptin® cycles administered was 13.2 (95% CI: 12.8- 13.6). Hormone therapy was administered to 47.5% of patients (95% CI: 41.9% - 53.1%). At 36 months, the iDFS rate was 84.1% (95% CI: 79.1% - 87.9%) for the entire cohort and 88.1% (95% CI: 80.7% - 92.8%) and 81.0% (95% CI: 73.8% - 86.4%) in pCR and non-pCR patients respectively.
Conclusions: The KADor study described the therapeutic management of HER2+ eBC patients who had initiated a Herceptin® based neoadjuvant treatment in France followed by a surgery and a Herceptin® based adjuvant therapy in real clinical setting. These findings indicate that routine practice aligns with the recommendations for therapeutic management.

4433 | Treatment patterns and clinical outcomes of patients with metastatic non-small cell lung cancer receiving immune checkpoint inhibitor monotherapy in the first-line setting in community-based practices in the United States

Evie Merinopoulou[1], Beth Nordstrom[2], Samuel Huse[2], Nataliya Trunova[3], Christianah Kolajo[3], Engels Chou[3] and Alyssa B. Klein[3]
[1]*Evidera, London, United Kingdom;* [2]*Evidera, Waltham, MA;* [3]*AstraZeneca Oncology Unit, Gaithersburg, MD*

Background: Until recently, platinum-based combination chemotherapy was the standard of care for first line (1L) therapy in NSCLC with little improvement on patient prognosis, especially at later stages. Despite the emergence of novel therapies marking a rapidly shifting treatment paradigm in mNSCLC, little is known on treatment patterns and clinical outcomes in the real-world setting.
Objectives: To describe patient characteristics and treatment patterns after initiating IO monotherapy in the mNSCLC setting, and to assess survival and progression outcomes.
Methods: Patients in the Flatiron Health Oncology electronic medical record database with a mNSCLC diagnosis, who had 1L IO monotherapy between 1 October 2016 - 31 May 2018 were identified. Patients were ≥18 years old, had no evidence of mixed small-cell histology, epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations prior to or at the start of 1L (index date). Clinical outcomes included overall survival (OS) and progression-free survival (PFS) from index and start of second line (2L), and second PFS (PFS-2), defined as the time from index to disease progression during 2L. Treatment patterns and clinical outcomes were described by line of therapy using descriptive statistics and Kaplan-Meier methods.
Results: A total of 1,851 patients who were diagnosed with mNSCLC during the study period initiated 1L IO monotherapy. Mean (standard deviation) age at index date was 70.7 (9.7) years, 54.8% were male, and 49.9% had Eastern Cooperative Oncology Group status 0-1 (missing: 32.9%). The most common 1L IO monotherapies were pembrolizumab (62.0%) and nivolumab (33.5%). Of the 508 patients who initiated 2L, 256 (50.4%) received chemotherapy alone, and 82 (16.1%) received anti- vascular endothelial growth factor (VEGF) regimens in combination with chemotherapy. Out of 160 patients initiating 3L, 78 (48.8%), received chemotherapy alone and 30 patients (18.8%) received IO monotherapy. Median OS and PFS from 1L were 12.2 months (95% confidence interval:11.4-13.5), and 9.2 months (8.5-10.2), and PFS-2 was 17.5 months (15.9-19.7). Starting from 2L, median OS and PFS were 9.7 months (8.3-11.3) and 7.0 months (6.3-7.9).
Conclusions: This real-world study found median survival of patients starting on IO monotherapy to be just over 1 year. Despite the introduction of new innovative therapies, clinical outcomes in mNSCLC

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

remain suboptimal, indicating a need for further improvements in treatment options.

4441 | Treatment patterns and clinical outcomes of patients with metastatic non-small cell lung cancer receiving immune checkpoint inhibitors in combination with chemotherapy in the first-line setting in community-based practices in the United States

Evie Merinopoulou[1], Beth Nordstrom[2], Samuel Huse[2], Nataliya Trunova[3], Christianah Kolajo[3], Engels Chou[3] and Alyssa B. Klein[3]
[1]*Evidera, London, United Kingdom;* [2]*Evidera, Waltham, MA;* [3]*AstraZeneca Oncology Unit, Gaithersburg, MD*

Background: For patients with mNSCLC, clinical trials have demonstrated that IO therapies plus chemotherapy provide considerable survival benefit compared to chemotherapy alone, however, current information from the real-world setting is limited.
Objectives: To assess patient characteristics, treatment patterns, survival and progression outcomes in patients with mNSCLC initiating IO in combination with chemotherapy (IO+chemo) in the United States.
Methods: Patients ≥18 years old with a mNSCLC diagnosis in the Flatiron Health Oncology electronic medical record database, who initiated first line (1L) IO (pembrolizumab, nivolumab, or atezolizumab) plus chemotherapy between 1 October 2016 - 31 May 2018, were included. Patients with evidence of mixed small-cell histology, epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations prior to or at the start of 1L (index date) were excluded. Kaplan-Meier methods estimated overall survival (OS) and progression-free survival (PFS) from index and start of second line (2L), and second PFS (PFS-2), from index to disease progression during 2L. Treatment patterns and clinical outcomes were described by line of therapy.
Results: A total of 700 patients diagnosed with mNSCLC during the study period initiated 1L IO+chemo and qualified for the cohort. Mean (standard deviation) age at index date was 66.9 (9.8) years, 56.9% were male, and 60.6% had Eastern Cooperative Oncology Group status 0-1 (missing: 28.9%). At 1L, 686 (98.0%) of patients received IO plus platinum-based chemotherapy (cisplatin, carboplatin), and 14 (2.0%) received IO plus other chemotherapy regimens. The most common treatments in 2L were chemotherapy only (77 [38.9%]), anti-vascular endothelial growth factor (VEGF) regimens plus chemotherapy (60 [30.3%]) and IO combinations (23 [11.6%]). Of the 63 patients who started on third line, 35 (55.6%) had chemotherapy, and 20 (31.7%) had anti-VEGF plus chemotherapy. Median OS and PFS from 1L were 12.5 months (95% confidence interval:10.2-14.4), and 8.6 months (7.5-9.7), and PFS-2 was 14.8 months (12.0-18.3). Starting from 2L, median OS and PFS were 8.2 months (6.8-9.6) and 4.9 months (4.1-6.5), respectively.
Conclusions: Despite the increasing use of innovative therapies in combination chemotherapy for the treatment of mNSCLC, survival and progression data from the real-world setting reveal a continued unmet need for improved therapies.

4503 | Use of proton pump inhibitors and histamine-2 receptor antagonists and risk of gastric cancer in two population-based studies

Peipei Liu[1], Úna McMenamin[1], Brian Johnston[2], Peter Murchie[3], Lisa Iversen[3], Amanda Lee[3], Pauline Vissers[4] and Christopher Cardwell[1]
[1]*Queen's University Belfast, Belfast, United Kingdom;* [2]*Belfast Health and Social Care Trust, Belfast, United Kingdom;* [3]*University of Aberdeen, Aberdeen, United Kingdom;* [4]*Netherlands Comprehensive Cancer Organisation, Utrecht, Netherlands*

Background: Previous studies have shown increased gastric cancer risk in users of proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA), questioning the safety of gastric acid suppression.
Objectives: To investigate PPI and H2RA and gastric cancer risk in two large independent study populations.
Methods: We conducted a nested case-control study within the Primary Care Clinical Informatics Unit (PCCIU) database. Each gastric cancer case was matched to up to five controls. Conditional logistic regression model was used to calculate odds ratios (OR) and 95% confidence intervals (CI). We also conducted a prospective cohort study within the UK Biobank in which medication use was identified from self-report at baseline and Cox regression was used to calculate hazard ratios (HR) and 95% CI.
Results: PCCIU contained 1,119 gastric cancer cases and 5,394 matched controls. PPI users had a higher gastric cancer risk (unadjusted OR=1.45, 95% CI 1.25, 1.68; fully adjusted OR=1.49, 95% CI 1.24, 1.80) but this was attenuated after excluding prescriptions in the 2 years before diagnosis (fully adjusted OR=1.13, 95% CI 0.91, 1.40). A similar pattern was seen for H2RA in the PCCIU database. UK Biobank contained 250 gastric cancers in 471,779 participants. PPI use was associated with increased gastric cancer risk (unadjusted HR=1.53, 95% CI 1.10, 2.12) but this was not apparent after adjustments (adjusted HR=1.28, 95% CI 0.86, 1.90) and further attenuated when excluding cancers within 2 years of baseline (adjusted HR=1.15, 95% CI 0.73, 1.82).
Conclusions: Overall, we observed evidence of associations between PPI/H2RA use and gastric cancer risk but these associations were sensitive to the duration of lag time used in the analysis, suggesting reverse causation.

4519 | Identifying microsatellite instability associated cancer patients in the veterans affairs healthcare system

Shahed Iqbal[1], Amanda M. De Hoedt[2], Kai-Li Liaw[1], Stephen J. Freedland[2,3], Mayur Amonkar[1], Deepti Aurora-Garg[1] and Zachary Klaassen[4,5]
[1]*Merck & Co., Inc., Kenilworth, NJ;* [2]*Veterans Affairs Health Care System, Durham, NC;* [3]*Cedars-Sinai Medical Center, Los Angeles, CA;* [4]*Medical College of Georgia, Augusta, GA;* [5]*Georgia Cancer Center, Augusta, GA*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Microsatellite instability (MSI) is a biomarker of active interest for targeted drug development for multiple cancers as patients with high MSI have been found to respond well to cancer therapy. Identifying MSI tested patients in electronic health records (EHR) is a difficult and complex process. In this era of precision medicine, it is important to understand and identify patients with biomarker data for epidemiologic and health outcomes research.

Objectives: To develop an optimal approach to identify MSI tested patients in the Veterans Affairs (VA) healthcare system.

Methods: A comprehensive list of 93 MSI-related 'search terms' and 47 CPT codes was generated by the study team that included oncologists, epidemiologists, bioinformatics and biomarker scientists. Structured and unstructured data (laboratory results, clinical and physician notes, etc.) in the VA healthcare database were searched using the CPT codes and search terms, respectively. From the identified records, a maximum of five randomly selected records for each search term or CPT code were manually reviewed to identify MSI tested cases. Frequently appearing MSI-related terms (e.g., MSI, microsatellite instability, etc.) found in the charts of MSI tested patients were used to further narrow down the search terms. A combination of CPT codes and search terms were explored for an optimal approach to identify MSI tested cases. Sensitivity (Sn), specificity(Sp), and positive predictive value (PPV) were calculated for all approaches.

Results: A total of 444 charts identified using 93 search terms were reviewed of which 129 (associated with 69 search terms) were found to be MSI tested cases. Another 198 charts identified using CPT codes were reviewed; 53 of which (associated with 26 CPT codes) were found to be MSI tested cases. In total, 642 unique patients were reviewed with 181 having MSI testing with at least one of the search terms or CPT codes. Search terms were narrowed down to 21 after reviewing all the frequently appearing MSI-related terms. Compared to 21 search terms (Sn: 40%, Sp: 85%, PPV: 52%,) or 26 CPT codes (Sn: 62%, Sp: 75%, PPV: 49%) separately, a combination of 21 search terms and 20 CPT codes more efficiently (Sn: 45%, Sp: 98%, PPV: 89%) identified MSI tested patients.

Conclusions: Most of the cases (89%) identified by a combination of search terms and CPT codes were found to be truly MSI tested. This is an efficient approach to identify and study MSI tested patients for outcomes of clinical interest. Similar approaches could identify patients with other biomarker data in other EHR systems where patients are not readily identifiable.

4663 | Characteristics and study eligibility of British lung cancer patients for clinical trials evaluating targeted therapies (TTS) or immune checkpoint inhibitors (ICIS)

Ard van Veelen[1,2], Shahab Abtahi[1], Patrick Souverein[2], Johanna H.M. Driessen[1], Olaf H. Klungel[2], Anne-Marie Dingemans[1], Robin van Geel[1], Frank de Vries[1,2] and Sander Croes[1]

[1]*Maastricht University Medical Centre, Maastricht, Netherlands;*
[2]*Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands*

Background: Inclusion and exclusion criteria used in clinical trials often lead to a homogeneous study-population. In this study we explored the characteristics of patients included in pivotal phase III clinical trials evaluating new drugs for patients with non-small cell lung cancer (NSCLC) with the characteristics of British patients diagnosed with lung cancer in daily practice.

Objectives: To study the characteristics and representativeness of British lung cancer patients compared to patients included in phase III clinical trials).

Methods: A retrospective study using the Clinical Practice Research Database (CPRD) GOLD was performed. All patients (N = 9239) with a first ever lung cancer registration (2014 - 2018) were included. Eligibility for inclusion was assessed for twelve clinical trials (evaluating osimertinib, alectinib, nivolumab, pembrolizumab, durvalumab, and atezolizumab) by applying all in- and exclusion criteria used in the clinical trials. Reasons for potential exclusion and the total number of unmet criteria were assessed for each study independently. Kaplan Meier analysis was used to compare overall survival between eligible and ineligible patients for each trial. In addition, Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals (CI).

Results: The proportion of eligible patients based on for trials evaluating TTs was approximately 64.8%, while this was lower for studies evaluating ICIs (42.5%). Most patients would be eligible in the AURA3-study, for which 78.1% of the British patients population met inclusion criteria. While most patients would be excluded due to 1 or 2 criteria, the maximum number of unmet criteria was higher for studies evaluating ICIs. For all studies, the overall survival was longer for eligible patients compared to ineligible patients. Age and sex adjusted HRs ranged from 1.17 (95% CI = 1.14 - 1.20) to 1.24 (95% CI = 1.19 - 1.29).

Conclusions: A large proportion of British lung cancer patients would not have been eligible to be included in clinical trials evaluating drugs used in the treatment of NSCLC. A more lenient approach could be considered to increase the proportion of patients eligible for study participation and to better represent patients treated in daily practice.

4691 | Clinical value of oncology medicines in Europe: Is it different for conditionally approved medicines?

Lourens T. Bloem[1,2], Rosa E. Bot[1], Aukje K. Mantel-Teeuwisse[1], Menno E. van der Elst[2], Olaf H. Klungel[1,3], Hubert G.M. Leufkens[1] and Jarno Hoekman[1,4]

[1]*Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands;* [2]*Dutch Medicines Evaluation Board, Utrecht, Netherlands;* [3]*Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark;* [4]*Innovation Studies, Copernicus Institute of Sustainable Development, Utrecht University, Utrecht, Netherlands*

Background: To allow early access to innovative medicines that address an unmet medical need, the European Medicines Agency

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(EMA) may grant conditional marketing authorisation (CMA) based on less comprehensive data. EMA then requires post-approval trials to provide comprehensive data, after which standard marketing authorisation (SMA) can be granted. However, while addressing unmet medical need suggests a promise of added clinical value, it remains unknown whether that is achieved once comprehensive data are available.

Objectives: To determine whether CMA oncology medicines for which comprehensive data are available post-approval are associated with higher clinical value than SMA oncology medicines at approval.

Methods: We identified all CMA oncology medicines for which comprehensive data were available before March 2019. As reference group, we identified innovative non-CMA oncology medicines that had initially been granted SMA before March 2019 and were similar with regard to pharmacotherapeutic group and initial indication. For all medicines, we identified all pivotal trials that supported initial approval. For CMA medicines, we also identified all required post-approval trials. For each trial, we assessed the associated clinical value using the European Society for Medical Oncology Magnitude of Clinical Benefit Scale, which ranges 0-5 and indicates whether substantial clinical value is provided (≥4). We tested for differences between the groups with regard to maximum clinical value score available for each medicine and the chance that medicines provided substantial clinical value once comprehensive data were available post-approval (CMA) versus at approval (SMA). We therefore used the Wilcoxon Rank Sum test and calculated risk ratios (RR) and Wald 95% confidence intervals (CI), respectively.

Results: We identified 14 CMA and 22 SMA medicines. The median of the maximum clinical value of CMA medicines at approval was 3 (interquartile range [IQR] 2-3), and 13% provided substantial clinical value. Once comprehensive data were available, their maximum clinical value increased and was higher than that of SMA medicines (median 3 [IQR 2.5-4] vs. 3 [IQR 1-3], p=0.03), as was their chance to provide substantial clinical value (47% vs. 17%, RR 2.7 [95% CI 0.9-7.6]).

Conclusions: Compared to SMA oncology medicines, CMA oncology medicines are associated with higher clinical value and provide more often substantial clinical value once comprehensive data are available. This suggests that the EMA's use of the conditional approval pathway so far provides early access to clinically important oncology medicines.

4746 | Antiplatelet drug use and breast cancer risk in a prospective cohort study of postmenopausal women

Manon Cairat[1], Marie Al Rhamoun[2], Gianluca Severi[2], Marc Gunter[1], Laure Dossus[1] and Agnes Fournier[2]

[1]*International Agency for Research on Cancer, Lyon, France;* [2]*Centre de Recherche en Epidémiologie et Santé des Populations (CESP), équipe "Exposome, Hérédité, Cancer et Santé", Inserm UMR1018, Facultés de Médecine, Université Paris-Saclay, Université Paris-Sud, Gustave Roussy, Villejuif, France*

Background: By inactivating platelets and consequently blocking the release of growth and inflammatory factors, antiplatelet drugs (APDs), including low-dose aspirin and clopidogrel, could have anticancer properties. Epidemiological studies found consistent inverse associations between low-dose aspirin use and colorectal cancer risk whereas results for other cancers such as breast cancer (BC) are limited.

Objectives: We investigated the association between the use of low-dose aspirin or clopidogrel and BC incidence in the French E3N prospective cohort.

Methods: E3N includes 98,995 French women born between 1925 and 1950 and insured by a health insurance plan that covers mostly teachers. Information on lifestyle, anthropometric and reproductive factors, and medical history were collected biennially by self-questionnaires and matched with data from a drug reimbursement database pertaining to years 2004-2014. Women with at least two reimbursements in any 3-month period since 2004 were defined as ever exposed to APDs. Considering exposure as time-varying, multivariable Cox regression models were used to estimate hazard ratios (HRs) for the association of APD use with BC, overall and by BC subtypes. Effect modification by breast cancer risk factors and comorbidities that might be associated with APD use was also assessed.

Results: In the current analysis, 62,390 postmenopausal women were followed between 2004 and 2014 (9 years on average, starting at a mean age of 63 years; 2,887 BCs). Of them, 17% were exposed to low-dose aspirin and 3% to clopidogrel during follow-up. Use of low-dose aspirin use was not associated with BC risk [HR= 1.03 (0.91 - 1.17) for ever exposed compared to non-exposed women], except when it lasted more than four years [HR=0.68 (0.47 - 0.98)]. Clopidogrel use was associated with an increased breast cancer risk [HR= 1.30 (1.00 - 1.67)], regardless of the duration of use. This increase in risk was significant only for estrogen receptor negative (ER-) BC [HR_{ER+}= 1.14 (0.83 - 1.55), n exposed cases=44; HR_{ER-}= 3.16 (1.72 - 5.79), n exposed cases=13; P homogeneity=0.01].

Conclusions: In this large prospective cohort of postmenopausal women, low-dose aspirin use for more than four years was associated with a decreased risk of BC, whereas clopidogrel was associated with an increased risk of ER- BC, regardless the duration of use.

4777 | The potential of claims data for long-term follow-up of breast cancer patients in Germany

Miriam Heinig[1] and Ulrike Haug[1,2]

[1]*Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany;* [2]*University of Bremen, Bremen, Germany*

Background: Population-based data on long-term treatment patterns and clinical outcomes in cancer patients are important but hardly available from German cancer registries.

Objectives: Exemplified by breast cancer (BC) patients, we aimed to explore the potential of German claims data for providing long-term follow-up information on cancer patients.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: We used the German Pharmacoepidemiological Research Database (GePaRD) containing claims data from four statutory health insurances with information on ~25 million persons. Based on previously developed algorithms using ICD-10 codes, we identified patients newly diagnosed with BC in 2008 and classified them into three groups: no affected lymph nodes/metastasis (noNM), affected lymph nodes only (onlyN) or distant metastasis (M) at diagnosis. The cohort was followed up until end of 2016 or death. We characterized the groups regarding initial and subsequent therapies (surgery, medical therapy and radiotherapy), metastases and deaths occurring during follow-up.

Results: After exclusion of patients switching health insurance during follow-up (9% of the initial cohort) we included 11,717 BC patients diagnosed in 2008 (noNM: 82%, onlyN: 12%, M: 7%) with a mean age of 63 years (median follow-up: 8.4 years). During the observation period, 11% of the cohort received no breast surgery (group M: 21%), 28% received more than one surgery (second surgery in first year: 81%; later: 19%) and 29% had a mastectomy (in first year: 91%, only later: 9%). Of the total cohort, 8% received neoadjuvant therapy and 7% received both neoadjuvant and adjuvant (systemic) therapy. Regarding systemic therapy, 7% ever received monoclonal antibodies, 74% ever received hormone therapy, and 52% never received chemotherapy (group noNM: 92%). Of all patients, 28% never received radiotherapy. Overall, 25% of the cohort died (group M: 22%).

Conclusions: Claims data provide valuable information on the long-term course and treatment of cancer patients, avoiding substantial loss-to-follow-up and incomplete reporting of therapies. Combining claims data with cancer registry data containing detailed tumor information may create synergies that should be explored.

4847 | Approximating line of treatment using drug exposure data and clinical information of patients with metastatic breast cancer using U.S. electronic health record data

Thibaut Sanglier[1], Jinjoo Shim[1], M.K. Downer[2], Carlos Flores[2] and Patricia Luhn[2]

[1]*F.Hoffmann-La Roche, Basel, Switzerland;* [2]*Genentech Inc., South San Francisco, CA*

Background: In oncology, the number of lines of treatment (LoT) since metastatic cancer diagnosis is an important predictor of subsequent outcomes. Yet accurate LoT information is often unavailable from healthcare claims or electronic health records (EHR) data and is challenging to estimate. Most studies use the number of unique antineoplastic regimens (ANR) observed since diagnosis as a proxy for LoT. However, for metastatic breast cancer (mBC) this may lead to substantial misclassification; changes in ANR may occur for reasons besides worsening disease (e.g. toxicity, safety). EHRs with data on timing of both ANR changes and clinical events can help assess the clinical relevance of ANR changes to estimate LoT.

Objectives: To identify changes in ANR and estimate their association with clinical events in a cohort of patients with mBC.

Methods: Using data from the US-based Flatiron Health EHR-derived de-identified database, we selected patients diagnosed with mBC between January 1, 2011 - October 30, 2019 treated with at least two ANRs after mBC diagnosis. The cohort was stratified by mBC subtype: HR+/HER2-, HER2+ and TNBC. A single ANR included any exposure to antineoplastic drug recorded within the 28 days following the first drug initiation, subsequent incident drug exposure recorded more than 28 days after the ANR initiation defined the subsequent ANR. Any drug change in an ANR defined a treatment event. Notes in the medical records suggestive of disease worsening (e.g. progression of the disease) between first treatment initiation of the prior ANR +14 days and 14 days after first treatment initiation of the subsequent ANR defined a clinical event.

Results: 6551 patients (4453 HR+/HER2-, 1348 HER2+, 710 TNBC) mBC patients were included. The frequency ranges of the five most frequent treatment events grouped by drug class were [411-1060], [114-296] and [65-358] and the ranges of probabilities to observe a clinical event were [51%-89%], [13%-85%] and [9%-86%] for the HR+/HER2-, HER2+ and TNBC cohorts respectively.

Conclusions: The probability of observing concurrent clinical and treatment events varied, even for the most common treatment events. These results mostly reflect clinical guidelines and suggest drug exposure-based algorithms counting number of ANR from mBC as proxy for LoT may lead to substantial misclassification. Identifying common treatment events unlikely to be associated with concurrent clinical events can help to improve these algorithms and reduce misclassification.

4862 | Performance of QRISK-3 scores in predicting cardiovascular disease in adult cancer survivors compared to matched cancer free controls

Helen Strongman[1], Emily Herrett[1], Rod Jackson[2], Michael Sweeting[3], Alexander R. Lyon[4], Susannah Stanway[5], Claire Lawson[3], Umesh Kadam[3], Liam Smeeth[1] and Krishnan Bhaskaran[1]

[1]*London School of Hygiene & Tropical Medicine, London, United Kingdom;* [2]*University of Auckland, Auckland, New Zealand;* [3]*University of Leicester, Leicester, United Kingdom;* [4]*Imperial College London, London, United Kingdom;* [5]*Royal Marsden Hospital, London, United Kingdom*

Background: Survivors of many site-specific cancers have elevated medium to long term risks of coronary heart and stroke compared to the general population. QRISK-3 scores, which inform statin prescribing decisions in the UK, may therefore underpredict coronary heart and cerebrovascular disease in cancer survivors.

Objectives: To assess the predictive performance of the QRISK-3 tool in predicting coronary heart and cerebrovascular disease in cancer survivors.

Methods: We conducted a cohort study using linked Clinical Practice Research Datalink primary care, hospital, cancer registration and death registration data from 1990 to 2015. We identified adult cancer survivors with a first cancer diagnosis for one of the 20 most common cancers and who were followed-up for at least one year before and after diagnosis. These were matched by age, gender, practice and index date

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

to a cancer-free comparison group. We removed individuals with pre-existing cardiovascular disease and current statin users, and calculated QRISK-3 scores one year after the index date in both groups. Coronary heart and cerebrovascular disease outcomes that occurred during follow-up were identified using Read and ICD-10 codes. We plotted 10 year predicted and observed risks for each decile of predicted risk to assess calibration using a naïve Kaplan-Meier approach to estimate observed risks. We used the Harrell's C statistic to assess discrimination.

Results: One year after cancer diagnosis, there was close correspondence between predicted and observed 10-year risk in cancer survivors except for a degree of overprediction at higher deciles of risk (1.9% and 0.3% underprediction in males and females respectively in the lowest decile; 13.4% and 9.8% overprediction in males and females respectively in the highest decile). In cancer free controls, similar patterns were observed with tighter calibration (0.7% and 0.1% underprediction in males and females respectively in the lowest decile; 7.6% and 4.1% overprediction in males and females respectively in the highest decile). Overprediction in each group was highest in older individuals. The Harrell's C statistic was 0.67 and 0.68 in male cancer survivors and controls respectively and 0.77 in females in both groups.

Conclusions: We observed no underprediction of coronary heart and cerebrovascular disease by QRISK-3 scores in cancer survivors and cancer free controls, but some overprediction at higher deciles which was strongest in cancer survivors and for older people. This may be due in part to depletion of susceptibles and poorer performance of QRISK3 in older people.

4873 | Association of surgical complications with in-hospital mortality among patients undergoing major pancreatic resection

Joseph Guilfoyle[1], Neal Bhutani[2], Stephen Johnston[1], Hari Dwarakanathan[3], Anuprita Patkar[4] and Robert CG Martin[5]

[1]Johnson and Johnson, New Brunswick, NJ; [2]University of Louisville, Louisville, KY; [3]Mu Sigma, Bangalore, India; [4]Ethicon, Somerville, NJ; [5]University of Louisville, Louisville, KY

Background: Surgical complications are common in major pancreatic resection. Whereas prior research has associated surgical complications with increased length of stay and costs for the hospitalization during which the surgery was performed, little research has been published on whether such complications are associated with increased risk of mortality.

Objectives: To examine the association of surgical complications with the incidence of in-hospital mortality among patients undergoing distal pancreatectomy (DP) or pancreaticoduodenectomy (PD).

Methods: Retrospective, cross-sectional analysis of U.S. data from the Premier Healthcare Database. Included patients were aged ≥18 years undergoing pancreatic resection between October 2015 and March 2019 (first=index admission). Surgical complications (intra/post-operative) were measured during the index admission using secondary diagnosis codes; complications were compiled based on expert clinical knowledge and included infective, cardiac, pulmonary, genitourinary and several other groupings. The primary study outcome was in-hospital mortality (discharge status of 'expired') during the index admission. Multivariable generalized estimating equations were used to compare the adjusted risks of mortality between patients with vs. without ≥1 surgical complication, accounting for hospital level-clustering and patient/surgeon/hospital characteristics; recycled prediction was used to calculate absolute and between-group risk differences.

Results: A total of 5,931 patients underwent PD and 4,010 underwent DP. During the index admission, 3,428 (57.8%) PD patients and 1,648 (41.1%) DP patients developed ≥1 surgical complication; 170 (2.9%) PD and 72 (1.8%) DP patients experienced mortality. As compared with patients with no surgical complications, the relative risk of mortality among patients with ≥1 surgical complication was 15.0 for PD (risk difference=4.2 percentage points [95% CI=3.4-4.9], 4.5% vs 0.3%, p<0.0001) and 10.3 for DP (risk difference=2.8 percentage points [95% CI=2.0-3.6], 3.1% vs 0.3%, p<0.0001). When examining individual surgical complication groups, cardiac, genitourinary, and infective complications had the strongest associations with mortality in both PD and DP.

Conclusions: In-hospital mortality rates were dramatically elevated among patients who experienced surgical complications during PD or DP. Measures to decrease the incidence and severity of surgical complications may help to decrease the risk of in-hospital mortality among patients undergoing major pancreatic resection.

4934 | Hydrochlorothiazide and risk of melanoma subtypes

Laurel A. Habel[1], Ninah Achacoso[1], Bruce Fireman[1], Sidsel Arnspang Pedersen[2] and Anton Pottegard[3]

[1]Kaiser Permanente Northern California, Oakland, CA; [2]University of Southern Denmark, Odense, Denmark; [3]Institut for Sundhedstjenesteforskning Syddansk Universitet, Odense, Denmark

Background: Hydrochlorothiazide (HCTZ), a common diuretic known to be photosensitizing and previously associated with non-melanoma skin cancer, was recently reported to be associated with two melanoma subtypes, nodular and lentigo, among residents of Denmark.

Objectives: Our goal was to examine whether Danish findings could be replicated in a US cohort, using a similar study design and analysis.

Methods: Among non-Hispanic White enrollees of Kaiser Permanente Northern California, we conducted an analysis of 9,176 melanoma cases and 264,781 controls, matched on age, sex and time in health plan. We examined use of HCTZ prior to cancer diagnosis (cases) or comparable date for controls, categorized as never use, ever use and high use (≥50,000 mg). Electronic health records provided data on prescriptions, cancer diagnoses, and covariates. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for education, income and number of dermatology, internal medicine and urgent care visits.

Results: We observed a small increase in risk of melanoma, all types combined, associated with high use (≥50,000 mg) of HCTZ (OR=1.11,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

95% CI 1.00-1.23) and no evidence of a dose-response. Risk was more elevated for lentigo subtype (OR=1.57, 95% CI 1.01-2.42). The somewhat elevated risk for nodular subtype was not statistically significant (OR=1.22, 95% CI 0.78-1.90). There was very little association of high use with the superficial spreading subtype (OR=1.05, 95% CI 0.80-1.37).

Conclusions: Our findings support a recent report of an association between high use of HCTZ and increased risk of the lentigo subtype of melanoma.

5054 | Site-specific cancer risk from exposure to cobalt alloys in orthopedic implants or cobalt in occupational settings: A systematic review and meta-analysis

Chantal Holy[1], Shumin Zhang[1], Laura Perkins[2], Laurence B. Katz[3], Jason Brown[4], Luca Orlandini[5], Gion Fessel[5], Behrooz Nasseri-Aghbosh[6], Gary Eichenbaum[1], Natalie S. Egnot[7] and Paul M. Coplan[1]

[1]Johnson & Johnson, New Brunswick, NJ; [2]Abbott Vascular, Santa Ana, CA; [3]LifeScan, Malvern, PA; [4]Medtronic, Minneapolis, MN; [5]Smith & Nephew, Baar, Switzerland; [6]Stryker, Elstree, United Kingdom; [7]Cardno ChemRisk, Pittsburgh, PA

Background: The European Commission recently up-classified metallic cobalt as presumed human carcinogenic. This decision was based primarily on two rodent inhalation studies of metallic cobalt. This up-classification raised questions regarding risk posed by exposure to implants containing cobalt alloys and in work places.

Objectives: Evaluate the risk of site-specific cancer associated with exposure to implants containing cobalt alloys and occupational exposures.

Methods: A systematic review in Pubmed and meta-analysis were performed to evaluate site-specific cancer risks in patients with total joint replacements (TJR) or workers in occupational cohort (OC) exposed to particulate cobalt. These study types were selected as they represent possible long term and high-level exposures. Estimates for organ-specific cancers were extracted, grouped in 27 distinct cancer types, and aggregated using random-effects models (REM). Models were stratified by metric (Standardized Incidence Ratio (SIR) vs Standardized Mortality Ratio (SMR) or other rate ratios) and study type (registry vs database vs occupational cohort (OC)).

Results: 21 TJR and 12 OC studies, including 979,262 people with average 7.8 years follow-up were included. Of 27 cancer types assessed, 3 had pooled estimates significantly lower in cobalt-exposed groups (lung/lower respiratory tract, stomach and intestinal cancers) while 2 were higher in the cobalt exposed groups: prostate cancer (estimate = 1.08 CI: 1.03-1.13: SIR = 1.10 (1.05-116), SMR = 1.07 (0.80-1.43)) and myeloma (estimate= 1.12, CI: 1.05-1.19, 13 out of 14 data points reported SIR, no SMR data).

Conclusions: Of the 27 cancers assessed, 22 were not different from, and 3 were below the null. Risk for detection, but not mortality, was slightly greater than the null for prostate cancer, suggesting detection bias. For myeloma, risk of detection was slightly increased. Myeloma, often detected via blood work from regular follow-up, is prone to detection bias through incidental finding, more so than many other cancer types. Findings for these 2 cancer types resulted in weak associations and were likely not clinically relevant.

5092 | Patterns of recurring colorectal polyps and risk of colorectal cancer in commercially insured US adults

Laura L. Hester[1], Christopher Knoll[2] and Dina M. Gifkins[2]

[1]Janssen R&D, LLC, Titusville, NJ; [2]Janssen R&D, LLC, Raritan, NJ

Background: Limited evidence is available on whether patients with frequently recurring colorectal polyp diagnoses (dx) have an increased risk of colorectal cancer (CRC). Understanding the incidence of recurrent colorectal polyp dx and transformation to CRC over time can aid in interception efforts targeting high-risk patients.

Objectives: To characterize patients with recurrent colorectal polyps and to estimate the risk of recurrent polyp dx and transformation to CRC over time.

Methods: Using Optum© Clinformatics® Datamart commercial claims (2001-2018), we identified US patients with (1) an initial colorectal polyp dx with a polypectomy in the prior 30 days, (2) >=365 days prior continuous enrollment, (3) no colorectal polyp or CRC history, and (4) no polypectomies or CRC dx 60 days postdiagnosis. Five-year risks of 2nd and 3rd polyp dx subsequent to the initial polyp dx were calculated using competing risk models with CRC as a competing risk. To generate hypotheses on risk factors for recurring polyp dx, we compared the prevalence of prior conditions, drugs, and procedures among patients with only 1 vs 3+ polyp dx in 5 years using standardized differences. Additionally, we assessed risk of CRC, defined with 2 primary malignant colorectal lesion codes 90 days apart, over a 5-year period from first and subsequent polyp dx using Cox proportional hazards models. Screening patterns were also assessed.

Results: Over 1.5 million patients with a colorectal polyp were identified during the study period. Within 5 years of an initial polyp dx, the risk of a 2nd polyp dx was 21%, and the risk of a 3rd polyp dx was 3%. Patients at the highest risk for CRC transformation with 3+ subsequent polyp dx compared to those with only 1 polyp dx were more likely to be older (median 67 v 61 yrs), male (61% v 55%), and have baseline conditions such as abnormal keratinization (17% v 10%), eye lesions (28% v 19%), and gall bladder disorders (14% v 8%). Overall, the 5-year risk of CRC dx among all patients was 1.1%, which increased to 2.1% in a subset with a subsequent polyp dx.

Conclusions: CRC risk increased with subsequent polyps, which were experienced by 1 in 5 patients within 5 years of an initial polyp. Patients with 3+ polyps dx in 5 years had a greater prevalence of diseases known to occur in the genetic condition, Lynch Syndrome, which has a high CRC risk and is often undiagnosed until CRC lesions are tested. Current efforts to develop a machine learning prediction model will aid in earlier identification of persons who could benefit from CRC chemoprevention, like those with Lynch Syndrome, and the design of future interventional studies.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5115 | Incidence and management trends for cervical HSIL in a large US cohort from 2008 through 2018

Katherine C. Hughes[1], Timothy Herring[2], Jennifer Song[1], Robert Gately[1], Lindsay Nowak[3], Judy Wong[1], Mark Twyman[2], Prakash Bhuyan[2] and John D. Seeger[1]
[1]*Optum Epidemiology, Boston, MA;* [2]*Inovio Pharmaceuticals, Inc., Plymouth Meeting, PA;* [3]*None, Tonawanda, NY*

Background: Cervical HSIL is the precursor condition to invasive cervical cancer, which remains one of the most prevalent causes of morbidity and mortality, respectively, worldwide for women in the 21st century. Several improvements in the standard-of-care have occurred, such as the introduction of human papillomavirus (HPV) prophylactic vaccines and improved cervical cancer screening approaches. This analysis describes the observed overall impact of these improvements on the occurrence of cervical HSIL and frequency of initial surgical management.
Objectives: In a U.S. commercially insured population, 1) to longitudinally describe the detected occurrence of HPV-16/18 vs. non-HPV-16/18 associated cervical HSIL, and 2) to describe what portion of women received surgical management versus non-interventional medical monitoring.
Methods: Between 2008 and 2018 within the Optum Research Database, we identified a cohort of women aged 18+ with health insurance claims for cervical HSIL and described their management patterns.
Results: Among 65,527 women with cervical HSIL identified over the 10-year study period, 47,067 (72%) received HSIL initial treatment (surgery) while 18,460 (28%) did not. Initially, the number of incident cervical HSIL cases per year declined from a high of 9,470 in 2008 to 4,681 in 2014. Then, in the last three full years of the study period the annual number of HSIL cases appeared to stop declining (4,952, 5,357, and 5,354 cases in 2015, 2016, and 2017, respectively). The proportion of incident cervical HSIL cases that received initial surgical treatment for their HSIL diagnosis slightly increased from 68% in 2008 to 73% in 2017.
Conclusions: An initial decline in the occurrence of detected cervical HSIL was observed, which likely represents the implementation of improved adherence to screening guidelines as well as the impact of HPV prophylactic vaccination. The stabilization in the number of detected HSIL cases in the final years of the study period indicates that, in spite of improved screening approaches, the use of prophylactic vaccines, and surgical treatment, a significant incidence of cervical HSIL persists in the U.S. which can lead to and thus does not eradicate cervical cancer.

Disease Epidemiology/Clinical Course -> Cardiovascular

2392 | Uncontrolled blood pressure and therapeutic inertia in treated hypertensive patients: A descriptive cohort study in clinical practice research datalink (CPRD)

Céline Darricarrère[1], Marc Bénard[2], Stéphanie Bricout-Hennel[1], Caroline Louis[1] and Emmanuelle Jacquot[1]
[1]*Servier, Suresnes, France;* [2]*Aixial, Boulogne-Billancourt, France*

Background: Hypertension is a major and fast-growing cause of cardiovascular (CV) diseases and deaths. Treatment and control of this condition are crucial to reduce CV events and related burden. One of the identified factors contributing to uncontrolled hypertension is therapeutic inertia, which is the failure of health-care provider to modify therapy when blood pressure (BP) targets are not reached.
Objectives: To quantify uncontrolled BP over time and therapeutic inertia in UK patients treated for hypertension in Primary Care.
Methods: A retrospective cohort of patients diagnosed with primary hypertension and receiving antihypertensive drugs from January 2015 to June 2017, was created from the CPRD (GOLD). Patients with secondary hypertension were excluded. Index date (ID) is the first prescription of hypertensive drug during study period. Patients were followed for 18 months. Primary outcomes were proportions of patients with uncontrolled BP (one BP record, Systolic ≥ 140 mmHg or Diastolic ≥ 90 mmHg) at ID and over time; time to first BP control (one BP record Systolic < 140 mmHg and Diastolic < 90 mmHg) in patients uncontrolled at ID and proportion of therapeutic inertia defined as 2 consecutive uncontrolled BP records with no treatment change.
Results: 581 260 treated hypertensive patients (mean age 67.8 years, 51.3% women) were included, among whom 37.2% (N=216 014) had an uncontrolled BP record at ID, 32.6% had a controlled BP record (N= 189 291) and 30.3% (N=175 955) did not have any BP record. At ID, 516 231 patients (88.8%) were prevalent users of HT drugs and mean duration since first antihypertensive medication prescribed was 8.3 years. The mean number of BP records per patients during follow-up was 2.1 at 1 year, with 1.1 and 1.0 for uncontrolled and controlled values respectively. Over a median follow-up of 18 months, 59.2% of the patients had at least one uncontrolled BP record and 12.8% of patients did not have any BP record. Focusing on uncontrolled population at ID (N=216 014), 72.9% had at least one uncontrolled BP record during the follow-up and 28.3% had only uncontrolled BP records. Therapeutic inertia occurred at least once for 55.7% of the uncontrolled population. However BP control was reached for 61.5% of the uncontrolled population at ID, within 185 days in median.
Conclusions: This cohort study showed that recording of BP measures in hypertensive patients' medical record is poor. Based on this low number of measures, uncontrolled BP and therapeutic inertia remain common.

2465 | Identification of an appropriate time window for the exclusion of prevalent cases recorded following registration with the clinical practice research datalink

Thomas P. Leahy[1], Cormac Sammon[1] and Sreeram Ramagopalan[2]
[1]*PHMR Ltd, London, United Kingdom;* [2]*London School of Economics and Political Science, London, United Kingdom*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Defining incidence cases of a disease in primary electronic health records such as the Clinical Practice Research Datalink (CPRD) is complicated by the lack of patient history prior to registration with a CPRD-registered practice. In the CPRD it has been shown that prevalent conditions are often recorded shortly after registration with a GP practice and therefore to avoid the inappropriate inclusion of these individuals as incident cases, first diagnoses recorded in a specified period post registration are typically excluded. However, CPRD publications rarely report how the time period post-registration is chosen, with many appearing to use a default choice of 12 months.

Objectives: To compare approaches to determine the length of the period post-patient registration required to avoid the inclusion of non-incident cases in a study population.

Methods: As a case study, all patients with a first recorded non-valvular atrial fibrillation (NVAF) diagnosis in the CPRD between 2006 and 2015 were identified. Five different approaches were then used to choose a period post-registration to exclude patients (i) a standard 12-month period (ii) visual inspection of a plot of the incidence of the condition over time since registration, (iii) visual inspection of a plot of the cumulative sum (CUMSUM) over time since registration, (iv) a variance changepoint method to identify the point at which the incidence variance changes post-registration, and (v) a reverse time series trend approach. The impact of each approach on the size of the incident study population was assessed.

Results: In the period 2006 to 2015 there were 48638 patients with a NVAF diagnosis. The use of a 12-month period under approach (i) resulted in a study population of 43992. Approaches (ii), (iii), (iv) and (v) resulted in the identification of 7 months, 3 months, 3 months and 5 months as being the suitable exclusion periods, respectively. Application of these periods resulted in study populations of 45439, 46825, 46825 and 46080 respectively. These reflected relative increases in the study population of 3.29%, 6.44%, 6.44% and 4.75% respectively.

Conclusions: Using the standard 12-month period post-patient registration may unnecessarily reduce the study population size. We suggest alternative approaches are used which at a minimum involve visual inspection of relevant plots of the incidence over time since registration and potentially use objective, data driven approaches to choose the cut-off. Sensitivity analyses could be used to illustrate any impact of using periods of differing length.

2564 | Transatlantic differences in healthcare systems captured by large administrative databases: Assessing the burden of COPD in patients admitted for heart failure

Claudia Gulea[1], Rosita Zakeri[2] and Jennifer K. Quint[1]

[1]Imperial College London, London, United Kingdom; [2]King's College London, London, United Kingdom

Background: Patients hospitalized for heart failure (HF) are at increased risk of unplanned readmission if they have comorbid COPD in addition to HF. It is unclear whether regional variation in readmission risk estimates is due to patient characteristics alone or additionally influenced by healthcare system differences.

Objectives: To compare the impact of comorbid COPD on short-term readmission risk among patients with HF using patient-level data from two nationally-representative databases.

Methods: We identified patients with an index hospitalisation for HF in the National Readmissions Database (NRD) in the US (1/1/12-30/11/12) and in Hospital Episode Statistics in the UK (1/1/12-30/11/13). To ensure valid comparisons, we standardised diagnosis definitions across datasources using validated ICD codelists. Using Cox regression we assessed 30-day readmission risk associated with COPD in individual and merged datasets, allowing adjustment for confounding factors including age, gender, length of stay [LOS] and comorbidities. As NRD did not provide data on smoking status, medications or out-of-hospital mortality status, we did not include these in the merged dataset.

Results: Of 225,160 patients in the US and 10,171 in the UK, one quarter had COPD. Patients in the US were younger, with higher prevalence of comorbidities, such as coronary artery disease and hypertension. In adjusted analyses COPD was positively associated with 30-day readmission risk in both the UK (HR: 1.18, 95% CI 1.06 to 1.3) and US (HR 2.01, 95%CI 1.96 to 2.06, p-value for country interaction <0.001). In the US, baseline in-hospital mortality was lower (2.8% vs. 9.3%) and LOS was shorter (median, days [IQR]: 4 [3- 7] vs. 7 [3-14]) than in the UK. Proportions of circulatory (50% US vs. 41% UK) and respiratory readmissions (16% US vs. 26% UK) also differed.

Conclusions: Using national administrative datasources from the US and UK, we identified diverging patterns of healthcare utilisation and in-hospital mortality among patients with HF, which were incompletely explained by differences in patient characteristics. We found that COPD carries a higher readmission tarrif in the US compared to the UK, suggesting a lower threshold for readmission in the US, while late disease detection and coding practices tuned to capture more severe patients may underlie the high baseline in-hospital mortality in the UK. Future analysis of differences in diagnostic pathways and reimbursement elements may reveal pertinent practice-related factors that affect patient outcomes.

4013 | Cumulative exposure to bisphosphonates and risk of cardiovascular and cerebrovascular events

Elena Olmastroni[1], Manuela Casula[1,2], Federica Galimberti[1], Elena Tragni[1], Giovanni Corrao[3,4], Lorenza Scotti[5] and Alberico L. Catapano[1,2]

[1]Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [2]IRCCS MultiMedica, Sesto S. Giovanni (MI), Italy; [3]National Centre for Healthcare Research & Pharmacoepidemiology, Milan, Italy; [4]Laboratory of Healthcare Research & Pharmacoepidemiology, Department of Statistics and Quantitative

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods, University of Milano-Bicocca, Milan, Italy; [5]Unit of Biostatistics, Epidemiology, and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

Background: Although bisphosphonates have been suggested to protect against atherosclerotic cardiovascular (CV) events, evidence is still conflicting.

Objectives: We aimed at investigating the effect of bisphosphonates on cardiovascular and cerebrovascular events.

Methods: We carried out a retrospective cohort study selecting from administrative databases of Lombardy (Italy) all patients aged> 40 years with a first prescription for bisphosphonates (index date) between 2003/01/01 and 2006/12/31. Subjects were followed from the index date until the date of the first hospitalization for cardio-cerebrovascular event, death, migration, or end of follow-up (2012/12/31), whichever occurred first. Exposure to bisphosphonates was characterized based on cumulative doses (proportion of days covered, PDC). Treatment's adherence was classified as low (PDC<41%), intermediate (PDC 41% and 80%), or high (PDC>80%). Cox models were fitted to estimate the association between time-dependent exposure to bisphosphonates and cardiovascular and cerebrovascular events (adjusted hazard ratios [HRs] and 95% confidence intervals). The model was adjusted for age, sex, comorbidities, and concomitant treatments.

Results: Among 82,704 incident bisphosphonates users (females 87.0%; mean age±SD 70.7±10.6 years), we identified 13,337 individuals (16.1%) with a first hospitalization for cardiovascular and cerebrovascular event, occurred on average (SD) 3.5 (2.3) years after the index date. Compared with individuals with an exposure <41% of follow-up, those exposed for 41% and 80% or more than 80% showed HRs of 0.95 [0.91-0.99] and 0.75 [0.71-0.81], respectively. In the subanalysis based on type of event, a PDC>80% was associated with a reduction of both cardiovascular and cerebrovascular events (HRs 0.75 [0.68-0.83] and 0.76 [0.70-0.83], respectively). The protective effect was confirmed both in the analyses stratified by sex and age classes, and in those performed at 1 and 3 years of follow-up.

Conclusions: These results suggested a strong CV risk reduction (up to 25%) with increasing number of days covered by bisphosphonate treatment. Although further studies to investigate possible mechanisms are warranted, it is important to consider bisphosphonates, and a strict adherence to this treatment, as having a potential effect also in the prevention of cardiovascular events.

4017 | Apolipoprotein B and risk of cardiovascular disease: A meta-analysis of randomized controlled trials

Federica Galimberti[1,2], Alberico L. Catapano[1,3], Julius L. Katzmann[2,4], Arjen J. Cupido[2,5] and Brian A. Ference[2]

[1]*University of Milan, Department of Pharmacological and Biomolecular Sciences, Epidemiology and Preventive Pharmacology Service (SEFAP), Milan, Italy;* [2]*University of Cambridge, Department of Public Health and Primary Care, MRC/BHF Cardiovascular Epidemiology Unit, Cambridge, United Kingdom;* [3]*IRCCS MultiMedica, Sesto S. Giovanni (MI), Italy;* [4]*Department of Cardiology, University Hospital Leipzig, Leipzig, Germany;* [5]*Amsterdam UMC, University of Amsterdam, Department of Vascular Medicine, Amsterdam, Netherlands*

Background: Recent evidence from Mendelian randomization studies suggest that the clinical benefit of any lipid-lowering therapy should be proportional to the absolute change in apolipoprotein B (apoB) containing lipoproteins. This finding implies that the clinical benefit of any lipid-lowering therapy should be proportional to the absolute change in apoB.

Objectives: We sought to compare and to estimate the magnitude of the expected clinical benefit per unit reduction in apoB for several classes of lipid-lowering therapies.

Methods: We conducted a study-level meta-analysis of randomized trials evaluating 6 different classes of lipid-lowering therapies (statins, ezetimibe, PCSK9-inhibitors, CETP-inhibitors, niacin, and fibrates). We included all randomized trials reporting apoB levels and cardiovascular (CV) outcomes, with at least 1000 participants and 1-year follow-up. The primary outcome for this meta-analysis was major CV events - defined as the first occurrence of CV death, non-fatal myocardial infarction, stroke or coronary revascularization. We estimated the relative risk (RR) of major CV events standardized for a 30 mg/dl reduction in apoB using fixed effect inverse-variance weighted meta-analysis (adjusted for study duration) separately for each class of therapy and in a combined analysis including all classes of lipid-lowering therapies. Heterogeneity between the different classes of lipid-lowering therapies was measured with the I2 statistic.

Results: A total of 25 trials that enrolled 285,241 participants (mean age: 63.3 years; female sex: 24.7%) who experienced 40,244 first major CV events were included. The mean baseline apoB level was 93.9 mg/dL. The mean absolute difference in apoB between the treatment and comparison groups at one year was 24.1 mg/dL. The overall RR per 30 mg/dL reduction in apoB levels was 0.79 (95% confidence intervals (CI) 0.77-0.81) for major CV events, consisting of separately significant reductions in non-fatal myocardial infarction (RR 0.76; 95% CI 0.73-0.79), in coronary revascularization (0.78; 0.73-0.82), in stroke (0.79; 0.76-0.81) and in CV death (0.87; 0.82-0.92). No significant heterogeneity was detected.

Conclusions: All the lipid-lowering therapies are associated with very similar reductions in the risk of major CV events per unit change in apoB, suggesting that the clinical benefit may be proportional to the achieved absolute reduction in apoB, regardless of the observed changes in other lipids. These finding can be used to inform the design of randomized trials evaluating novel lipid-lowering therapies.

4022 | Evaluation of the effect of omega-3 polyunsaturated fatty acids supplementation on cardiovascular outcomes: An updated meta-analysis of randomized controlled trials

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Elena Olmastroni[1], Manuela Casula[1,2], Marta Gazzotti[1], Federica Galimberti[1], Elena Tragni[1], Alberto Zambon[3] and Alberico L. Catapano[1,2]

[1]*Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy;* [2]*IRCCS MultiMedica, Sesto S. Giovanni (MI), Italy;* [3]*Department of Medicine-DIMED, University of Padua, Padua, Italy*

Background: There has been a great deal of controversy about the role of dietary supplementation with omega-3 long-chain polyunsaturated fatty acids (n-3 PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the prevention of cardiovascular (CV) disease.

Objectives: This meta-analysis aimed at investigating the effect of n-3 PUFA administration on CV events in all published randomized clinical trials (RCTs), updating the available results with the recently published REDUCE-IT trial.

Methods: Data search was carried out using PubMed, Cochrane and EMBASE (inception - March 2019). Inclusion criteria were: (1) RCTs; (2) patients had used n-3 PUFA at least 1 gram/day dosage for at least 1 year; (3) effects on outcomes (all-cause mortality, cardiac death, major adverse cardiovascular events [MACE], fatal/nonfatal myocardial infarction [MI], and fatal/nonfatal stroke) reported. Odds ratios (ORs) with 95% confident intervals (95%CI) were used as summary statistics.

Results: Overall, supplementation of n-3 PUFA was associated with a significant reduction of 13% of the risk of cardiac mortality (OR 0.87 [95%CI 0.79-0.97]) and of 22% of the risk of MI (OR 0.78 [95%CI 0.65-0.94]. In subgroup analyses by type of patients' prevention the risk reduction of cardiac mortality and MI associated with the supplementation of n-3 PUFA was confirmed only in RCTs that enrolled patients in secondary prevention (-23% and -45%, respectively). Stratified analyses based on doses of n-3 PUFA, highlight that only the administration of more than 1 gram per day of n-3 PUFA seems to be effective in reducing the risk of cardiac death (OR 0.71 [95%CI, 0.54-0.95]), MACE (OR 0.68 [95%CI, 0.47-0.99]), and MI (OR 0.67 [95%CI, 0.59-0.77]). In subgroup analyses by type of administration, EPA+DHA provision was only associated with a statistically significant risk reduction of cardiac death compared with EPA administered alone (OR 0.87 [95%CI, 0.79-0.97] vs OR 0.84 [95%CI, 0.57-1.24]). On the other hand, the efficacy of EPA administered alone seems to be greater in terms of risk reduction of MI (OR 0.70 [95%CI, 0.61-0.80] vs OR 0.83 [95%CI, 0.66-1.06] with EPA+DHA administration).

Conclusions: The pharmacological approach with n-3 PUFA significantly improves cardiovascular outcomes. The efficacy of n-3 PUFA administration appears to relate to the type of active components, dosage and patients' CV risk.

4055 | Venous thromboembolism and risk of cancer in users of statins: A Danish population-based cohort study

Nils Skajaa, David Nagy, Frederikke Schønfeldt Troelsen, Dóra Körmendiné Farkas and Henrik Toft Sørensen

Aarhus University, Aarhus N, Denmark

Background: Venous thromboembolism (VTE) may be the first symptom of cancer. Statins are suggested to prevent VTE, but the risk of cancer in VTE patients using statins remains poorly understood.

Objectives: To examine the risk of cancer among VTE patients using statins.

Methods: We performed a nationwide, population-based cohort study based on prospectively recorded data in Danish health and administrative registries. The study period was 2006-2017. We identified first-time hospital-diagnosed VTE patients with a dispensed prescription for any statin within 90 days preceding the VTE diagnosis. We classified patients as current users if they initiated statin therapy before the preceding year of the VTE diagnosis and as new users if they initiated statin therapy within one preceding the diagnosis. We followed statin users from the date of VTE diagnosis to that of an incident cancer diagnosis, death, migration, or 31 December 2017, whichever occurred first. We computed absolute cancer risks, with death as a competing cause, and age-, sex-, and calendar-period standardized incidence ratios (SIRs), comparing the observed cancer incidence with the expected based on national cancer statistics.

Results: Among 8,286 (88%) current users of statin and 1,136 (12%) new users, we observed 1,230 and 183 cancer diagnoses during a median follow-up of 2.4 years (interquartile range: 0.7-5.1 years) and 3.6 years (interquartile range: 1.1-7.0 years), respectively. The one-year risk for any cancer was 7.0% (95% confidence interval [CI]: 6.5-7.6) for current users and 6.6% (95% CI: 5.3-8.2) for new users. The one-year SIRs for any cancers were 3.1 (95% CI: 2.9-3.4) for current users and 3.5 (95% CI: 2.8-4.4) for new users; the SIRs decreased to 1.2 (95% CI: 1.1-1.3) and 1.1 (95% CI: 0.9-1.4) in the following years of follow-up.

Conclusions: The risk of cancer was elevated approximately three-fold during the first year following a VTE diagnosis among patients using statins.

4117 | Coprevalence of comorbidities in medicare older adults with chronic obstructive pulmonary disease

Tham T. Le and Linda Simoni-Wastila

University of Maryland, Baltimore, MD

Background: Comorbidities increase with age and in the presence of chronic conditions, such as chronic obstructive pulmonary disease (COPD). The presence of multiple comorbid conditions (MCCs) pose challenges for COPD management and can lead to poor outcomes.

Objectives: To quantify the coprevalence of MCCs in Medicare older adults with COPD.

Methods: Design: A retrospective cohort study using a 5% Medicare beneficiary sample between 1/1/2012 and 12/31/2015. **Settings:** We included beneficiaries aged ≥65 years who were diagnosed with COPD by or before 12/31/2014. **Main outcomes:** Coprevalence of 40 comorbidities were identified using the Medicare Chronic Conditions files. **Statistical analyses:** Coprevalence was estimated as percentage of MCCs ever diagnosed at the end of the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

study (12/31/2015) using all eligible beneficiaries as the denominator.

Results: Of 461,268 eligible beneficiaries, 60% were female, 86% were white, with mean (standard deviation [SD]) age of 79 (8) years. Among these, 89.2% had at least five and 50.4% had at least ten MCCs. Most prevalent comorbidities included hypertension (92.6%), hyperlipidemia (86.4%), anemia (74.9%), rheumatoid arthritis (RA) (68.0%), congestive heart failure (CHF) (49.6%), diabetes (46.7%), depression (43.7%), peripheral vascular disease (PVD) (42.9%), chronic kidney disease (CKD) (38.6%), asthma (38.3%), hypothyroid (36.3%), and pain (34.4%). Top co-prevalence of two conditions included hypertension-hyperlipidemia (82.4%), hypertension-anemia (71.7%), and hyperlipidemia-anemia (66.9%). The most common co-prevalence of three comorbidities were hypertension-hyperlipidemia-anemia (65.0%), hypertension-hyperlipidemia-RA (59.1%), and hypertension-anemia-RA (54.1%). Coprevalence of three, four, and five comorbidities were most likely between conditions such as hypertension, hyperlipidemia, anemia, arthritis, diabetes, CHF, PVD, and CKD.

Conclusions: Older COPD patients encounter a high burden of MCCs. The high coprevalence of chronic conditions underlines drug-drug interaction risks and the necessity of integrated care to improve health outcomes in patients with COPD.

4453 | History of lipid lowering therapy use among adults initiating treatment with proprotein convertase subtilisin/kexin type 9 antibody inhibitors in the United States, 2015-2019

Sara N. Levintow[1,2], Catie Wiener[1], Kate K. Orroth[3], Karminder Gill[3], Andrew Mullard[3], M. Alan Brookhart[1,4] and Leah J McGrath[1]
[1]*NoviSci, Durham, NC;* [2]*University of North Carolina, Chapel Hill, NC;* [3]*Amgen Inc., Thousand Oaks, CA;* [4]*Duke University, Durham, NC*

Background: Proprotein convertase subtilisin/kexin type 9 antibody inhibitors (PCSK9i) are novel treatments for patients with atherosclerotic cardiovascular disease and are effective at further reducing low-density lipoprotein cholesterol when combined with other lipid-lowering therapies (LLT). Cholesterol treatment guidelines discuss adding PCSK9i once maximally tolerated statin therapy has been reached, and documented statin therapy is a prior authorization criterion for many health plans in the US. Little is known about real-world treatment patterns of other LLT use among patients initiating a PCSK9i.

Objectives: To characterize the one-year history of other LLT use among PCSK9i initiators using Sankey visualizations.

Methods: We used the MarketScan Commercial and Medicare Supplemental claims to identify adults initiating a PCSK9i from August 2015 to March 2019. Patients were required to have 12 months of continuous enrollment in a healthcare plan before PCSK9i initiation. We used fill dates and days' supply from the pharmacy claims to capture LLT use in the one year preceding PCSK9i initiation. Treatment was assumed to occur from the fill date to 30 days after the end of the days' supply. We estimated the cross-sectional prevalence of LLT use (statin, ezetimibe, or none) on the initiation date and at 3, 6, 9, and 12 months before the initiation date.

Results: Among 11,958 adults initiating a PCSK9i, 6,221 (52%) had no other LLT use at the time of PCSK9i initiation. In the 6 months prior to PCSK9i initiation, 34% of all patients had no LLT use, and for the full 12 months before initiation, 26% had no LLT use. Patients who were female, older (>65 years), and initiated PCSK9i in earlier years (2015-2017) had a lower prevalence of prior use of other LLT. Among the 5,737 patients who were receiving other LLT at PCSK9i initiation, 44% were on a high-intensity statin (with or without ezetimibe). Other specific drug combinations included statin and ezetimibe combination therapy (27%), high-intensity statins without ezetimibe (26%), and ezetimibe alone (24%).

Conclusions: Despite treatment guidelines and prior authorization requirements for PCSK9i use as an adjunct to other LLT, many patients had no statin or ezetimibe use in the year before PCSK9i initiation. Future research is warranted on the real-world effectiveness of PCSK9i for patients with and without other LLT use.

4472 | Real world treatment patterns following the initiation of proprotein convertase subtilisin/kexin type 9 antibody inhibitors among adults in the United States, 2015-2019

Catie Wiener[1], Sara N. Levintow[1,2], Kate K. Orroth[3], Karminder Gill[3], Andrew Mullard[3], Leah J. McGrath[1] and M. Alan Brookhart[1,4]
[1]*NoviSci, Durham, NC;* [2]*University of North Carolina, Chapel Hill, NC;* [3]*Amgen Inc., Thousand Oaks, CA;* [4]*Duke University, Durham, NC*

Background: Clinical trials have demonstrated the efficacy and safety of proprotein convertase subtilisin/kexin type 9 antibody inhibitors (PCSK9i) for decreasing low-density lipoprotein cholesterol and reducing the risk of major cardiovascular events. However, there is limited real-world evidence on patterns of PCSK9i use. Specifically, treatment persistence and concurrent use of other LLT (statins and ezetimibe) are not well understood in patients initiating PCSK9i therapy.

Objectives: We used Sankey visualizations to depict treatment patterns of PCSK9i and other LLT use in the one year following PCSK9i initiation.

Methods: We used the MarketScan Commercial and Medicare Supplemental claims to identify adults initiating a PCSK9i from August 2015 to March 2019. Patients were eligible if they had 12 months of continuous enrollment prior to PCSK9i initiation and at least 3 months of follow-up data. We used fill dates and days' supply from the pharmacy claims to capture patterns of use for PCSK9i, statins, and ezetimibe after PCSK9i initiation. Treatment use was assumed to occur from the fill date to 30 days after the end of the days' supply. We assessed the cross-sectional prevalence of PCSK9i and other LLT treatments (statin, ezetimibe, or none) at 3, 6, 9, and 12 months following PCSK9i initiation. Inverse probability weights were used to address potentially informative censoring due to disenrollment and end of data over follow-up.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Among 11,958 adults initiating a PCSK9i, 88% were on a PCSK9i at 3 months, decreasing to 79% at 6 months, 74% at 9 months, and 70% at 12 months following initiation. PCSK9i use at 12 months was more common among males (73% vs. 66% for females), and slightly increased over time (67% for patients initiating in 2015 vs. 71% for 2018), but did not vary by age group (<65 years, ≥65 years). At PCSK9i initiation, 48% of patients had concurrent use of statins or ezetimibe. This percentage decreased over follow-up to 38% at 3 months, 34% at 6 months, 31% at 9 months, and 30% at 12 months. Further, 18% of patients were on no LLT at 12 months following initiation.

Conclusions: Using real-world data, we found that persistence with PCSK9i therapy remained relatively high at one year following treatment initiation. Although PCSK9i therapy is recommended as an adjunct to maximally tolerated statin therapy, fewer than half of PCSK9i initiators had concurrent use of statins or ezetimibe. Future studies could expand follow-up beyond one year to capture longer-term treatment patterns and clinical outcomes.

4581 | The prevalence and determinants of over- and undertreating hypertension and cholesterol levels in the Rhineland study

Nersi Alaeddin[1], Folgerdiena M. de Vries[1], Gökhan Pehlivan[1] and Monique M.B. Breteler[1,2]

[1]*German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany;* [2]*Institute for Medical Biometry, Informatics and Epidemiology (IMBIE), Bonn, Germany*

Background: Elevated blood pressure and cholesterol levels are major risk factors for cardiovascular disease (CVD). Although emphasis on control of these risk factors has increased, they often remain uncontrolled. Increased emphasis could also cause overtreatment, however evidence here is scarce.

Objectives: We aim to assess the prevalence and determinants of over- and undertreatment of hypertension and cholesterol levels in the general German population.

Methods: We used data from the Rhineland Study, a population-based cohort in Bonn, Germany, including people aged ≥30 years. Information on medical history and medication use were collected interview-based. We determined the prevalence of overtreatment (antihypertensive treatment and systolic blood pressure (SBP) <120 mmHg) and undertreatment (SBP ≥140 and/or diastolic blood pressure ≥90 mmHg) of hypertension and quantified determinants for this by using multinomial logistic regression (controlled hypertension as reference). Subsequently, we determined the prevalence of undertreating dyslipidemia (following ESC/ EAS guidelines) in the population aged 40-65 years and quantified determinants for this by using a binomial logistic regression model. We adjusted for age, sex, CVD, chronic kidney disease (CKD), diabetes, Body Mass Index, educational level and income in all models.

Results: Analyses were based on 3,875 out of 4,000 participants. Within the sample of participants with hypertension (n=1,483, mean age 63.8 years, standard deviation (SD) 12.4; 56% women), 12.9% (n=181) were over- and 54% (n=802) were undertreated. With increasing age the odds of overtreatment decreased (OR 0.97 95% confidence interval (95%CI) 0.96-0.98). Higher odds of overtreatment were observed in women compared to men (OR 0.43 95%CI 0.29-0.65) and in individuals with CKD compared to individuals without CKD (OR 2.14, 95%CI 1.25-3.65). Lower odds of undertreatment were observed for individuals with CVD (OR 0.53, 95%CI 0.38-0.74) and diabetes (OR 0.58, 95%CI 0.38-0.87) compared to individuals without the disease. Within the sample of participants with dyslipidemia (n=716, mean age 53.0 years, SD 7.0; 57% women)86.9% (n=622) were undertreated. With increasing age, the odds of undertreatment increased (OR 1.12 95%CI 1.07-1.18). Lower odds of undertreatment were observed in individuals with diabetes (OR 0.14 95%CI 0.07-0.29) and CVD (OR 0.10 95%CI 0.06-0.19) compared to individuals without the disease.

Conclusions: The high prevalence of undertreatment shows a need of optimizing medication use. However, we should be aware of the risk of overtreatment.

4726 | Beta-blockers and initial heart rhythm in out-of-hospital cardiac arrest: A multi-country case-control study

Talip Eroglu[1], Carlo Barcella[2], Michiel Hulleman[1], Asger Granfeldt[3], Patrick Souverein[4], Grimur Mohr[2], Rudolph Koster[1], Mads Wissenberg[2], Anthonius de Boer[4], Christian Torp-Pederson[5], Fredrik Folke[2], Marieke Blom[1], Gunnar Gislason[2] and Hanno Tan[1]

[1]*Amsterdam Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands;* [2]*Herlev and Gentofte Hospital, University of Copenhagen, Gentofte, Copenhagen, Denmark;* [3]*Aarhus University Hospital, Aarhus, Denmark;* [4]*Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands;* [5]*Aalborg University Hospital, Aalborg, Denmark*

Background: Out-of-hospital cardiac arrest (OHCA) is a leading cause of death in Western societies. Survival from OHCA with a non-shockable rhythm (NSR) [asystole, pulseless electrical activity] as initial heart rhythm is very low (2-3%), while survival from OHCA with a shockable rhythm (SR) [ventricular tachycardia/ventricular fibrillation] has increased to approximately 30%. Prior studies examining the association between beta-blockers and NSR reported conflicting results.

Objectives: To evaluate whether use of beta-blockers is associated with NSR as initial rhythm in OHCA.

Methods: We conducted two case-control studies using data from Emergency Medical Services attended OHCA-registries in Denmark and the Netherlands. Cases were patients with NSR following OHCA and controls were patients with SR following OHCA. Beta-blocker use was defined as a prescription 90 days prior to OHCA (the Netherlands) or when the prescription's theoretical end date occurred later than the OHCA-data (Denmark), and was further defined as use of either non-selective beta-blockers, β1-selective beta-blockers or α-β-dual-receptor blockers within 90 days prior to OHCA.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Multivariable logistic regression analyses were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CI) to estimate associations between beta-blockers and NSR compared to no use of any beta-blockers. As covariates we included age, sex, resuscitation factors, cardiovascular disease and diabetes mellitus.

Results: We identified 15 997 cases and 7367 controls in Denmark, and 764 cases and 820 controls in the Netherlands. Compared to no beta-blocker, use of non-selective beta-blockers (Denmark: cases: 2.3%, controls: 1.1%; the Netherlands: cases: 3.8%, controls: 1.7%) was associated with a higher probability of NSR (Denmark: OR 1.86, 95%-CI 1.42-2.44; the Netherlands: OR 2.52, 95% CI 1.15-5.49), whereas use of β1-selective blockers (Denmark: cases: 22.7%, controls: 23.4%; the Netherlands: cases: 27.4%, controls: 28.1%) was not associated with NSR (Denmark: OR 1.04, 95%-CI 0.95-1.13; the Netherlands: OR 0.99, 95% CI 0.74-1.31). Use of α-β-dual-receptor blockers (Denmark: cases: 4.6%, controls: 5.2%; the Netherlands: cases: 2.9%, controls: 1.8%) was significantly associated with NSR in Denmark (OR 1.21; 95% CI 1.03-1.42) and not significantly in the Netherlands (OR 1.37; 95% CI 0.61-3.07).

Conclusions: Non-selective beta-blockers, but not β1-selective beta-blockers, are associated with NSR in OHCA. Further research is needed to explore the role of underlying morbidity on development of (non)shockable rhythms.

4767 | Metabolic surgery and cardiovascular benefits: The consequence of information bias in a real-world evidence study

William Murk[1], Jeremy Rassen[2] and Sebastian Schneeweiss[3]

[1]*Jacobs School of Medicine, University at Buffalo, Buffalo, NY;* [2]*Aetion, Inc, New York, NY;* [3]*Harvard Medical School, Boston, NY*

Background: Aminian et al. recently reported an analysis of electronic health records (EHRs) showing that metabolic surgery is associated with a 39% reduction in the risk of major adverse cardiovascular events (MACE) compared with non-surgery, among obese patients with diabetes (JAMA 2019).

Objectives: We hypothesized that this previous finding is spurious due to differential information bias, since non-surgical controls do not undergo the same pre-diagnostic workup as patients undergoing surgery. To evaluate this, we replicated the original study and then modified its design so that the comparison groups had similar levels of baseline information. This was done by choosing a control group that consisted of patients undergoing an unrelated surgery (total hip/knee replacement) and using high-dimensional propensity score (HDPS) to match patients.

Methods: We conducted a cohort study using the Optum® de-identified Electronic Health Record dataset, an aggregation of inpatient and ambulatory records from 81 million patients between January 2007 through March 2018. Diabetes patients were selected as previously described. We performed an analysis that replicated the original study design, where metabolic surgery patients were compared against risk-set sampled non-surgery controls and matched by propensity score. We then conducted a subsequent analysis where the control group was changed to patients undergoing total hip/knee replacement and a high-dimensional propensity score (HDPS) model was used to match patients. The matched groups included 338 metabolic surgery and 547 hip/knee replacement surgery patients. Outcomes included 6-component MACE (mortality, coronary artery disease, cerebrovascular disease, heart failure, atrial fibrillation, or nephropathy).

Results: The results of Aminian et al. were replicated using the same analytical design (HR [95% CI] for MACE: 0.61 [0.55, 0.69] in the original study vs. 0.67 [0.61, 0.73] in the present study). When the comparison group was changed to patients undergoing hip/knee replacement and HDPS was used, there was no protective effect of metabolic surgery (HR [95% CI]: 0.99 [0.76, 1.30]).

Conclusions: We demonstrated that information bias is the most likely explanation for the substantial cardiovascular benefit reported in the earlier study. Limitations in the present study include a small sample size in the matched comparison groups. Our findings highlight the importance of symmetric comparison groups when working with healthcare data without randomization.

4786 | Epidemiology and treatment of atrial fibrillation in patients with type 2 diabetes mellitus 2001-2016: An electronic database study in the United Kingdom

Hassan Alwafi[1], Ian Wong[1,2], Amitava Banerjee[3,4], Pajaree Mongkhon[5,6], Cate Whittlesea[1], Abdallah Y. Naser[7], Wallis Lau[1,2] and Li Wei[1]

[1]*Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom;* [2]*Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong;* [3]*Institute of Health Informatics, University College London, London, United Kingdom;* [4]*School of Health Sciences, University of Central Lancashire, Preston, United Kingdom;* [5]*Division of Pharmacy Practice, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand;* [6]*Pharmacoepidemiology and Statistics Research Center (PESRC), Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand;* [7]*Faculty of Pharmacy, Al-Isra University, Amman, Jordan*

Background: Diabetes and cardiovascular diseases are often coexistent, and patients with Type 2 diabetes mellitus (T2DM) have an increased risk of Atrial fibrillation (AF). Previous studies that examined the incidence, prevalence and treatment of AF among patients with T2DM are limited.

Objectives: To investigate the prevalence, incidence and treatment of atrial fibrillation (AF) in type 2 diabetes mellitus (T2DM), assess the impact of direct oral anticoagulants (DOACs) introduction on oral anticoagulant (OACs) prescribing rates, and investigate factors associated with warfarin versus DOACs initiation in patients with T2DM and AF.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: The Health Improvement Network (THIN) database (2001-2016), was used to examine the annual prevalence, incidence and treatment of AF in T2DM. The impact of DOACs introduction on OAC prescribing rates were investigated using interrupted time series analysis (ITS). Factors associated with warfarin versus DOACs initiations were also identified using multivariable logistic regression. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results: The prevalence of AF increased from 2.7 (95% confidence intervals (CI) 2.5 - 2.8) in 2001 to 5.0 (4.9 - 5.1) in 2016 per 100 persons, whereas the incidence decreased over the study period from 1.0 (0.9 - 1.1) to 0.7 (0.7 - 0.8) per 100 persons. OACs prescribing within 30-days of AF diagnosis increased from 21.5% in 2001 to 56.8% in 2016. ITS analysis showed that OAC prescribing increased after DOAC introduction (P<0.001), however, no immediate change was observed (P=0.23). Older age (≥75 years old), history of bleeding and chronic kidney disease were strongly associated with DOAC prescriptions.

Conclusions: This study highlighted that there was an increase in prevalence of AF in patients with T2DM during the study period, particularly in both older patients and males. Further studies are warranted to investigate factors contributing to the underuse of OAC in patients with T2DM and AF.

4872 | Characteristics of patients newly diagnosed with atrial fibrillation after ischemic stroke hospitalization

Lu Zhang, Anna Watzker, Tiffany S. Woodworth, Mark Friedman and Joseph Menzin
Boston Health Economics, Boston, MA

Background: Studies suggests up to a quarter of ischemic stroke patients may be subsequently diagnosed with incident atrial fibrillation (AF), which may have been an undiagnosed and treatable risk factor for preventing ischemic strokes. There is limited real world evidence describing these patients.

Objectives: To evaluate the characteristics of patients with ischemic stroke and newly diagnosed AF.

Methods: We identified hospitalized Medicare-enrolled patients aged ≥66 years with primary ischemic stroke diagnosis code from January 1, 2010 to December 31, 2015, in a 5% sample of Medicare claims. Patients had no evidence of commercial enrollment, stroke, or AF in the 365 days prior to hospitalization. We assessed incidence of post-stroke AF diagnoses during a fixed 90-day follow-up window. Patients who died or were disenrolled during this window were excluded. We assessed demographic and clinical characteristics, including Quan Charlson Index (QCI), $CHADS_2$, and CHA_2DS_2-VASc score in the 365-day baseline period, among those with and without post-stroke AF. Statistical significance was tested using T-test and Pearson's chi-squared test.

Results: Among 24,237 patients hospitalized with incident ischemic stroke, 4,583 (18.9%) were newly diagnosed with AF within 90 days. Patients with post-stroke AF diagnoses were older (79.58 vs. 77.77 years, p<0.01) and more likely to be Caucasian (87.89 vs. 83.44%, p<0.01), but exhibited minor differences in comorbidity indices when compared to patients without post-stroke AF diagnoses (QCI: 1.41 vs 1.47, p=0.04; $CHADS_2$: 2.21 vs 2.17, p=0.06; CHA_2DS_2-VASc: 4.05 vs 4.03, p=0.42). However, AF and non-AF patients exhibited differential comorbid conditions included in the scores. In addition to being older, AF patients were more likely to have prevalent congestive heart failure (CHF) (15.95 vs. 12.19%, p<0.01), while non-AF patients were more likely to have prevalent diabetes (33.17 vs. 37.38%, p<0.01).

Conclusions: Consistent with previous studies, our data may indicate nearly one-fifth of stroke patients presented with undiagnosed AF. Based on common risk scores for stroke, patients newly diagnosed with AF after stroke were largely similar to patients that did not have AF. However, comorbid CHF and advanced age appeared to be the most significant differentiating factors between patients with and without post-stroke AF diagnoses. More research is needed to identify candidate predictors for AF, with focus on related factors of CHF, as targeted screening for AF may improve patient outcomes for ischemic stroke.

Disease Epidemiology/Clinical Course -> Diabetes

2533 | Differential risk of Parkinsons disease according to diabetes treatments: A cohort study

Ruth Brauer, Li Wei, Tiantian Ma, Dilan Athauda, Christine Girges, Nirosen Vijiaratnam, Grace Auld, Cate Whittlesea, Ian Wong and Thomas Foltynie
University College London, London, United Kingdom

Background: The elevated risk of Parkinson's Disease (PD) in patients with diabetes might be mitigated depending on the type of drugs prescribed to treat diabetes. Population data for risk of PD in users of the newer types of drugs used in diabetes, ie exenatide, are scarce.

Objectives: To compare the risk of PD in patients with diabetes exposed to thiazolidinediones (glitazones), glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors, with the risk of PD of users of any other oral glucose lowering drugs.

Methods: We conducted a population-based cohort study using primary care data by The Health Improvement Network (THIN). Patients with a diagnosis of diabetes and at least two prescriptions for drugs used in diabetes between January 2006 and January 2019, were included in our study. The index date for each patient was the first prescribing date that qualified them for study entry. The primary outcome was the first recording of a diagnosis of PD after the index date, as identified from clinical records. We compared the risk of PD in individuals treated with glitazones (GTZ) or DPP-4 inhibitors and/or GLP-1 receptor agonists to people treated with other antidiabetic agents using a Cox regression with inverse probability of treatment weighting based on propensity scores. Multiple imputation was used for missing smoking status(1%), alcohol use(2%), BMI(4%) and HbA1c level(3%) prior to the index date.

Results: Among 100,288 patients (mean age 62.8 years [SD 12.6]), 329 (0.3%) were diagnosed with PD during the median follow-up of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3.33 years. The incidence of PD was 8 per 10,000 person years (PY) in 21,175 patients using GTZ, 5 per 10,000 PY in 36,897 patients using DPP-4 inhibitors and 4 per 10,000 PY in 10,684 using GLP-1 mimetics, 6,861 of whom were prescribed GTZ and/or DPP-4 inhibitors prior to using GLP-1 mimetics. Compared with the incidence of PD in the comparison group (10 per 10,000 PY), adjusted results showed no evidence of an association between the use of GTZ and PD in the primary analysis (IRR 1.17; 95% CI 0.76-1.63), but there was strong evidence of an inverse association between use of DPP-4 inhibitors and GLP-1 mimetics and the onset of PD (IRR 0.64; 95% CI 0.43-0.88 and IRR 0.38; 95% CI 0.17-0.60, respectively).

Conclusions: The incidence of PD in patients diagnosed with diabetes varies depending on the treatment for diabetes received. The incidence of PD is nearly two times lower in users of DPP-4 inhibitors and/or GLP-1 receptor agonists compared to users of other oral antidiabetic drugs. Our study provides unique evidence to support further investigation of GTZ, DPP-4 inhibitor and GLP-1 mimetic use in PD.

2546 | Dental resource service utilization among type 2 diabetes patients: A real-world analysis using a linked claims and dental database

Ellen R. Thiel, Kristin Evans, Christopher Gregory and Debra E. Irwin
IBM Watson Health, Cambridge, MA

Background: Type 2 diabetes mellitus (T2DM) is associated with higher risk of dental disease. Differences in dental services utilization between T2DM patients and healthy controls using real world data is underreported in the literature.

Objectives: The aim was to use linked dental and administrative insurance claims to compare dental resource utilization among T2DM patients vs. controls without T2DM.

Methods: A retrospective, case-control design was used to analyze patient dental and medical claims from the IBM® MarketScan® Dental Database linked to the MarketScan Commercial and Medicare Supplemental Databases. The case cohort included adult patients with at least 2 medical claims with diagnoses for T2DM and no claims for type 1 diabetes. The control cohort included adult patients without diabetes diagnoses who were randomly selected from patients enrolled in MarketScan in 2016. During 2015 and 2016, cases and controls were required to be continuously enrolled with medical benefits, and during 2016 both cohorts were continuously enrolled in dental benefits and had at least 1 dental service. Data from 2015 were used to identify baseline demographic and clinical characteristics of the cohorts. Multivariate logistic regression modeling was used to control for differences in baseline characteristics and to evaluate the odds of experiencing at least one dental procedure of a specific type, comparing cases and controls.

Results: The analysis included 140,858 T2DM patients, and 236,811 non-T2DM control patients. Besides diagnostic and preventive visits, the most common dental procedures were restorative services (T2DM 43%; controls 39%), periodontics (T2DM 19%; controls 13%), oral/maxillofacial surgery (T2DM 12%; controls 7%), endodontics (T2DM 7%; controls 6%), and prosthodontics (T2DM 5%; controls 2%). T2DM patients were more likely to have endodontics (OR=1.17; CI 1.14-1.21); periodontics (OR=1.40; CI 1.37-1.43); oral/maxillofacial surgery (OR 1.56; CI 1.52-1.6); prosthodontics (OR 1.80; CI 1.73-1.87); restorative services (OR 1.04; CI 1.03-1.06) compared to controls.

Conclusions: This study provides real-world evidence of the association between T2DM and increased likelihood of dental disease. Future research into the specific T2DM oral health risks may provide valuable insights for prevention strategies.

2678 | Individualized glycemic control in type 2 diabetes in the US and Europe

Dominik Lautsch[1], Euan McLeod[2], Tongtong Wang[1], Swapnil Rajpathak[1], Claudio Gonzalez[1], Seema Malkani[1], Gary Milligan[3], James Jackson[3] and Victoria Higgins[3]
[1]Merck & Co., Inc, Kenilworth, NJ; [2]Pfizer Inc, Tadworth, United Kingdom; [3]Adelphi Real World, Bollington, United Kingdom

Background: Clinical guidelines in type 2 diabetes recommend individualization of glycemic goals, however clinical databases and real-world studies typically do not capture this measure.

Objectives: We used the 2018 Adelphi T2DM Disease Specific Programme (where individualized HbA1c goals are available) to understand the relationship between individual glycaemic goals, factors associated with goal attainment and treatment modification.

Methods: The 2018 Adelphi T2DM Disease Specific Program included a survey involving 730 physicians and 8794 patients in US and 4 European countries (Germany, Italy, Spain, and United Kingdom). Data on age, sex, body mass index (BMI), HbA1c, comorbid medical conditions and prescriptions were collected. Antihyperglycemic treatment regimens included were Metformin, Sulfonylureas (SUs), Thiazolidinediones (TZDs), dipeptidyl peptidase-4 inhibitors (DDP4i), glucagon-like peptide-1 receptor agonist (GLP-1RA), sodium-glucose cotransporter-2 inhibitors (SGLT2i), insulin plus any combination of the above. Patients had been prescribed current antihyperglycemic therapy $\geq$3 months were included in the analysis. Physician-reported target HbA1c values for individual patients were used to assess mean individual HbA1c goal.

Results: Our results suggested that the most recent mean HbA1c was 7.3%, mean individual HbA1c goal was 6.8% [Standard Deviation (SD) =0.69] with 38% patients having achieved their individualized goal. Patients achieving their individual HbA1c goal were older (62 vs 59 years), had lower BMI (29.5 vs 30.3), slightly lower diabetes duration (6.4 vs 6.8 years) or more likely to have chronic kidney disease (8.3% vs 7.5%). Mean HbA1c at diagnosis of type 2 diabetes was 8.4% (SD=1.8). Switch from one line of therapy typically occurred at higher mean HbA1c levels >8%. More specifically, the mean HbA1c in 2,348 patients who switched from 1st line of therapy was 8.3% (SD=1.4%). The mean HbA1c in 624 patients who switched from 2nd line of therapy was 8.4%

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(SD=1.3%). The mean HbA1c in 126 patients who switched from 3rd line of therapy was 8.5% (SD=1.6%). The mean HbA1c in 17 patients who switched from 4th line of therapy was 9.3% (SD=1.8%).

Conclusions: The mean individualized HbA1c goal was 6.8% and was attained by 38% of the patients. Switch from one line of therapy typically occurred at higher mean HbA1c levels >8%.

3694 | Metabolic factors and lifestyle habits associated with prevalence of polyneuropathy in early type 2 diabetes: A cross-sectional study of 5,249 patients in the Danish DD2 cohort

Diana H. Christensen[1,2], Søren T. Knudsen[3], Sandra S. Gylfadottir[2,4,5], Lotte B. Christensen[1], Jens S. Nielsen[6], Henning Beck-Nielsen[6], Henrik T. Sørensen[1], Henning Andersen[2,4], Brian C. Callaghan[2,7], Eva L. Feldman[2,7], Nanna B. Finnerup[2,4,5], Troels S. Jensen[2,4,5] and Reimar W. Thomsen[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark; [2]International Diabetic Neuropathy Consortium, Aarhus University, Aarhus N, Denmark; [3]Steno Diabetes Center Aarhus (SDCA), Aarhus University Hospital, Aarhus N, Denmark; [4]Department of Neurology, Aarhus University Hospital, Aarhus N, Denmark; [5]Danish Pain Research Center, Aarhus University, Aarhus N, Denmark; [6]Danish Center for Strategic Research in Type 2 Diabetes (DD2), Odense University Hospital, Odense, Denmark; [7]University of Michigan, Ann Arbor, MI

Background: Diabetic polyneuropathy (DPN) has a lifetime prevalence of up to 50% in type 2 diabetes, and many patients experience pain. The effectiveness of neuropathic pain medications is limited, and prevention of DPN and neuropathic pain is therefore crucial. High body mass index increases risk of DPN, whereas knowledge on other metabolic and lifestyle risk factors is sparse and conflicting.

Objectives: To examine the association of central obesity, other metabolic factors, and lifestyle habits with DPN and neuropathic pain in patients with early type 2 diabetes.

Methods: We characterized 6,726 patients with recently diagnosed diabetes enrolled into the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort according to metabolic factors and lifestyle habits using both primary collected data and register data. After a median of 2.8 years, we sent a detailed questionnaire on neuropathy, including the Michigan Neuropathy Screening Instrument questionnaire (MNSIq) to identify possible DPN (score ≥4) and the Douleur Neuropathique en 4 Questions (DN4) questionnaire for associated possible neuropathic pain (MNSIq ≥4 + pain in both feet + DN4-score ≥3). We used log-binomial and Poisson regression analyses to calculate age, sex, and diabetes duration-adjusted prevalence ratios (aPRs) of DPN and of painful DPN associated with the risk factors of interest.

Results: Among 5,249 patients with data on both DPN and pain, 17.9% (n=938) had DPN, including 7.4% (n=386) with neuropathic pain. Central obesity (waist circumference, waist-hip ratio, and waist-height ratio) was markedly associated with DPN. Other important metabolic factors associated with DPN included hypertriglyceridemia ≥1.7 mmol/L: aPR 1.36 (1.17; 1.59), decreased HDL cholesterol <1.0/1.2 mmol/L (male/female): aPR 1.35 (1.12; 1.62), high-sensitive CRP ≥3.0 mg/L: aPR 1.66 (1.42; 1.94), C-peptide ≥1,550 pmol/L: aPR 1.72 (1.43; 2.07), HbA1c ≥78 mmol/mol: aPR 1.42 (1.06; 1.88), and antihypertensive drug use: aPR 1.34 (1.16; 1.55). Smoking: aPR 1.50 (1.24; 1.81) and lack of physical activity (0 vs ≥3 days/week): aPR 1.61 (1.39; 1.85) were also associated with DPN. Among patients with DPN, smoking, high alcohol intake, and failure to increase physical activity after diabetes diagnosis associated with neuropathic pain.

Conclusions: We found strong evidence that metabolic syndrome factors, insulin resistance, and inflammation are associated with DPN in type 2 diabetes. Unhealthy, modifiable lifestyle habits associate with both DPN and neuropathic pain.

3706 | Polyneuropathy in early type 2 diabetes is associated with higher risk of subsequent cardiovascular disease: Evidence from the Danish centre for strategic research in type 2 diabetes (DD2) cohort

Sia Kromann Nicolaisen[1], Lasse Bjerg[2,3], Diana Hedevang Christensen[1], Reimar Wernich Thomsen[1], Jens Steen Nielsen[4,5], Signe Toft Andersen[2,6], Henning Beck-Nielsen[4,5], Troels Staehelin Jensen[6,7], Annelli Sandbæk[2,3], Daniel Witte[2,3] and Morten Charles[3,8]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Public Health, Aarhus University, Aarhus, Denmark; [3]Steno Diabetes Center Aarhus, Aarhus, Denmark; [4]DD2, Steno Diabetes Center Odense, Odense, Denmark; [5]Research Unit of Steno Diabetes Center Odense, University of Southern Denmark, Odense, Denmark; [6]Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [7]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; [8]Research Unit of General Practice, Aarhus University, Aarhus, Denmark

Background: Diabetic polyneuropathy (DPN) may be associated with subsequent risk of cardiovascular disease (CVD) and mortality in patients with early type 2 diabetes (T2D), but evidence is sparse.

Objectives: We used follow-up data in the DD2 research database to compare the risks of CVD and mortality among T2D patients with and without DPN.

Methods: Patients were assessed for DPN by a neuropathy questionnaire survey conducted in 2016 in the DD2 cohort of recently diagnosed T2D patients and linked to Danish prospective national healthcare registries. A score ≥4 on the Michigan Neuropathy Screening Instrument questionnaire (MNSIq) indicated DPN. We defined CVD as hospitalization with ischemic heart disease, stroke, peripheral artery disease, or heart failure. We followed the patients from the time of the neuropathy questionnaire survey and calculated adjusted incidence rate ratios (IRRs) of CVD and mortality using Poisson regression with adjustment for age, sex, HbA1c, BMI, smoking, alcohol consumption, LDL-cholesterol, systolic blood pressure, antihypertensive and lipid lowering medication, diabetes duration, albumin-creatinine-ratio, and prior cardiovascular event.

Results: A total of 5,028 T2D patients were included in the study. Median diabetes duration at the time of the questionnaire was 4.6 (IQR

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3.5-5.7) years. In total, 818 (16.3%) patients had DPN. Patients with DPN were slightly younger than those without DPN (median 62.3 [IQR 54.8-70.1] vs. 65.7 [IQR 57.2-71.2] years) and a larger proportion were women (47.2 vs. 41.1%). Among patients with DPN, 30.3% had a prior cardiovascular event versus 19.7% of patient without DPN. Use of cardiovascular drugs was higher for antihypertensive drugs (75.8 vs. 72.7%) and aspirin (26.0 vs 21.9%) among patients with DPN, but lower for lipid-lowering drugs (70.8 vs. 72.3%). During a median of 2.2 (IQR 2.2-2.2) years of follow-up, 10.8% of the patients were diagnosed with CVD and 5.0% died. After adjustment, the risk of CVD was 57% (IRR 1.57 [95% CI 1.27-1.94]) and mortality was 20% (IRR 1.20 [95% CI 0.76-1.89]) higher in individuals with DPN compared to those without. Sensitivity analyses among patients without a history of CVD and complete case analyses showed similar results.

Conclusions: We found that DPN defined by MNSIq ≥4 associates with significantly higher risk of CVD after adjustment for well-known CVD risk factors. Notably, these associations were found in patients with early T2D emphasizing the importance of screening for this neglected diabetic complication.

3725 | Sex differences in the risk of diabetes mellitus among individuals with psoriasis

Raymond Milan[1], Jacques LeLorier[2], Ivan Litvinov[1], Kaberi Dasgupta[1] and Elham Rahme[1]

[1]McGill University, Montreal, QC, Canada; [2]Université de Montréal, Montreal, QC, Canada

Background: The choice of therapy for managing psoriasis varies according to its severity. It is also well established that psoriasis severity is associated with diabetes mellitus (DM) and severe psoriasis is more common in male than female individuals. However, sex differences in the risk of DM among individuals with psoriasis has not been examined.

Objectives: We assessed the risk of DM by psoriasis severity and identified predictors in male and in female individuals with psoriasis.

Methods: We conducted a retrospective cohort study using Quebec health administrative databases (1997 - 2015). Individuals ages ≥20 years were included if they received a first psoriasis diagnosis in 2000 - 2012 (Index date, ID), and either a second diagnosis or ≥1 claim for psoriasis treatment anytime afterward (N=27,582). Those who received a psoriasis treatment in the prior year, and those with a DM diagnosis in the prior or following year were excluded (to consider delays in DM diagnosis). Psoriasis treatments served as surrogates for disease severity: untreated, mild (topical agents), moderate (phototherapy), severe [conventional systemic agents (CSA) and biologic agents]. This definition was used as a time-varying exposure. DM was defined as 2 outpatient visits within 2 years or 1 hospitalization with a principal or secondary diagnosis for DM. Time-dependent multivariate Cox regression models (with 12-month lag) were used. Analyses were stratified by sex. Sensitivity analyses were conducted using other definitions for DM, different lag periods, and censoring individuals receiving methotrexate and cyclosporine because of their possible association with DM.

Results: This study included 11,236 individuals with psoriasis (52.4% females). DM incidence was higher in males (20/1000 person-years vs 17/1000 person-years for females). DM risk increased with psoriasis severity in both sexes (severe vs untreated individuals: hazard ratio; 95% CI: males 2.16, 1.44-3.25; and females 2.27, 1.42-3.63). The effect of age on DM differed between sexes and psoriatic arthritis was associated with DM only in male individuals (1.57, 1.10-2.24). Results were robust in most sensitivity analyses, except for censoring both CSA in which severe psoriasis was not associated with DM in both sexes.

Conclusions: Psoriasis severity, defined by the treatment received, is associated with DM in both males and females. Screening for DM should be considered for both sexes with high psoriasis severity and for male individuals with psoriatic arthritis.

3729 | Using Rwd to assess changes in GFR among DKD patients and the rate of heart failure

Seth Kuranz and Christian Haudenschild

TriNetX, Inc, Cambridge, MA

Background: Electronic medical records (EMRs) are a rich source of clinical data for the examination of disease progression in diabetic kidney disease (DKD) patients. EMR networks do not always have a clear source population or definition of time at risk.

Objectives: The objectives of this analysis were to examine glomerular filtration rate (GFR) as a predictor of heart failure (HF) among DKD patients, and to assess the impact of varying person time (PT) definitions.

Methods: The study was conducted using a US-based federated EMR network of 38M patients. DKD was defined as type 2 diabetes patients aged 20+ with an incident CKD diagnosis between 2015-2019 (index event (IE)). Patients were excluded if they had a kidney transplant, end stage renal disease, heart failure, or were deceased prior to or in the first year after the IE. Of those patients at risk for the outcome (n=76,240), 30,704 patients had at least one MDRD defined GFR measure in the year before and after the IE. Patients with increasing or decreasing GFR was further stratified by healthy (GFR ≥ 60 units) and unhealthy (15 ≤ GFR < 60 units) kidney function and categorized as follows: no change healthy (reference); no change unhealthy; increase from unhealthy to healthy; increase and remain unhealthy; decrease from healthy to unhealthy; decrease and remain unhealthy. The outcome was defined as the first HF diagnosis at least 1 year following the IE. Crude rate ratios (RRs) and differences (RDs) and 95% CIs were calculated. A Poisson regression model was used to calculate RRs adjusting for baseline confounders. The analyses were repeated with three varied definitions of PT, which involved adding 30-, 183-, and 365-day windows before and after each visit in the EMR during follow up. All patient characteristics were defined by ICD, LOINC, CPT, or RxNorm terminology.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Patients were 48% female with a mean age between 65 (12) and 71 (10) at the IE. In the unadjusted analyses, assuming a 30-day PT window, patients whose GFR decreased from healthy to unhealthy or decreased and remained unhealthy had 1.6 (1.2-2.2) and 1.5 (1.1-2.0) times the rate of HF. Accompanying RDs found 4.7 and 3.7 more cases of HF per 100,000 person days. Adjusted models [RR:1.4 (1.0-1.8); RR:1.1 (0.8-1.5), respectively] and increases in the PT window consistently attenuated results.

Conclusions: Patients whose GFR decreased from healthy to unhealthy levels experienced the highest rate of HF with PT definitions strongly influencing the results. Researchers should clearly communicate assumptions around PT definitions and further analyses should continue to explore necessary assumptions when using EMR networks.

3962 | Statin therapy and risk of polyneuropathy in type 2 diabetes: A population-based cohort study

Frederik Pagh Kristensen[1,2], Diana Hedevang Christensen[1,2], Brian Callaghan[2,3], Søren Tang Knudsen[4], Søren H. Sindrup[2,5], Eva L. Feldman[2,3], Leif Østergaard[2,4], Henning Andersen[2,6], Troels Staehelin Jensen[2,6], Henrik Toft Sørensen[1] and Reimar Wernich Thomsen[1]

[1]Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark; [2]International Diabetic Neuropathy Consortium, Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark; [3]University of Michigan, Ann Arbor, MI; [4]Aarhus University Hospital, Aarhus, Denmark; [5]Odense University Hospital, Odense, Denmark; [6]Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

Background: 50% of all diabetes patients may experience diabetic polyneuropathy (DPN) during their life with diabetes. Statin therapy may prevent DPN through lipid-lowering and anti-inflammatory effects, or increase DPN risk through neurotoxic effects.

Objectives: To investigate the impact of statin therapy on risk of development of DPN.

Methods: We conducted a 15-year, population-based cohort study by linking medical health databases to include all Danish, first-time diabetes patients <30 years from 2002-2016. First diabetes record was defined as either a first-time hospital contact for diabetes or a first-time glucose-lowering drug prescription. New statin users filled their first statin prescription between 180 days before and 180 days after their first diabetes record. Prevalent statin users filled statin prescriptions both during and before this period. DPN was defined by a validated algorithm based on ICD-10 hospital diagnosis codes (positive predictive value = 74%). We followed patients from 180 days after first diabetes record (index date) until first-time DPN, death, emigration, or study end. We used Cox proportional hazard regression analysis to compute hazard ratios (aHRs) controlling for confounding factors.

Results: The type 2 diabetes study population consisted of 59,255 (22.8%) new statin users, 75,528 (29.0%) prevalent users, and 124,842 (48.1%) statin non-users. Patients were followed for a median of 6.7 years (IQR 3.4-9.6 years). Incidence rates of DPN per 1000 person-years were similar in new users (4.0 events), prevalent users (3.7 events) and statin non-users (3.8 events). The aHR for DPN was 1.05 (95% CI, 0.98-1.11) in new users, and 0.97 (95% CI, 0.91-1.04) in prevalent users, as compared with statin non-users. There was an increased DPN risk in new statin users during the first year (aHR 1.30 (95% CI, 1.12-1.53)) that disappeared after ≥2 years of follow-up, suggesting either detection bias or an early detrimental effect of statins. For new statin users, the overall null-association persisted in propensity score matched analyses (HR 1.02 (95% CI, 0.93-1.12)) and in a subgroup of patients after additional adjustment for baseline blood lipids (aHR 1.04 (95% CI, 0.92-1.19)). Additional on-treatment analyses showed a slightly increased DPN risk in new statin users (aHR 1.17 (1.09-1.27)), however, this was mainly restricted to the first year (aHR 1.42 (95% CI, 1.21-1.68)).

Conclusions: Statin therapy was not associated with reduced or increased risk of subsequent DPN in type 2 diabetes.

3979 | Daily lifestyle behaviors associated with initiating of renal replacement therapy in Japanese patients with chronic kidney disease: A descriptive study using a claims database linked with specific health checkup results

Kazuaki Enomoto[1], Azusa Hara[1], Nanae Tanemura[1], Takumi Hirata[2], Tomonori Okamura[1] and Hisashi Urushihara[1]

[1]Keio University, Tokyo, Japan; [2]Hokkaido University Faculty of Medicine, Sapporo, Japan

Background: A chronic kidney disease (CKD) eventually progresses to end-stage renal disease, requiring dialysis or kidney transplantation. It is important to explore the prognostic factors associated with the progression of CKD to prevent initiation of renal replacement therapy.

Objectives: We investigated the effects of the daily lifestyle behaviors on the initiation of renal replacement therapy among CKD patients using an employment-based large-scale claims database linked with specific health checkups (SHC) data.

Methods: This retrospective study included 149,620 CKD patients aged 40-74 years who took SHC between April 2008 and March 2016 from the Japanese claims database. CKD patients were identified using ICD-10 codes and/or according to the following information obtained from the SHC data; eGFR less than 60 ml/min per 1.73 m^2 or the presence of positive proteinuria in a urine sample. We investigated the 11-item daily lifestyle behaviors recorded in the questionnaire survey at annual SHC, including current smoking, regular exercise, regular walking, walking speed, frequent breakfast-skipping, eating speed, eating dinner late, frequent snacking, alcohol drinking frequency, alcohol consumption, and sleep quality. Initiation of renal replacement therapy was defined by medical procedure claims. Cox proportional hazards regression model with recency-weighted cumulative exposure as a time-dependent covariate was employed to identify daily lifestyle behaviors related to the initiation of renal replacement therapy.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: During 384,042 patient-years of follow-up by the end of March 2016, 295 dialysis and no kidney transplantation cases were identified. In time-dependent Cox regression models, frequent breakfast-skipping (hazard ratio [HR]: 9.28, 95% confidence interval [CI]: 2.81, 30.61), frequent snaking (HR: 7.20, 95%CI: 1.96, 26.43), drinking sake three glasses and more per day compared with those less than 1 glass of sake (HR: 14.04, 95%CI: 1.41, 139.62), and sleep quality (HR: 2.72, 95%CI: 1.09, 6.77) were associated with initiating renal replacement therapy.

Conclusions: Among CKD patients, daily lifestyles of skipping breakfast, snaking, heavy drinking, and sufficient sleep were independent predictors for initiating renal replacement therapy. Our study suggests that improving such daily lifestyles might delay the progression of CKD to prevent initiation of renal replacement therapy in the Japanese working generation.

4150 | Age- and sex-specific incidence of non-traumatic lower limb amputation in patients with type 2 diabetes mellitus in a claims database from the United States

Sampada Gandhi, Chuntao Wu, Maximiliano Waschbusch, Madlen Michael, Meng Zhang, Xinyu Li and Juhaeri Juhaeri
Sanofi, Bridgewater, NJ

Background: There is limited data on age- and sex-specific incidence rates (IR) of lower limb amputation (LLA) in patients with type 2 diabetes mellitus (T2DM). These data can be used to support the understanding of this risk associated with the use of newer antidiabetic agents (ADA).

Objectives: To estimate age- and sex-specific IRs of LLA in T2DM patients using a U.S. claims database for years 2007 to 2018.

Methods: Using a retrospective cohort study design, patients with T2DM who were 18 years and older and met one of the following criteria were identified during a study period from January 1, 2007 to September 30, 2018 from the Truven MarketScan database: (1) at least 2 diagnoses of T2DM and <=1 diagnosis of T1DM defined using ICD-9 or ICD-10 diagnosis codes, or (2) at least 1 diagnosis of T2DM, at least 1 claim for oral or injectable ADA, and <=1 diagnosis of T1DM. The index date for a patient was defined as the date of first diagnosis code of T2DM or date of first dispensing of ADA, whichever occurred first. All events of non-traumatic LLA occurring from the index date until the end of the study period were identified by the presence of ICD-9 or ICD-10 procedure codes. Patients were followed until the end of the study period or enrollment in the database, whichever occurred first. An overall and age- and sex-specific IRs per 1,000 person-years (PY) of LLA and their 95% confidence intervals (CIs) were calculated.

Results: Of the 6,117,981 T2DM patients identified during the study period, 52.0% were males, and 58.7% of the patients were in the age ranges of 50-69 years, with 14.0% 70 years and older. Of the 14,627 LLA events, 72.8% were minor LLA (at or below the ankle) and 27.2% were major LLA (above ankle). The overall IR (95% CI) of LLA, minor LLA, and major LLA per 1,000 PY were 0.86 (0.85, 0.88), 0.63 (0.62, 0.64), and 0.23 (0.23, 0.24), respectively. When stratified by sex, males had a higher IR compared to females regardless of the type of LLA [Overall: 1.24 (1.22, 1.26) Vs. 0.46 (0.45, 0.48); Minor: 0.92 (0.90, 0.94) Vs. 0.32 (0.31, 0.33); Major: 0.32 (0.31, 0.33) Vs. 0.14 (0.14, 0.15)]. When stratified by age and sex, an increase in overall LLA incidence was observed in both males and females with an increasing age, with the highest incidence reported in patients aged ≥80 years [Males: 1.91 (1.77, 2.05); Females: 1.02 (0.93, 1.11)]. A similar pattern was observed for both minor and major LLA.

Conclusions: In patients with T2DM, the majority of the non-traumatic LLA events were minor. The incidence rate of LLA increased with an increasing age and was higher among males compared to females.

4228 | Cardiorenal disease is the most common first cardiovascular manifestation in type 2 diabetes and associated with increased mortality

Jetty A. Overbeek[1], Esmé Lighaam[2], Gerard C.M. Linssen[3], Ron M.C. Herings[1,4] and Johan Bodegård[5]
[1]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands; [2]AstraZeneca, The Hague, Netherlands; [3]Hospital Group Twente, Almelo and Hengelo, Netherlands; [4]VU University Medical Center, Amsterdam, Netherlands; [5]AstraZeneca, Oslo, Norway

Background: Cardiorenal disease, defined by heart failure (HF) or chronic kidney disease (CKD), is a serious cardiovascular disease (CVD) complication among patients with type 2 diabetes (T2D). Several recent trials in T2D have shown significant reduced risk of cardiorenal disease during treatment with a sodium-glucose cotransporter-2 (SGLT-2) inhibitor. However, data on cardiorenal disease among T2D patients without established CVD is scarce.

Objectives: To determine the cardiorenal disease manifestation and, second, its associated mortality risks in T2D patients without CVD and renal disease, referred to as CVD-free patients.

Methods: In this observational study, all prevalent patients aged ≥18 years with at least two blood glucose lowering drug prescriptions prior to index date (i.e. 1st January 2012) were included and those with less than 12 months of medical history, T1D or gestational diabetes were excluded. In the Dutch PHARMO Database Network, patients without diagnoses of CVD or renal disease were defined as CVD-free. Firstly, CVD manifestation was determined by the first event of stroke, myocardial infarction (MI), peripheral artery disease (PAD) and cardiorenal disease. Secondly, we compared patients with a single diagnosis of HF, CKD, MI, stroke or PAD with CVD-free patients. Age and sex adjusted Cox regressions were used for risk estimations.

Results: Of 46,451 T2D patients; 36,903 (79%) were identified as CVD-free at index date and followed for a mean period of 4.6 years. Of the 4,498 (12.2%) T2D patients who developed a CVD during follow-up, cardiorenal disease was most common (57%; 23% HF and 35% CKD), followed by MI (17%), PAD (13%) and stroke (12%).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Compared with the CVD-free group, HF was associated with increased risk of CKD (HR 1.60 [95%CI: 1.06-2.42]), and CKD was numerically associated with increased risk of HF (HR 1.28 [95%CI: 0.74-2.22]). Cardiorenal disease, HF, CKD and HF+CKD were associated with increased risk of all-cause mortality, HR 2.48 (95%CI: 2.17-2.83), HR 2.73 (95%CI: 2.29-3.25), HR 2.18 (95%CI: 1.77-2.67), HR 4.08 (95%CI: 2.57-6.49), respectively, compared to CVD-free T2D.

Conclusions: In T2D patients without a history of cardiovascular or renal disease, cardiorenal disease was the most common first CVD manifestation and was associated with significantly increased risk of all-cause mortality. Cardiorenal disease is an important early complication in T2D that should be considered when choosing optimal preventive strategies.

4272 | The pharmo diabetes, management, and treatment (DIAMANT) cohort: A population-based cohort of people with type 2 diabetes

Jetty A. Overbeek[1], Louise Lemmens[1], Amber A.W.A. van der Heijen[2], Giel Nijpels[2] and Ron M.C. Herings[1,2]

[1]*PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands;* [2]*VU University Medical Center, Amsterdam, Netherlands*

Background: Despite better awareness and new developments in treatment of diabetes and prevention of type 2 diabetes (T2D), the number of persons with diabetes continues to rise. This increasing prevalence and the still unclear long-term safety and effectiveness of new and old blood glucose lowering treatments, stresses the need for more pharmacoepidemiological studies. A prospective, regularly updated cohort of people with T2D would provide quick and up to date-information regarding prevalence, treatment, long-term safety and effectiveness.

Objectives: To study the cohort profile of the PHARMO Diabetes, MANagement and Treatment (DIAMANT) cohort.

Methods: All people with T2D in the PHARMO Database Network are selected from the Out-patient Pharmacy (1998-2018) and the General Practitioner (GP) Database (2009-2018). T2D is defined as ≥2 dispensings/prescriptions for a non-insulin drug used to treat diabetes or a GP recorded diagnosis of T2D. The date of the second dispensing/prescription or the first GP recorded diagnosis, whichever occurred first, is defined as the index date. All patients are followed from index date until the end of the study period, data availability, or death, whichever occurred first. Patients are characterised in terms of demographics, medication use, comorbidities, and laboratory measurements.

Results: During 1998-2018, the DIAMANT cohort increased from 86,571 people in 1998 to 504,046 people in 2018. Overall, the mean (±SD) follow-up was 7.6 (± 5.0) years. In 2018 mean (±SD) age was 69 (±14) years and 48% was female. The most commonly used blood glucose lowering drug was metformin (58%), followed by sulfonylureas (27%) and insulin (19%). GLP-1 receptor agonists, DPP-4 and SGLT-2 inhibitors were used among 1.3%, 3.4% and 1.6% patients with T2D, respectively. The most common comorbidities reported were renal impairment and albuminuria/proteinurian The mean (±SD) BMI in 2018 was 29.7 (±5.3) kg/m^2 and 68% was current or former smoker. The mean (±SD) HbA1c in 2018 was 54 (± 12) mmol/mol. The mean (±SD) lipid values were 4.4 ± 1.0 mmol/l (total cholesterol), 2.4 ± 0.9 mmol/l (LDL), 1.21 ± 0.35 mmol/l (HDL), and 1.9 ± 1.2 mmol/l (triglycerides).

Conclusions: The PHARMO DIAMANT cohort provides the opportunity to gain real-world insights into the course of diabetes and treatment effects among people with T2D in daily practice. Furthermore, this cohort can be used for other unique purposes as well, such as linkage to other databases to study other questions and predictive analytics to support direct patient care.

4321 | Factors related to sodium glucose cotransporter 2 inhibitor (SGLT2i) and dipeptidyl peptidase 4 inhibitor (DPP4i) dispensing among naive, incident, and prevalent new users

Yandong Qiang[1], Casie H. Horgan[2], Andrew B. Petrone[2], Joy Kolonoski[2], Aaron Hansbury[2], Christian Hampp[1], Sarah Dutcher[1], Sruthi Adimadhyam[2] and Sengwee Toh[2]

[1]*Food and Drug Administration, Silver Spring, MD;* [2]*Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA*

Background: Observational studies with prevalent new users have been proposed to improve statistical power and generalizability. Failure to account for differences in characteristics among different types of new users may compromise internal validity.

Objectives: To identify factors related to SGLT2i dispensing among naïve, incident, and prevalent new users.

Methods: We identified type 2 diabetes patients in 8 Sentinel data partners with a dispensing of SGLT2i or DPP4i in 2013-2018. We classified patients as naïve users if they had no dispensing of any non-metformin (NM) antihyperglycemic agents (AHA) in the prior 365 days, incident new users if they had no baseline use of both SGLT2i and DPP4i, and prevalent new users if they were free of the cohort-defining drugs at baseline. We assessed factors related to the dispensing of SGLT2i over DPP4i among these types of users.

Results: During the study period, 93,369, 313,900, and 427,307 SGLT2i users were naïve, incident, and prevalent, respectively, as were 280,694, 723,705, and 758,232 DPP4i users, respectively. Among SGLT2i prevalent users, 27% had baseline DPP4i and 22% were naïve users. Among DPP4i prevalent users, 5% had baseline SGLT2i and 37% were naïve. On average, SGLT2i users were 6.9, 6.6. and 5.6 years younger than DPP4i users in the naïve, incident, and prevalent cohorts, respectively. The mean adapted Diabetes Complications Severity Index difference between SGLT2i and DPP4i users was 0.7 in the naïve users and 0.6 in both the incident and prevalent users. The imbalances in baseline covariates between SGLT2i and DPP4i weakened from naïve to incident and prevalent users. Compared to the DPP4i users, prevalent SGLT2i users were more likely to have prior use of thiazolidinedione (TZD, odds ratio [OR]=1.39; 95% confidence

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

interval=1.38-1.41), glucagon-like peptide 1 agonist (GLP1, OR=4.40; 4.34-4.46), short-acting (SI, OR=1.87; 1.85-1.90), and long-acting insulins (LI, OR=1.89; 1.88-1.91); while incident SGLT2i users were less likely to have prior use of sulfonylureas (OR=0.89; 0.88-0.90) but more likely to have prior TZD (OR=1.30; 1.28-1.32), GLP1 (OR=5.76; 5.68-5.85), SI (OR=2.23; 2.20-2.27), and LI (OR=2.16; 2.14- 2.18).

Conclusions: Baseline characteristic imbalances between SGLT2i and DPP4 initiators varied between naïve, incident, and prevalent new users. Prior NM AHA use played an important role in the choice of SGLT2i over DPP4i. Proper design and analytic approaches addressing these imbalances require consideration in epidemiologic studies including all new users.

4363 | The pattern of incident fractures in patients with newly diagnosed type 2 diabetes mellitus

Johanna H.M. Driessen[1], Cindy Sarodnik[2], Nicklas H. Rasmussen[3], Sandrine P.G. Bours[1], Nicolaas C. Schaper[1], Peter Vestergaard[3], Patrick C. Souverein[4], Morten Jensen[3], Frank de Vries[1] and Joop P.W. van den Bergh[5]

[1]Maastricht University Medical Centre, Maastricht, Netherlands; [2]Maastricht University, Maastricht, Netherlands; [3]Aalborg University Hospital, Aalborg, Denmark; [4]Utrecht Institute of Pharmaceutical Sciences, Utrecht, Netherlands; [5]Viecuri Medical Center, Venlo, Netherlands

Background: Fracture risk is associated with an increased risk of mortality and morbidity, e.g. hip fractures have been associated with an excess mortality risk of more than 30%. Patients with type 2 diabetes mellitus (T2DM) are at an increased risk of fracture. However, it is unclear whether fracture risk is already increased in patients with newly diagnosed T2DM, whether this risk differs across fracture locations and whether this is different for men and women.

Objectives: To study fracture risk according to location and sex in patients with newly diagnosed T2DM compared to matched controls.

Methods: A population-based retrospective cohort study using data from the UK Clinical Practice Research Datalink (CPRD) GOLD was conducted. All patients aged 30 year and older with a T2DM diagnose code and a first ever prescription of a non-insulin anti-diabetic drug (NIAD) between 1987 and 2017 were included. Each patient was matched by year of birth, sex and practice to one control. The date of the first NIAD prescription determined the index date and this date was also assigned to the matched control. Patients were followed from their index date up to the date of death, end of data collection, end of study period, or the date of the fracture of interest, whichever came first. Fractures were identified using Read codes and broken down by location. Fracture location and sex specific incidence rates (IRs) and incidence rate ratios (IRRs) were calculated using a Poisson model and Wald confidence limits.

Results: We included 124,328 patients with T2DM and 124,328 matched controls (44% women, mean age 63 years, mean follow-up 7.5 years). The overall fracture IR was lower in patients with newly diagnosed T2DM as compared to controls (IRR: 0.97; 95% confidence interval (CI): 0.94-0.99). The IR of a major osteoporotic (IRR: 0.93; 95%CI: 0.89-0.97), clavicle (IRR: 0.67; 95%CI: 0.56-0.80), radius/ulna (IRR: 0.81; 95%CI: 0.75-0.86) and vertebral (IRR: 0.83; 95%CI: 0.75-0.92) fracture was also lower in patients with T2DM as compared to controls. In contrast, the IR of an ankle (IRR: 1.16; 95%CI: 1.06-1.28), foot (IRR: 1.11; 95% CI: 1.01-1.22), humerus (IRR: 1.11; 95% CI: 1.03-1.20) and tibia/fibula (IRR: 1.17; 95% CI: 1.03-1.32) fracture was higher in patients with T2DM as compared to controls. Similar results were found in women. While in men only clavicle (lower) ankle and foot (both higher) fracture IRs were significantly different as compared to controls.

Conclusions: Fracture incidence rates differ per fracture location and by sex when comparing patients with T2DM to controls, with a higher incidence of fractures at the lower extremities and the humerus.

4391 | Ethnic differences in statin prescribing for people with type 2 diabetes

Sophie V. Eastwood[1], Rohini Mathur[2], Liam Smeeth[2], Krishnan Bhaskaran[2] and Nishi Chaturvedi[1]

[1]University College London, London, United Kingdom; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: In the UK, people of South Asian and African Caribbean descent have higher rates of type 2 diabetes (T2DM) complications (e.g. cardiovascular disease [CVD]) than European-origin people. Poorer risk factor control may contribute. UK guidelines recommend statin treatment for primary prevention at ≥10% 10 year CVD risk in people with T2DM.

Objectives: To assess ethnic differences in statin prescribing in T2DM.

Methods: Primary care cross-sectional study using the Clinical Practice Research Datalink. Prevalent T2DM was algorithmically defined, high CVD risk designated by a 10 year risk score≥10% in the absence of prevalent CVD, and statin use (any timepoint) ascertained from medication records. Associations between ethnicity and statin use were studied using logistic regression models, firstly for all people with T2DM and secondly for those with high CVD risk. Models were adjusted for: age, gender, ever smoking, anti-hypertensive use and prevalent CVD (whole sample only). Analyses were stratified by gender, practice location and age group.

Results: A total of 152,499 (87%) European, 15,978 (9%) South Asian and 6,555 (4%) African Caribbean people with T2DM were identified. South Asians and African Caribbeans were younger than Europeans (median ages: 62, 61 and 71 yrs) and more likely to be in London, but less likely to have smoked, taken antihypertensives or have CVD. Rates of CVD risk score recording (38-40%) did not differ by ethnicity. Comparable proportions of South Asian and European people were prescribed statins (OR [95% CI] in an age- and gender-adjusted model: 0.99 [0.95,1.03], after further adjustment for smoking, antihypertensives and CVD: 1.14 [1.09,1.19]). Results were similar for the high

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

CVD risk group. However, marked differences in statin prescribing were seen between African Caribbean and European people, with the former group being about 40% less likely to receive a statin, regardless of CVD risk (African Caribbean vs. European ethnicity ORs in T2DM population: 0.57 [0.53,0.60] in an age- and gender-adjusted model and 0.60 [0.57,0.64] in the fuller model; ORs in the high CVD risk population: 0.60 [0.53,0.68] and 0.58 [0.51,0.66] respectively). Patterns were identical in all strata of age, gender and location.

Conclusions: African Caribbean people with T2DM are substantially less likely than their European counterparts to be prescribed statins, regardless of 10 year CVD risk. Statin prescribing did not differ between South Asians and Europeans. Further research should focus on explanations and informing policy to address ethnic differences in prescribing and ultimately diabetes outcomes.

4458 | Impact of policy changes on the delivery of community medication review services among adults with diabetes in Ontario

Ahmad Shakeri[1], John-Michael Gamble[2], Lori MacCallum[1], Lisa Dolovich[1], Nancy He[1] and Suzanne M. Cadarette[1]
[1]University of Toronto, Toronto, ON, Canada; [2]University of Waterloo, Kitchener, ON, Canada

Background: Adults with diabetes often take multiple medications to manage not only hyperglycemia, but also hypertension, hyperlipidemia and other comorbidities. The risk of drug therapy problems is therefore substantive and medication reviews are one method to optimize the safety and effectiveness of a patient's medication regimen. Since 2007, the Ontario government has funded pharmacy medication review services (MedsCheck Annual [MCA]) for residents taking 3+ drugs. In 2010, MedsCheck was broadened to include patients with diabetes (MCD). In an effort to standardize service delivery, a policy change was initiated in 2016 that added structured pharmacist documentation, including extra diabetes-specific education and goal-setting. In addition, pharmacists needed to provide evidence of diabetes educator training to provide MCD.

Objectives: To examine the impact of the policy change on the use of MedsCheck services among adults with diabetes.

Methods: We identified adults (19+ years) living in the community with diabetes in Ontario 12-months pre- and post-intervention (October 2016) using linked healthcare administrative data. Service uptake was calculated as the monthly rate of MedsCheck services per 10,000 adults with diabetes. Interrupted time series analysis (segmented linear regression with autoregressive error models) was used to identify the change in use after intervention (compared to predicted absent policy change), and the trend 12 months after; while accounting for seasonality, non-stationarity, and autocorrelation.

Results: 1,368,211 adults with diabetes received 705,578 MedsCheck services (34% of patients) over the study period. Service delivery was stable in the year prior to intervention with rate of 153 for MCD and 75 for MCA in September 2016. An immediate decline in use was observed (−81% MCD, −38% MCA) in October 2016. Thereafter, a significant increase in MCA services was seen that exceeded predicted values by September 2017 (+21%). In contrast, minimal change was seen for MCD and rates remained lower than predicted by September 2017 (−54% MCD). Overall (MCA or MCD), fewer patients accessed MedsCheck services following the policy change (-37%) by September 2017.

Conclusions: A decline in the rate of adults with diabetes receiving MedsCheck services was seen after a policy change that required more pharmacist training and additional documentation; with evidence of some displacement from MCD to MCA. Better understanding of the barriers that resulted in the shift from MCD to MCA and the decline overall will help inform future policy changes to improve access to MCD.

4757 | Assessing the impact of a non-alcoholic fatty liver disease (NAFLD) diagnosis on prescribing of GLP-1RA, DPP4i, and TZD medications

Danni Zhao, Matthew J. Alcusky and Anthony P. Nunes
University of Massachusetts Medical School, Worcester, MA

Background: No medications have been approved to treat non- alcoholic fatty liver disease (NAFLD) by the FDA. However, beneficial effects of select antidiabetic drugs (i.e., liraglutide, exenatide, and pioglitazone) on improving metabolic and histologic features of NAFLD have been demonstrated in randomized controlled trials. It is unknown whether diagnosis of NAFLD affects clinicians' preferential prescribing of antidiabetic drugs.

Objectives: To assess the timing of a NAFLD diagnosis relative to the initiation of glucagon- like peptide- 1 receptor agonists (GLP-1RAs), dipeptidyl peptidase- 4 inhibitors (DPP- 4is) and thiazolidinediones (TZDs).

Methods: We conducted a retrospective cohort study from 2012 to 2019 among adult patients with NAFLD who newly initiated GLP-1RAs (i.e., albiglutide, dulaglutide, exenatide, and liraglutide), DPP- 4is (i.e., alogliptin, linagliptin, saxagliptin, and sitagliptin), and TZDs (i.e., pioglitazone and rosiglitazone) using MarketScan® Explorys® Claims- EMR Data Set. The initiation date of an antidiabetic agent was used as the index date. We specified a 12- month baseline and follow up period before and after the index date, respectively, to ascertain the earliest date of a NAFLD diagnosis. Each patient can contribute multiple initiation episodes. We described the frequency distribution of NAFLD diagnoses relative to initiation of antidiabetic agents. Using principles of sequence symmetry analyses (SSA), we estimated the crude and adjusted sequence ratios and 95% confidence intervals from conditional logistic regression models, controlling for time- constant confounders and time trends that may artificially introduce an asymmetry.

Results: Overall, 4,640 patients initiated GLP- 1RAs (n = 2,243), DPP-4is (n = 2, 587), or TZDs (n = 350) over the study period. About 60% initiation episodes were subsequent to diagnosis of NAFLD. The crude sequence ratios were 1.63 (95% CI: 1.49- 1.77) for GLP- 1RA

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

initiators, 1.46 (95% CI: 1.35- 1.58) for DPP- 4i initiators, and 1.59 (1.28- 1.98) for TZD initiators. After controlling for time trends that may artificially introduce an asymmetry, patients who initiated GLP-1RAs, DPP- 4is and TZDs had sequence ratios of 1.39 (95% CI: 1.32-1.45), 1.29 (95% CI: 1.23- 1.34) and 1.42 (95% CI: 1.27- 1.59), respectively.

Conclusions: Patients were more likely to initiate GLP- 1RAs, DPP-4is, or TZDs following diagnosis of NAFLD over a 12- month period. The increased odds suggest that clinicians may shift their prescribing towards these clinically appropriate medications despite NAFLD not being a labeled indication.

4986 | Characterizing trajectories of HbA1c control and associations with vascular outcomes in adults with type 2 diabetes

Rohini Mathur[1], Christopher Rentsch[1], Sophie V. Eastwood[2], Nish Chaturvedi[2], Jessica Franklin[3], Niteesh Choudhry[3], Ian Douglas[1] and Liam Smeeth[1]

[1]*London School of Hygiene and Tropical Medicine, London, United Kingdom;* [2]*University College London, London, United Kingdom;* [3]*Brigham & Women's Hospital Department of Medicine, Boston, MA*

Background: In Type 2 diabetes (T2DM), intensive glycaemic control is key to reducing the risk of major vascular outcomes. Characterizing clinical features associated with good control is an important step towards characterizing populations in highest need of intervention.

Objectives: To identify and characterize clinically useful trajectories of HbA1c control in a UK cohort of newly diagnosed T2DM and determine associations with vascular outcomes.

Methods: An observational cohort study using the Clinical Practice Research Datalink was conducted using 234,191 adults aged 18 and over diagnosed with T2DM between 1988 and 2017 (mean follow-up 6.2 years). Annual mean HbA1c measures were derived by averaging all HbA1c values for each year of follow-up. Latent class growth curve modelling was used to identify groups based on the first five years of follow-up. The ideal number of trajectories was selected based on model fit criteria and clinical relevance. Multinomial logistic regression was used to identify demographic and baseline characteristics associated with trajectory membership. Amongst those free from prevalent vascular disease, multivariable cox-proportional hazards regression was used to compare risk of incident cardio- and micro-vascular disease between trajectory groups after the initial five-year trajectory definition period.

Results: Three clinically meaningful HbA1c trajectories were identified; 63.7% of the population were classified as having 'Optimal control; 29.2% were classed as having 'Adequate control', while 7.1% were classed as having 'Poor control'. Compared to those with optimal control, individuals with adequate or poor control were younger at diagnosis, more likely to be smokers, from more deprived areas, with higher HbA1c, BMI, and vascular co-morbidities at diagnosis. Risk of incident cardiovascular disease was 25% in the adequate control group relative to the optimal control group (95%CI 1.14-1.37) and 83% higher in the poor control group (95%CI 1.57-2.13). Risk of microvascular disease was similarly increased by 18% in the adequate control group (95%CI 1.12-1.24) and 69% in the poor control group (95%CI 1.55-1.84).

Conclusions: We characterized clinically useful differences between individuals belonging to three distinct classes of HbA1c control. Non-optimal glycaemic control was found to be strongly associated with increased risk of vascular outcomes. Further investigation of the relationship between glycaemic trajectories and treatment patterns will be key to developing strategies to target those with persistently poor control.

Disease Epidemiology/Clinical Course -> Neurological/Mental Health

2501 | Threatened abortion and risk of epilepsy, cerebral palsy and attention-deficit/hyperactivity disorder in offspring: A registry-based cohort study in Denmark

Elena Dudukina, Erzsébet Horváth-Puhó, Henrik Toft Sørensen and Vera Ehrenstein

Aarhus University, Aarhus, Denmark

Background: Children born following a pregnancy complicated by threatened abortion (TAB) are at increased risk of autism spectrum disorders. It is unknown whether TAB is associated with other neurologic and behavioral disorders.

Objectives: To examine incidence rate (IR), incidence rate difference (IRD), and hazard ratio (HR) of epilepsy, cerebral palsy, and attention-deficit/hyperactivity disorder (ADHD) in offspring born from a pregnancy affected with TAB as compared with offspring born from a pregnancy unaffected with TAB.

Methods: : In this cohort study, we included singletons live-born in Denmark, 1979-2010. The exposed cohort included children born from a TAB-affected pregnancy before 20th gestational week. The comparison cohort included children born in the same calendar period from a TAB-unaffected pregnancy. The three study outcomes were hospital diagnosis of epilepsy, cerebral palsy, and hospital ADHD diagnosis or use of ADHD drugs. We applied a sibling comparison design to estimate HRs of the outcomes in pairs of discordantly exposed full siblings born in 1991-2010. We followed the children from birth until the earliest of each of the outcomes, 16th birthday, emigration, death, or December 31, 2016. For each outcome, we computed crude IR and IRD (per 1000 person-years). Using Cox proportional hazards regression, we computed HRs with 95% confidence intervals (CIs) while adjusting for the calendar year, birth order, parental age, maternal pre-pregnancy somatic, psychiatric and neurologic morbidity, medication use, employment, education, and income.

Results: In the total population (N=1 864 221), 59 134 (3.2%) offspring were in TAB cohort and 1 805 087 offspring were in the comparison cohort. The population of full siblings included 20 091 discordantly exposed pairs. In the TAB cohort of the total population, the IRs of epilepsy, cerebral palsy, and ADHD were 1.6 (1.5-1.7), 0.4 (0.3-0.4), and 3.2 (3.0-3.4), respectively. The IRD with the comparison

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

cohort was small (0.4 for epilepsy, 0.1 for cerebral palsy, and 0.8 for ADHD). In the total population, the offspring from TAB cohort was at 1.2-fold (1.2-1.3) increased hazard of epilepsy, at 1.4-fold (1.2-1.6) increased hazard of cerebral palsy, and at 1.2-fold (1.1-1.3) increased hazard of ADHD. In the sibling analyses, all associations were attenuated: HR=1.0 (0.9-1.2) for epilepsy, HR=1.2 (0.8-1.6) for cerebral palsy and HR=1.1 (0.9-1.2) for ADHD.

Conclusions: We found a weak association between TAB and offspring's subsequent risk of the neurological and behavioral outcomes of interest.

2525 | Associations of benzodiazepines, Z-drugs and other anxiolytics with subsequent dementia in patients with affective disorders: A nationwide cohort and nested case-control study

Merete Osler[1] and Martin B. Jørgensen[2]
[1]*Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospitals, Frederiksberg, Denmark;* [2]*Psychiatric Center Copenhagen Department O, Copenhagen, Denmark*

Background: Benzodiazepines and Z-drugs are of the most prescribed agents worldwide. Due to cognitive side effects the question of their influence on risk of dementia has been raised.

Objectives: To examine the associations of benzodiazepines, Z-drugs and other anxiolytics with incident dementia in patients with affective disorders.

Methods: We did a cohort and nested case-control study of 235,465 patients above 20 years with a first-time hospital contact for an affective disorder from 1996 through 2015 identified in the Danish National Patient Registry. From the Danish Prescription Registry we obtained information on all prescriptions for benzodiazepines, Z-drugs and other anxiolytics and followed patients for incident dementia (defined by hospital discharge diagnoses or acetylcholinesterase inhibitor use). Cox proportional hazard and conditional logistic regression were used to calculate hazard and odds ratios with adjustment for sociodemographic and clinical variables.

Results: A total of 75.9% n=171,287) of patients with affective disorders ever used BZD or Z-drugs and during the median follow-up of 6.1 year (IQR 2.7-11), 9,776 (4.2%) patients were diagnosed with dementia. Ever use of BZD or Z-drugs showed no association with subsequent dementia after multiple adjustments neither in the cohort or nested case-control design. In the cohort analyses number of prescriptions or cumulated dose of BZD or Z-drugs at baseline were not associated with dementia, while in the nested case-control study where prescriptions were counted from 1995 until 2 years before the index date, there was a slightly higher odds ratio for dementia in patients with lowest use of BZD or Z-drugs (odds ratio 1.08, 95%CI, 1.01-1.15) relative to never users. However, those with highest use had the lowest odds of dementia (odds ratio 0.83, 95%CI, 0.77- 0.88).

Conclusions: This large cohort study of patients with affective disorders did not show associations between use of BZD or Z-drugs and subsequent dementia even when exposures were cumulated or split into long and short-acting drugs. Some results were actually in favour of a protective effect.

2527 | Treatment patterns of patients with major depressive disorder and suicidal ideation or attempt

David M. Kern, M. Soledad Cepeda and Frank Wiegand
Janssen R&D, Titusville, NJ

Background: Patients diagnosed with major depressive disorder (MDD) and having suicidal ideation comprise approximately one-quarter of those with MDD, yet little is known about how they are treated.

Objectives: To understand the treatment patterns of medications and procedures for subjects with MDD and suicidal ideation (SI) or suicide attempts (MDD+SI/SA) 1 year following their first occurrence of SI/SA.

Methods: We identified patients diagnosed with MDD and a diagnosis for conditions related to SI/SA from a large US claims database of commercially insured individuals during 1/1/2014 to 6/30/2019. The index date was the first observed medical claim in the database for SI/SA. Patients were required to have continuous enrollment in the database ≥1 year prior to the index date, with no minimum follow-up required. Patients with evidence of autism, mania, psychosis or dementia any time prior to index were excluded. Treatment patterns included procedures for electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS), and medications of selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, other antidepressants (mainly bupropion and trazodone), anxiolytics, hypnotics/sedatives, lithium, psychostimulants, and atypical antipsychotics. Changes in class-based regimens were determined according to switching or adding of a new medication class to an existing regimen. Treatment patterns were captured up to 1 year following the index SI/SA.

Results: We identified 49,575 patients diagnosed with MDD+SI/SA. Patients were followed for 265 days on average, with 51% having a full year of observation. During this time, 75% received ≥1 treatment of interest. Of the treated, 57% received ≥2 distinct regimens, while 32% received ≥3 and 17% received 4 or more. Use of multiple therapy classes simultaneously was common, occurring in 62% of patients. There was heterogeneity in treatments received, with SSRI alone the most common first treatment (17%) followed by other antidepressants (10%), anxiolytics (9%), antipsychotics (7%) and anticonvulsants (6%). Use of ECT (0.9%) and TMS (0.3%) any time during follow-up was rare.

Conclusions: Of patients with MDD+SI/SA receiving pharmacotherapy or ECT/TMS, nearly two-thirds received multiple medication classes simultaneously at some point in the year following their first recorded SI/SA event. Use of medications other than antidepressants during this time was relatively common practice. Switching or adding-on classes was also frequent.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2607 | Prevalence and incidence of narcolepsy in Japan: A study using Japanese claims data

Motonobu Sakaguchi[1], Motonobu Sakaguchi[1], Yumiko Ogino[1], Chao Chen[2] and Shreya Davé[2]
[1]*Takeda Pharmaceutical Company Limited, Osaka, Japan;* [2]*Takeda Pharmaceuticals International Co., Cambridge, MA*

Background: Previous studies suggest a relatively higher prevalence of narcolepsy in Japan than in Europe and North America, however these studies with Japanese data had some methodological limitations such as reliance on self-report questionnaires. More data is therefore, required to accurately estimate the epidemiology of narcolepsy in Japan.

Objectives: The objective of the study was to determine the prevalence and incidence of narcolepsy overall, and by age and gender, and estimate the numbers of total narcolepsy cases across Japan.

Methods: A retrospective cross-sectional study was conducted using the JMDC database. Patients who were continuously enrolled from January 2014 to December 2017 were eligible. Prevalence cohort was composed of the eligible population, and incident cohort was restricted to those without any narcolepsy diagnoses any time before 1st January 2017 from the eligible population. Considering the local practice in diagnosing narcolepsy, narcolepsy cases were identified by two definitions to obtain a range of prevalence and incidence rates within which the true rate was likely to lie. A) broad case definition (upper limit): patients having one diagnosis (ICD-10 code, G474) followed by a confirmed diagnosis; B) narrow case definition (lower limit): patients having at least one sleep test, including electroencephalogram, polysomnography, or multiple sleep latency test, and any subsequent confirmed diagnosis. Descriptive analyses were used to summarize the demographics for the patients with narcolepsy. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results: Among the prevalent cohort, 1,066 cases and 571 cases were fulfilled using the broad and narrow definition respectively. Among the incident cohort, 121 cases and 76 cases were met by the broad and narrow definition respectively. The age-sex adjusted prevalence of overall narcolepsy was 22.3-45.3 per 100,000 persons, projected to 28-57 thousand narcolepsy patients across Japan. The highest prevalence occurred among those 20-29 years of age. The age-sex adjusted incidence rate was 0.37-0.64 per 100,000 person-years, suggesting 500-800 newly diagnosed patients every year.

Conclusions: We concluded that the prevalence of overall narcolepsy is not as high as previously reported in Japan, but may still be higher than the prevalence in Western countries. In this study, it appears that the incidence rate was the highest in the second decade, fitting the natural history. The reason for the lower prevalence in the age 10-19 years needs to be further explored.

2671 | Increased risk of falls and fractures in patients with psychosis and Parkinson disease

Joan Forns[1], J. Bradley Layton[2], Jennifer Bartsch[2], Mary Ellen Turner[3], Colleen Dempsey[3], Mary Anthony[2], Mary E. Ritchey[2] and George Demos[3]
[1]*RTI-HS, Barcelona, Spain;* [2]*RTI-HS, Research Triangle Park, NC;* [3]*ACADIA Pharmaceuticals, San Diego, CA*

Background: Psychosis is a common complication of Parkinson disease (PD), particularly at advanced stages of the disease, with prevalence up to 75%. Both PD and PD with psychosis (PDP) have been implicated as risk factors for falls and fractures due to cognitive and motor impairment. Yet it has not been established whether the risk of falls and fractures is higher in patients with PDP compared with patients with PD.

Objectives: To evaluate whether the risk of falls and fractures differed in patients with PD or PDP at a similar disease stage.

Methods: This study was conducted using the MarketScan (IBM Watson Health) commercial and Medicare claims databases from 2008 to 2018. Patients with a PD diagnosis without psychosis were followed from the first identified PD diagnosis date during the study time period. After a noted psychosis diagnosis, patients were included in the PDP cohort. Patients with PD and patients with PDP were matched at similar points in their disease trajectories using a sequential propensity score matching approach. Falls and fractures were captured both as composite and separate outcomes. The incidence rates (IR), expressed per 100 person-years, and 95% confidence intervals (CI) of falls and fractures were estimated. Incidence rate ratios (IRRs) compared patients with PDP with patients with PD without psychosis in the matched samples.

Results: We identified 154,306 patients with PD without psychosis who did not have falls or fractures before the index date; the IR for falls and fractures was 11.41 events (95% CI, 11.29-11.53). Most of the events were falls. There were 12,127 (7.8%) patients with a subsequent diagnosis of PDP that met the inclusion/exclusion criteria. These patients with PDP had higher prevalences of most comorbidities and risk factors for falls and fractures than those without psychosis. The IR of falls and fractures among patients with PDP was 29.03 (95% CI, 28.27-29.81); falls were most commonly recorded. After matching, 24,144 (15.6%) patients with PD without psychosis and 12,077 (99.6%) with PDP were retained. Within the matched groups, patients with PDP had higher incidences of falls and fractures than those without psychosis (IRR = 1.44; 95% CI, 1.39-1.49). The increased rate was noted separately for falls (IRR = 1.48; 95% CI, 1.43-1.54) and any fractures (IRR = 1.17; 95% CI, 1.08-1.27) as well as within specific types of fracture, including pelvis and hip fractures.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: The present study suggests a modest but precise and consistent increased risk of falls and fractures in patients with PDP compared with patients with PD.

3775 | Excess deaths associated with treatment resistance in patients with major depressive disorder

Philip Brenner, Lena Brandt, Michel Nijs, Johan Reutfors and Therese Andersson
Karolinska Institutet, Stockholm, Sweden

Background: Patients with treatment resistant depression (TRD) have an increased mortality rate compared to other patients with depression, but it is not known how this translates into absolute numbers of excess deaths.
Objectives: To determine the number of excess deaths among patients with TRD compared to other depressed patients.
Methods: Nationwide Swedish governmental registers were used to identify a cohort of 118,774 antidepressant initiators 18-69 years old with a depression diagnosis. Patients with bipolar disorder, psychotic disorder and dementia were excluded. Patients who initiated a third consecutive, adequate treatment trial were classified as having TRD. An adequate trial was defined as lasting at least 30 days of antidepressant treatment or add-on treatment with antipsychotics, anticonvulsants or lithium, or a series of neurostimulation treatment. Flexible parametric survival models were used to estimate the rate of deaths due to all causes, as well as due to external causes (accidents or suicide) only, comparing TRD to patients with other depression. Analyses were adjusted for clinical and sociodemographic covariates, and included interactions with TRD, age, and major somatic comorbidities (expressed as Charlson Comorbidity Index, CCI). Standardized survival was estimated. Numbers of excess deaths within five years per 1000 patients with TRD were calculated and stratified by age and somatic comorbidity categories, and compared to if patients with TRD had had the same survival as the other patients with depression.
Results: A significant number of excess deaths were found among patients with TRD in all age and comorbidity categories, except for patients with CCI 2 or over, where numbers were too low for significance. The highest number of excess all-cause deaths per 1000 patients within 5 years was 16 (95% CI 5-28) among patients 18-29 years old with CCI 1. For deaths due to external causes, numbers of excess deaths were highest among patients 50-69 years old with 1 major somatic comorbidity (15 per 1000 patients; 95% CI 2-28).
Conclusions: A number of excess deaths due to both any cause of death and to external causes may be avoidable among patients with TRD had they similar survival rates as other patients with depression.

3779 | Incidence rates (IR) and IR ratios of Parkinson disease in patients with cataract compared to the general population: Analyses using the clinical practice research datalink (CPRD)

Claudia Becker[1,2], Laura Eggenschwiler[2], Susan S. Jick[3,4] and Christoph R. Meier[1,2,3]
[1]University of Basel, Basel, Switzerland; [2]University Hospital Basel, Basel, Switzerland; [3]Boston Collaborative Drug Surveillance Program, Lexington, MA; [4]Boston University, Boston, MA

Background: Previous research suggests a link between cataract and Parkinson disease (PD). This has been confirmed in one observational study (Lai et al 2015). If there was more evidence that cataracts may precede PD, cataract patients could be informed earlier about their future risk of PD.
Objectives: To analyse the incidence of PD in patients with or without cataract.
Methods: In the UK-based CPRD database, we identified incident PD patients in a cohort of patients with cataract, aged over 39 years, between 1995 and 2018, and a random sample of the general population matched for age, sex, GP and year of cataract. We assessed PD incidence rates (IRs) and incidence rate ratios (IRRs). We defined PD similar to previous studies by diagnosis code, 2 or more prescriptions (Rx) for anti-PD drugs and no Rx for drugs inducing parkinsonism within 180 days prior to the PD date. We excluded individuals with secondary PD or atypical parkinsonian disorders. Since we observed a large amount of patients with 2 or more Rx for anti-PD drugs but no PD diagnosis, we performed a sensitivity analysis, defining the outcome by 2 or more Rx for anti-PD drugs only (no PD diagnosis needed). In this analysis, we excluded patients with a disorder that could also be treated with anti-PD drugs (i.e., restless leg syndrome, acromegaly or hyperprolactinaemia). In a further sensitivity analysis we censored events occurring within one year after cohort entry to ignore PD cases diagnosed shortly after cataract occurrence. We assessed cases by age, sex, exposure, and year. We calculated person-time of exposure by adding up individual exposure times.
Results: In the main analysis, we included 152'500 patients with cataract and an equal amount of cataract free individuals. During follow-up, we identified 1'144 cataract patients with PD as well as 1'058 PD cases among controls. The crude IR of PD was 0.95 (95% CI 0.90-1.01) per 1'000 person-years (py) in patients with cataract and 0.94 (0.89-1.00) per 1'000 py in the comparisons. The IRR was 1.01 (0.93-1.10). The IRR was slightly increased in men (1.11, 0.99-1.24). The analysis based on drug Rx only included 50% more PD cases and also yielded an overall IRR around 1.00. The IRR for men was 1.19 (1.08-1.31). Results were similar in the analysis omitting the first year of follow-up.
Conclusions: In contrast to a previous study, we did not observe an increased risk of PD in patients with cataract compared to the general population overall. We plan to further study risk factors for PD on this association by means of a case-control study nested in our cataract cohort.

3806 | Caregiving burden, chronic pain and opioid utilization among parents of children with special healthcare needs

Wendy Camelo Castillo[1], Oluwadamilola Onasanya[1], Beth B. Hogans[2], Susan dosReis[1] and Gloria Reeves[1]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]University of Maryland Baltimore, Baltimore, MD; [2]Johns Hopkins School of Medicine, Baltimore, MD

Background: Parents of children with special needs are at high risk for developing chronic non-cancer pain (CNCP). Yet, the impact of caregiving burden on the physical health of parents of children with special needs has seldom been studied.

Objectives: To estimate the prevalence of CNCP and opioid utilization, and examine the association of caregiving burden with CNCP among parents of children with special needs.

Methods: A cross-sectional analysis of a nationally representative survey of households participating in the 2015 Medical Expenditure Panel Survey identified households with at least one child under the age of 18. Caregiver burden was defined as having at least one child with a mental health diagnosis only, functional limitation only, both or none. Parental CNCP was defined as having a diagnosis of back, head, neck, arthritis or chronic pain. Opioid use was defined as reporting at least one prescription fill. We estimated the prevalence of CNCP and opioid use overall and for each of the four subgroups. Multivariable logistic regression was used to examine the association between caregiver burden and CNCP, adjusted for caregiver mental health and disability, socio-demographics and family structure (single or dual parenting). All estimates and 95% confidence intervals (CI) were weighted to represent the national census-based population.

Results: The 7,582 caregivers were female (59.1%) and on average aged 38.5 (SD 8.9) years. CNCP prevalence was highest in households with a child with both conditions (42.7% CI 32.7-52.8) and lowest among households where the child had neither (17.6% CI 15.9-19.3). Opioid prevalence was highest among caregivers of children who only had functional limitations (4.58% CI 1.56-7.61). Caregivers with a child with both conditions were 2.35 (CI 1.41-3.89) as likely to report chronic pain when compared to households were children had none. Parental disability, depression and age were associated with higher odds of chronic pain.

Conclusions: Caregivers of children with functional and mental health impairment are an at-risk population for chronic pain and opioid use, and for whom evidence for best practices is lacking.

3983 | A population-based cohort study of disruptive mood dysregulation disorder among youth in the US

Xiaofeng Zhou[1], Prethibha George[1], Rongjun Shen[1], Gong Richard[1], Robert L. Findling[2] and Phillip B. Chappell[3]
[1]Pfizer Inc., New York, NY; [2]Virginia Commonwealth University, Richmond, VA; [3]Pfizer Inc., Groton, CT

Background: Disruptive mood dysregulation disorder (DMDD) is a childhood-onset depressive disorder that is characterized by a persistent pattern of outbursts and severe irritability. DMDD was introduced as a new diagnosis in the 5th edition of the Diagnostic and Statistical Manual in 2013. Epidemiology data about DMDD in youth are limited.

Objectives: To estimate incidence rates (IRs) and prevalence of DMDD among youth in United State; and investigate patients' demographic characteristics, comorbidities including suicidal behavior, and concurrent medications.

Methods: A retrospective cohort study using 2016-2018 Optum EHR data was conducted. Children aged 10-<18 years with ≥183 days of enrollment prior to cohort entry date and met study inclusion/exclusion criteria were included. DMDD was defined by ICD 10-CM code F34.81. Annual incidence rates (IRs) per 1000 patient year (PY), prevalence (%), and 95% confidence intervals (CIs) were estimated. Proportions of 13 comorbid psychiatric conditions and concurrently prescribed psychiatric medications within 6 months prior to or after 1st incident DMDD were calculated.

Results: A total of 7,677 youth with DMDD during 2016-2018 were identified. With a mean age of 13 years, the cohort had more males (64%), whites (73%), and non-Hispanic (87%). Nearly a third of patients each had the following insurance coverage: commercial (28%), Medicaid (31%), and uninsured (27%). IRs per 1000 PY rapidly increased from 0.87 [95%CI: 0.84, 0.91] in 2016 to 1.75 [95% CI: 1.67, 1.82] in 2018. A similar pattern was found for the prevalence (%) increasing rapidly from 0.08% [95% CI: 0.08, 0.08] in 2016 to 0.35% [95% CI: 0.08, 0.08] in 2018. Most prevalent comorbidities in DMDD youth were attention deficit hyperactivity disorder (ADHD) (72%), other depressive disorders (70%), and anxiety disorders (50%), followed by oppositional defiant disorder (36%), conduct disorder (27%), and suicidal ideation (27%). Examining concurrent medication prescription revealed that DMDD youth received ADHD medication (60%), antipsychotics (59%), any antidepressants (54%), any mood stabilizers (24%), and anxiolytic agents (15%). Further, 69% of patients were prescribed 2 or more different medications.

Conclusions: To our knowledge, this is the first study reporting incidence, prevalence, comorbidity, and concurrent medication of DMDD in US youth using a large longitudinal EHR database. Our results add real-world evidence to the scarce literature on the epidemiology of DMDD. Future analyses may benefit from medical chart review to confirm outcomes, confounder adjustment, and estimation with other databases.

4018 | Association of renal and cognitive function in an elder population: analysis of NHANES 2011 and 2013

David Vizcaya[1], Peter Kolkhof[2] and Montse Soriano-Gabarro[3]
[1]Bayer, Barcelona, Spain; [2]Bayer, Wuppertal, Germany; [3]Bayer, Berlin, Germany

Background: Impaired renal function is a natural consequence of ageing and of certain diseases and is associated with vascular damage and inflammation, which in turn may cause loss of cognitive function

Objectives: To assess the association between estimated glomerular filtration rate (eGFR) and three cognitive test scores in a US elder population

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: People aged 60 years or more participating in the National Health and Nutrition Examination Study (NHANES) editions of 2011 and 2013 conformed the study base. Those with cognitive testing and with serum creatinine value available were included in the analysis. Renal function was calculated as estimated glomerular filtration rate (eGFR) in mL/min/1.73 m^2 using the CKD-EPI formula and subjects were classified according to 3 groups: >60, 30 to 60 and <30. Cognitive function was assessed with three tests: The Consortium to Establish a Registry for Alzheimer's disease (CERAD) Word Learning subtest, the Animal Fluency test (AFT) and the Digit Symbol Substitution (DSS) test. We used Poisson and linear regression models to estimate the association between renal (by 10 units increase of eGFR, or eGFR categories) and cognitive function (score of each test, separately). All models were adjusted for age, educational level attained, ethnicity, gender, history of stroke, marital status and NHANES edition

Results: A total of 3126 (15.7%) participants from both NHANES editions were included in the analysis. No substantial demographic and clinical differences were observed between both editions. Study participants were aged 70.1±7.0 years old and 45% were non-Hispanic whites. Close to 6% never lived with a partner and 47.2% of the population had at least some college education. Near to 15% of the participants had an eGFR < 60. The results of the cognitive tests were similar in 2011 and 2013 being the mean±SD scores 5.8±2.4, 45.5 ±17.4 and 80.3±18.7 for CERAD, AFT and DSS tests, respectively. The analysis showed no adjusted association between CERAD score and neither with eGFR or with eGFR categories. In contrast both AFT and DSS were associated with eGFR: regression coefficients and (95% confidence intervals) (RC): 0.14 (0.03; 0.25) for AFT and 0.48 (0.19; 0.78) for DSS. Likewise, eGFR grouping showed a consistent association: eGFR>60 vs 30 to 60 RC: -1.10 (-1.64; -0.55) for AFT and -1.89 (-3.39; -0.39) for DSS; eGFR>60 vs <30, RC: -1.98 (-3.30; -0.66) for AFT and -6.46 (-10.10; -2.82) for DSS

Conclusions: Recent NHANES data shows a consistent link between renal and cognitive function assessed with AFT or DSS tests in elder population from the US regardless of age and other confounders

4180 | Leveraging real world data to characterize rates of elevated liver enzyme levels among patients diagnosed with migraine

William K. Mountford, Matthew Butler, Carissa Dukes and Jiatao Michael Ye
Allergan, plc, Madison, NJ

Background: Liver enzyme levels are closely evaluated throughout the drug development lifecycle and are commonly used in the post-marketing setting for monitoring liver safety for patients. Understanding the distribution of liver enzyme levels in a real-world patient population can aid in describing background rates of elevated liver enzymes.

Objectives: To characterize rates of elevated liver enzymes among treated and untreated migraine patients in a real-world healthcare setting in the United States.

Methods: We conducted a retrospective database study using Optum Integrated Database. Patients aged 18 years or older diagnosed with migraine between January 1, 2013 and January 30, 2016 were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision (ICD-10-CM). Patients were required to have at least 1 inpatient encounter, or, at least 2 outpatient encounters for migraine. The identified liver enzymes of interest were alanine aminotransferase (ALT) and aspartate aminotransferase (AST). A follow-up period of 1 year after earliest date of migraine encounter was used to capture AST and ALT values. Upper limit of normal (ULN) values were defined as 33 U/L for ALT and 36 U/L for AST in women and 40 U/L for ALT and 43 U/L for AST in men. Subgroups including: prescription treatment for migraine and migraine type (episodic/chronic) were analyzed as well as age and gender.

Results: Of 23,147 migraine patients analyzed, most were female (82.94%) between 18-65 years of age (86.11%). Patients with chronic migraine represented 5.63% of the sample and patients receiving prescription treatment for migraine represented 31.02%. During the 12-month follow up, the incidence proportions for patients with ALT or AST levels >1x ULN, >2x ULN, >3x ULN, and >5x ULN were reported as 16.4%, 3%, 1.8% and 0.9% respectively. The incidence of elevated enzymes >3x ULN was similar in patients with episodic migraine compared with chronic migraine (1.8% vs 1.24%, *P*= 0.20). Likewise, the incidence of elevated enzymes >3x ULN was not statistically significant for those receiving migraine treatment (1.67%) compared to no migraine treatment (1.81%) (*P*=0.53).

Conclusions: These data suggest approximately 1.8% of patients with migraine experience elevations of ALT or AST 3-fold or greater than the ULN in a real-world healthcare setting.

4316 | Hospital-diagnosed infections, community-based antibiotic prescriptions, and risk of subsequent Guillain-Barré syndrome: A 30-year nationwide population-based case-control study

Lotte S. Levison[1], Reimar W. Thomsen[1], Søren H. Sindrup[2] and Henning Andersen[1]
[1]*Aarhus University Hospital, Aarhus, Denmark;* [2]*Odense University Hospital, Odense, Denmark*

Background: Bacterial and viral infections may trigger Guillain-Barré syndrome (GBS) but the exact magnitude and duration of risk remain unclear.

Objectives: To investigate the association of different types of infection with risk of developing subsequent GBS.

Methods: Nationwide population-based case-control study including all patients with first-time hospital-diagnosed GBS in Denmark between 1987 and 2016, and 10 matched general population controls per case. Exposures were hospital-diagnosed infection for the entire

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

study period 1987 to 2016, and community-based antibiotic prescription in the period 2004 to 2016. We used conditional logistic regression to examine the relative risk of GBS associated with having a recent infection. Among GBS cases, we conducted an additional case-crossover analysis of having infection in a 60-day risk time window before becoming a GBS case versus in a 60-day control window 365 days earlier.

Results: Hospital-diagnosed infection within 60 days was observed in 4.3% of 2,414 GBS cases versus 0.3% of 23,909 controls, with a matched odds ratio (OR) of 13.7 (95% confidence interval [CI], 10.2-18.5). The strongest association with subsequent GBS was observed for lower respiratory infection (OR, 14.7; 95% CI, 8.5-25.6), gastrointestinal tract infection (OR, 15.5; 95% CI, 7.0-34.1) and septicemia (OR, 17.9; 95% CI, 6.0-53.3). Community antibiotic prescription within 60 days was observed in 22.4% of 1,086 GBS cases and 7.8% of 10,747 controls, with a matched OR of 3.5 (95% CI, 3.0-4.1). The risk of GBS declined substantially with time since infection, with ORs of 21.3 (95% CI, 14.5-31.2) and 4.7 (95% CI, 3.9-5.7) for hospital-diagnosed infection and community antibiotic prescription within the first month, but GBS risk was still increased 2.4-fold (95% CI, 1.1-5.5) and 1.5-fold (95% CI, 1.2-2.0) in the fifth month after infection. Risk estimates in the case-crossover analysis were similar to the results in the main analysis.

Conclusions: We found evidence for a strong, temporal association of community antibiotic use and in particular hospitalized infection with risk of subsequent GBS.

4443 | Co-occurrence of schizophrenia and dementia

Tobias Gerhard[1], T. Scott Stroup[2], Melanie Wall[2], Cecilia Huang[1] and Mark Olfson[2]

[1]*Rutgers University, New Brunswick, NJ;* [2]*Columbia University, New York, NY*

Background: Patients with schizophrenia have a significantly increased risk of developing dementia, including Alzheimer's Disease, but no guidelines exist for treating patients with both conditions. As a result, physicians face numerous clinical dilemmas, such as balancing the established efficacy of antipsychotics in older adults with schizophrenia against their known risks of premature mortality in older adults with dementia. Population-based studies examining the co-occurrence of schizophrenia and dementia have been limited to Northern Europe and Asia and provide only crude age stratification.

Objectives: To estimate the prevalence of diagnosed dementia in older US adults with schizophrenia compared to those without schizophrenia or other severe mental illnesses (non-SMI controls), stratified by single year of age.

Methods: Our study used a 50% random national sample of Medicare beneficiaries ≥65 years old with fee-for-service and Part D prescription drug coverage (2007-2017). Presence of schizophrenia was determined during a 1-year baseline period by 1 in- or 2 outpatient ICD9/10 codes for schizophrenia. The same baseline period was used to exclude patients with other SMI diagnoses from the control population. Dementia was defined using an algorithm previously validated against clinical dementia assessments (sensitivity 0.85; specificity 0.89). Once diagnosed, dementia was considered present for all following years. We then calculated the prevalence of dementia for older adults with schizophrenia and non-SMI controls, stratified by year of age.

Results: The study cohort included 75,326 older adults with schizophrenia (56.7% female) and 7,937,603 non-SMI controls (63.5% female) contributing 345,999 and 55,499,543 person years of follow-up, respectively. Dementia rates in the non-SMI controls were 1.5% (age 66), 6.5% (age 75), 21.8% (age 85), and 44.3% (age 95), comparable to US population estimates. Dementia rates in older adults with schizophrenia were 29.9% (age 66), 55.8% (age 75), 81.9% (age 85), and 91.3% (age 95), representing a 2-fold (age 95) to 20-fold (age 66) increased dementia prevalence. In sensitivity analysis, a more specific dementia algorithm resulted in marginally lower rates of diagnosed dementia, with no meaningful change in the prevalence ratio between the schizophrenia population and non-SMI controls.

Conclusions: Dementia diagnosis rates are dramatically increased in older adults with schizophrenia compared to age-matched non-SMI controls, particularly at younger ages. Clinical guidelines for the safe and effective management of patients with co-occurring schizophrenia and dementia diagnoses are urgently needed.

4497 | Infection dynamics in patients with multiple sclerosis over the past 15 years: A retrospective cohort study in the UK clinical practice research datalink

Melissa W.Y. Leung, Marloes T. Bazelier, Patrick C. Souverein, Hubert G.M. Leufkens and Romin Pajouheshnia

Utrecht University, Utrecht, Netherlands

Background: Disease-modifying treatments (DMTs) for multiple sclerosis (MS) are associated with causing an increased risk of infection. However, MS patients have an increased risk of mild and severe infections in the absence of DMT, which may be related to MS disease progression. Information on the dynamics of infection incidence in the MS population can help to disentangle the effects of DMTs from background MS prognosis.

Objectives: To examine over the past two decades the rates of infections in MS patients before and after MS diagnosis by patient subgroup.

Methods: A retrospective cohort study was conducted in the UK Clinical Practice Research Datalink (CPRD) Gold. 7219 patients diagnosed with MS were included from January 2003 to November 2019. Each MS patient was matched approximately 1:2 to patients from the general CPRD population by birth year, sex, practice and calendar year. Incidence rates per person year (IR) of urinary tract infection (UTI), skin and subcutaneous tissue infection, sepsis, respiratory infection, and gastrointestinal infection were calculated per study year. The average change in infection rate 5 years after patients' MS diagnosis

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

compared to 5 years before was calculated across the whole study and per year. Analyses were stratified by age at diagnosis, sex, number of infections within 12 months prior to cohort entry and whether the first recorded MS diagnosis was before or after 2003. All analyses will be replicated in a larger CPRD Aurum cohort (13752 MS patients).

Results: The incidence rate of infections in MS patients was 1.9 times higher than the general population over the study period (MS: 0.53 [0.52-0.53] vs non-MS: 0.28 [0.27-0.28], with UTIs most frequent (MS: 0.19 [0.19-0.20], non-MS: 0.056 [0.055-0.058]). A higher infection rate was found in CPRD Aurum (MS, any infection IR: 0.62 [0.62-0.63]). Infection rates were higher in women than men (0.59 [0.58-0.60], 0.36 [0.35-0.37], respectively). The incidence of infections was on average 30 percent higher within 5 years after MS diagnosis (IR 0.45, 95% CI 0.44-0.46) than the 5 years before (IR 0.35, 95% CI 0.34-0.35). The infection rates and differences in infection rate pre- and post-diagnosis declined over the study period across the subgroups. Full analyses in CPRD Aurum will be presented at the conference.

Conclusions: The rates of five key types of infection decreased between 2003 and 2018, but remained higher than in the general population. Consideration of patient characteristics associated with the risk of infection may be valuable for disease management decisions in MS.

4566 | Incidence, survivorship, and treatment of motor neuron disease in Hong Kong: A population-based study

Min Fan[1], Gary K.K. Lau[2,3], Xue Li[1,4,5], Ian C.K. Wong[1,6] and Celine S.L. Chui[1]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Hong Kong; [2]Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom; [3]Division of Neurology, Department of Medicine, University of Hong Kong, Hong Kong, Hong Kong; [4]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Hong Kong; [5]Department of Social Work and Social Administration, Faculty of Social Sciences, University of Hong Kong, Hong Kong, Hong Kong; [6]Research Department of Policy and Practice, University College London School of Pharmacy, London, United Kingdom

Background: Motor neuron diseases (MND) are a group of neurodegenerative disorders that affect the motor neurons in the brain and spine. Riluzole is an approved drug for treatment of amyotrophic lateral sclerosis (ALS), a subtype of MND. However, there are lack of local evidences on its effectiveness.

Objectives: To estimate the epidemiology and survivorship of motor neuron disease (MND) in a population-based sample in the Hong Kong.

Methods: This is a population-based study of people with MND from 1993 to 2018 in Hong Kong. The data is collected from the Clinical Data Analysis and Report System, which covered all public hospitals in Hong Kong. The patients having primary diagnosis (ICD-9-CM: 335.2-335.29 and ICD-10: G12.2) are the cohort of interest for the study. Descriptive statistics on patients' demographic characteristics, clinical features, prescriptions, and prognosis were reported. The Kaplan-Meier estimator was used to estimate the survival function among riluzole users and non-users and compared by the log-rank test. The data cleaning and analysis will be performed by R (version 3.6.0).

Results: In the study period, 1 949 new cases with MND diagnosis were identified. From 1995 to 2018, the incidence and prevalence of MND increased from 1.04 to 1.3 (p=0.001) and from 1.40 to 8.04 (p<0.001) per 100 000 persons respectively. The average age at first diagnosis for MND is 60.6 (SD 15.1), and the proportion of MND in male was 64.7%. Among them, 76.5% (n=1 491), 87.8% (n=1 711) and 92.6% (n=1 804) had hypertension, diabetes, and depression related diagnosis. The median survival time after the first diagnosis was 1.37 years. 12.8% (n=250) of the MND patients received at least one prescription of riluzole. Among them, 95.6% (n=239) were ALS. No statistical difference was found among survival between riluzole users and non-users, either in MND or ALS.

Conclusions: The incidence of MND patients is increasing from 1993 to 2018 in Hong Kong. Majority of them have comorbidities and the median survival year is 1.37. However, more prospective studies are needed for the clinical benefit for riluzole.

4639 | All-cause mortality, suicide and self-harm in patients with treatment-resistant depression

Frederikke Gronemann[1], Martin Balslev Jørgensen[2], Merete Nordentoft[2,3], Per Kragh Andersen[4] and Merete Osler[1,4]

[1]Center for Clinical Research and Prevention, Frederiksberg, Denmark; [2]Mental Health Centre Copenhagen, Copenhagen, Denmark; [3]Lundbeck Foundation Initiative for Integrative Psychiatric Research iPsych, Copenhagen and Aarhus, Denmark; [4]University of Copenhagen, Copenhagen, Denmark

Background: Patients with Treatment-resistant depression (TRD) seem to have an increased risk of mortality compared to patients with non-TRD. This has, however, only been scarcely investigated in large population-based studies.

Objectives: To investigate all-cause mortality, suicide and self-harm among patients with TRD in a nation-wide cohort of patients with depression.

Methods: In this cohort study, all citizens in Denmark diagnosed first time with depression at a hospital, either as in- or outpatient, between 1 January 1996 and 31 December 2014 were identified in Danish registers using the international Classification of Diseases, Tenth Revision (ICD-10), codes F32 and F33. Patients with a prior hospitalization for a comorbid diagnosis of bipolar affective disorder (ICD-10:F30-F31), other affective mood disorders (ICD-10:F38-F39), persistent mood disorder (ICD-10:F34) or schizophrenia spectrum (ICD-10:F20-F29) disorder were not included. TRD was defined as two shifts in antidepressant treatment, assessed from one year prior to depression diagnosis until one year after. Patients characterized with TRD before or

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

at time of MDD diagnosis were not included (N=10,602). Information on mortality and suicide was derived from the Causes of Death Register, while data on self-harm was obtained from the National Patient Register using ICD-codes X60-64, X66-84, T39, T42-43 and R458. Data was analyzed using Cox Proportional Hazard Regression with TRD as a time-varying covariate.

Results: Of 195,541 patients diagnosed with depression, 15.2% was characterized with TRD. We found an increased rate of both suicide (aHR 1.34, 95% CI 1.20-1.51) and self-harm (aHR 1.42, 95% CI 1.35-1.48) in patients with TRD. When stratified by depression severity, the rate of suicide was higher among TRD-patients diagnosed with mild (aHR 1.55, 95%CI 1.30-1.85) and moderate (aHR 1.40, 95%CI 1.17-1.67) depression, while no differences in suicide rate was observed in patients with severe depression. All-cause mortality was lower in patients with TRD (aHR 0.84, 95%CI 0.82-0.86) compared to patients with non-TRD.

Conclusions: Overall, patients with TRD have higher rates of both suicide and self-harm compared to patients with non-TRD, whereas TRD was associated with lower all-cause mortality.

4700 | Postnatal depression and infant "5-in-1" vaccine adherence in the United Kingdom

Holly C. Smith, Fahima Choudry and Irene Petersen
University College London, London, United Kingdom

Background: All infants in the United Kingdom are offered three doses of the 5-in-1 vaccination at 2, 3 and 4 months of age. This combined vaccination protects against diphtheria, tetanus, pertussis (whooping cough), polio and Hib disease (*Haemophilus influenzae* type b). There is a suggestion that there may be a lower uptake of infant vaccinations in children of mothers with postnatal depression; however, the evidence thus far has been mixed and the link between postnatal depression and infant vaccine uptake remains inconclusive.

Objectives: To examine if adherence of the infant 5-in-1 vaccination is lower in mothers who have postnatal depression.

Methods: We conducted a retrospective cohort study using UK primary care electronic health records from The Health Improvement Network (THIN) database. Linked mother-infant pairs were identified with infant date of birth between 1 January 2006 and 31 December 2015. Mother's records were examined to identify postnatal depression in the first year after childbirth. The primary outcome measure was completion of all three doses of the infant 5-in-1 vaccination before one year of age. Poisson regression models were used to compare the likelihood of infant 5-in-1 vaccination uptake in children of women with postnatal depression to women with no recorded postnatal depression.

Results: Of the 219,810 women included in the study, 23,151 (10.5%) had a record of postnatal depression in the first year after birth. There was no difference in infant's 5-in-1 vaccination completion between mothers with postnatal depression and those without (adjusted IRR: 1.01, 95% CI: 0.99-1.02). Those from more socially deprived areas were less likely to complete their infant vaccinations compared to those from the least deprived areas (IRR: 0.92, 95% CI: 0.90-0.92). The likelihood of completing infant 5-in-1 vaccination reduced over time, comparing 2006-07 to 2014-2015 (IRR: 0.91, 95% CI: 0.90-0.92).

Conclusions: Infants of mothers with postnatal depression were just as likely to have completed their 5-in-1 vaccine as infants of mothers without postnatal depression.

4915 | Infectious processes and schizophrenia: Is there any correlation?

Túlio Tadeu R. Sarmento[1], Isabella F. Zuppo[1,2], Pâmela S. Azevedo[1], Ludmila P. Gargano[1,2], Natália D. Brandão[1,2], Juliana Alvares-Teodoro[1,2], Francisco A. Acurcio[1,2], Augusto A. Guerra[1,2], Mariana B. Deleprane[2] and Rafael L.R. dos Santos[2]
[1]*SUS Collaborating Centre Technology Assessment and Excellence in Health, Belo Horizonte, Brazil;* [2]*Federal University of Minas Gerais, Belo Horizonte, Brazil*

Background: Schizophrenia is a severe, chronic and disabling psychotic disorder whose etiology is not fully understood, although it is postulated that genetic and environmental factors are involved in its pathogenesis. Understanding the etiology and pathogenesis of schizophrenia can fill a gap that will support the research and development of new drugs, in addition to improve the care of psychotic disorders.

Objectives: To evaluate if infectious processes are related to the etiology of schizophrenia using real-world evidence, and if positive, which pathogens ones are more important.

Methods: A systematic review (SR) and meta-analysis assessing a possible association between infections and schizophrenia was carried out by consulting the MEDLINE, EMBASE, LILACS and Cochrane Library databases, besides gray literature. Were included SR, cohort and case control studies that assessed the presence of schizophrenia and occurrence of previous infections. The selection of studies was carried out by two independent reviewers and, in cases where there was disagreement, it was resolved by a third reviewer. The meta-analysis was conducted using PythonMeta version 1.11 software.

Results: Our search retrieved 1198 studies and 66 were included in the meta-analysis: two cohorts and 64 case-control studies. There was no statistically significant difference in the meta-analysis of the cohorts assessing the risk related to the occurrence of schizophrenia in patients with a viral infection during childhood. Regarding the results from case-control studies, the meta-analysis suggest a greater chance of schizophrenia in individuals with antibodies against bacteria [OR 2.03 (IC95% 1.06 - 3.91)], protozoa [OR 2.01 (IC95% 1.42 - 2.84)] and virus [OR 1.57 (IC95% 1.15, 2.15)]. In addition, some studies have evaluated whether viral infections during pregnancy could be related to the onset of schizophrenia in the child, however, the results obtained have shown no statistical significance in this scenario.

Conclusions: Real-world evidence suggests that individuals with a history of infections by viruses, bacteria and protozoa are more likely to

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

develop schizophrenia. In addition, no evidence was found that infections during pregnancy women may be related to the onset of schizophrenia in children. The results presented here can support further discussions in order to better elucidate the relation between infections and schizophrenia, in addition to elucidate possible future paths for pharmaceutical development.

4972 | Characteristics of multiple sclerosis by ethnoracial groups in medicaid and electronic health records

Nydjie Grimes, Cortney Hayflinger and Cynthia Jones
Biogen, Cambridge, MA

Background: Publications on African American, Hispanic, and Asian populations with multiple sclerosis (MS) are available; however, large population-based samples are needed to better understand these subgroups.
Objectives: This study describes demography, comorbid conditions, and drug utilization among ethnoracial populations with MS in Medicaid and electronic health records (EHR).
Methods: MS patients were selected from 2 large databases (2013-2017): 1) Truven Health Marketscan® Medicaid and 2) Optum® EHR. MS cases were defined as those with ≥ 2 medical claims for MS. Non-white MS cases were defined as patients identified as black, Asian, or other. Hispanic MS cases were defined as patients identified as Hispanic. White and non-Hispanic controls were selected and matched on age (10-year bands), gender, time in the database, and pharmacy benefit eligibility. Comorbid diagnoses were grouped using the Clinical Classification System. Medications were classified using the Uniform System of Classification. Comparisons of comorbidities between cases and controls were estimated using prevalence rate ratio (PRR) and 95% confidence intervals.
Results: Among 9,728 non-white MS cases identified in Truven Medicaid, 87%, 3%, and 10% were African American, Hispanic and other, respectively. In Optum EHR, 23,208 non-white MS cases were identified; 75%, 3%, and 22% were African American, Asian, and Hispanic, respectively (not mutually exclusive). The mean age (years) at onset for these subgroups was 45.3 in Truven Medicaid and 48.7 in Optum EHR, and 78% were female. Comorbidities were similar in non-white cases and white controls, with other nervous system disorders, other connective tissue disease, diseases of the urinary system, and hypertension among the most prevalent conditions. Among these, a statistically significant difference was only noted for hypertension. The top medications used among non-white MS cases were anti-infectives, narcotic analgesics, corticosteroids, anti-arthritis systemic medications, and anti-depressants. Subgroup stratifications are presented.
Conclusions: Our results indicate that overall characteristics of non-white and Hispanic MS patients are similar to white and non-Hispanic MS patients. Further analyses in these datasets are warranted to evaluate differences in MS severity and course, treatment patterns, and overall healthcare utilization as identified in other publications.

5032 | Prevalence of anxiety, depression and drug utilization of antidepressants among cancer patients in the inpatient settings: A cross-sectional study in Jordan

Abdallah Y. Naser[1], Anas Nawfal Hameed[1], Nour Mustafa[2], Hassan Alwafi[3] and Haya Khalil[2]
[1]Isra University, Amman, Jordan; [2]King Hussein Cancer Center, Amman, Jordan; [3]Umm Alqura University, Mecca, Saudi Arabia

Background: Psychiatric illnesses are common among cancer patients as the presence of cancer itself and receiving its treatment lead to depression and anxiety in many cases. Psychiatric illnesses are associated with poor adherence to cancer therapy and negatively affect disease management and therapy outcomes.
Objectives: To investigate the prevalence of anxiety, depression and drug utilization of antidepressants among cancer patients within the inpatient settings.
Methods: A cross-sectional study was conducted between October 2019 and February 2020 at the inpatient department in King Hussein Cancer Center in Jordan. patients' psychological status was assessed using the Hospital Anxiety and Depression Scale (HADS) and the Generalized Anxiety Disorder 7-item (GAD-7) scale. Prevalence rate of depression was estimated by dividing the number of patients who exceeded the borderline score (10 or more) of the HADS scale by the total number of the patients. Same procedure was followed to identify patients with anxiety and applied using the two scales (HADS (using a score of 10 or more) and GAD-7 (using a score of 15 or more)). Risk factors of anxiety/depression were identified using logistic regression.
Results: A total of 399 cancer patients were involved in this study. The prevalence rate of depression is around 37.1%. The prevalence rate of anxiety was comparable using the HADS and the GAD-7 scale and was 35.6% and 37.6%, respectively. Cancer metastasis was important predictor of depression (odds ratio (OR) 2.62 (1.61 - 4.28)) and anxiety using the two scales (OR: 2.10 (1.29 - 3.42) and 2.23 (1.32 - 3.74). Reaching stage three (OR: 5.26 (1.05 - 26.41)) and four (OR: 2.73 (1.61 - 4.62)) in the metastasis were other important predictors of depression. Reaching stage four in the metastasis was associated with higher odds of anxiety (OR: 2.39 (1.42 - 4.04)). Being treated with combination of surgery and chemotherapy was a protective factor from anxiety (OR: 0.54 (0.33 - 0.86)). Despite the high prevalence of depression among the study participants, only 14.2% were receiving antidepressant medications. The most commonly used antidepressant therapeutic class was selective serotonin reuptake inhibitors (23.8%).
Conclusions: The prevalence of depression and anxiety is high among cancer patients in the inpatient settings. High percentage of the patients are unaware about their illness, undiagnosed and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

consequently do not receive treatment for their psychiatric illnesses. Thorough psychological assessment should be directed towards critically ill cancer patients.

5134 | Medication use among migraine sufferers: An analysis of electronic medical records

Jessica D. Albano, Kelly Oh and Sara Ephross
Syneos Health, Morrisville, NC

Background: Twelve percent of the US population, 6% men and 18% women, suffer migraines. Treatment has primarily relied on general pain medications, acute migraine therapies and preventive use of drugs developed for other conditions. Emergence of a new class of prophylactic migraine drugs, calcitonin gene-related peptide inhibitors (anti-CGRPs), has the potential to significantly impact the treatment landscape.

Objectives: To describe demographic, clinical and treatment characteristics of migraine patients using a US database of electronic medical records.

Methods: EMR data of patients ≥15 years of age with at least two distinct migraine diagnoses (ICD-10 G43) within the past 5 years were analyzed in TriNetX "Analytics" (Cambridge, USA; Feb 2020), a live database of ~60M US patients. Disease diagnoses within one year prior to the first migraine diagnosis and medication use following the first migraine diagnosis are reported.

Results: A total of 65,147 men and 318,406 women migraine sufferers were included. Approximately 75% of patients were white and mean age was 45 years. Common comorbid conditions among men and women included disorders of the nervous system (29% and 27%), musculoskeletal system (27% and 29%), endocrine/metabolism (23% and 24%) and circulatory (22% and 17%). Mental/behavioral/neurodevelopmental disorders were diagnosed for 21% of both groups. Analgesics were used by 80% and 83% of men and women; most common were acetaminophen (50% and 55%), ibuprofen (23% and 30%) and aspirin (21% and 18%) among men and women, respectively. Opioids were used by up to 25% of men and 27% of women. Sumatriptan was used by 31% of men and 35% of women. Anticonvulsants were used by 42% of men and 48% of women with topiramate (19% and 29%) and gabapentin (21% and 23%) most frequently prescribed. Antidepressants were used more frequently among women (57%) compared to men (47%). Sedatives were used by 43% of men and 48% of women. Beta blockers were used by 30% of men and 29% of women, while calcium channel blockers were used by 18% of men and 15% of women. Anti-CGRPs were used by 1.8% and 2.3% of men and women, respectively.

Conclusions: Male and female migraine sufferers experience similar, high rates of comorbid conditions and concomitant medication use. Although CGRPs have been widely available for more than a year, they make up a small proportion of migraine prescriptions. Future analyses will focus on treatment pathways including those leading to anti-CGRP initiation.

Disease Epidemiology/Clinical Course -> Other

52 | Identifying patients with chronic kidney disease in a population-based laboratory database

Uffe Heide-Jørgensen[1], Christian F. Christiansen[1], Henrik Birn[1,2], Reimar W. Thomsen[1] and Søren V. Vestergaard[1]
[1]*Aarhus University Hospital, Aarhus, Denmark;* [2]*Aarhus University, Aarhus, Denmark*

Background: Hospital diagnoses of chronic kidney disease (CKD) are likely incomplete and do not reflect the time of onset, as most patients with CKD are managed in general practice. Population-based laboratory databases are attractive data sources for patient identification in pharmacoepidemiological studies, as CKD is defined by laboratory findings in the current guidelines.

Objectives: To apply different algorithms for identifying CKD from hospital and laboratory data, and to describe the resulting patient cohorts.

Methods: We used population-based laboratory-, hospital-, and administrative databases in Northern Denmark to identify and follow patients with CKD as defined by six algorithms in 2009-2016. Five algorithms were based on laboratory data, requiring A) one measurement of estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2, B) two such measurements at least 90 days apart, C) two such measurements at least 90 days apart with no eGFR > 60 mL/min/1.73m^2 observed in-between, D) two such measurements 90-365 days apart, E) two such measurements or two measurements of urine albumin creatinine ratio > 30 mg/g at least 90 days apart. Algorithm F included patients with a hospital diagnosis of CKD. We estimated prevalence and incidence of CKD in the adult population, described baseline characteristics, and estimated 1-year mortality in the resulting cohorts after applying each algorithm.

Results: Laboratory based algorithms A-E yielded CKD prevalences of 8.3%, 5.6%, 4.8%, 4.6%, and 5.9% as of 1 January 2009, and incidences of 8.9, 7.3, 5.9, 8.8, and 7.3 per 1000 person-years. The resulting cohorts A-E included 103,435; 84,688; 68,994; 75,031; and 100,957 patients, with corresponding median ages of 71, 74, 76, 75, and 73 years. The median eGFR levels at inclusion was 56, 55, 53, 54, and 56 mL/min/1.73m^2, and the median time since first ever observed eGFR < 60 mL/min/1.73m^2 was 0, 13, 17, 11, and 13 months. The 1-year mortalities were 8.1% (95% confidence interval 8.0-8.3), 8.1% (8.0-8.3), 7.9% (7.7-8.1), 8.6% (8.5-9.0), and 7.2% (7.1-7.4). Algorithm F resulted in a CKD prevalence of only 0.8%, and an incidence of 2.4 per 1000 person-years. The resulting cohort included 27,947 patients with a median age of 72 years, median eGFR of 47 mL/min/1.73m^2, and median time since first ever observed eGFR < 60 mL/min/1.73m^2 of 70 months. The 1-year mortality was 21.6% (21.2-22.1).

Conclusions: The choice of algorithm used to identify CKD patients from databases affected estimated occurrence and cohort composition. The greatest difference was seen between algorithms based on laboratory data compared to hospital diagnoses.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

53 | Identification of risk factors associated with mortality in neonatal sepsis patients

Vijayanarayana Kunhikatta[1], Puspita Sahu[1], Meenakshi Srinivasan[1], Shivakumar M.[2] and Leslie Edward Lewis[3]

[1]Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka State, India; [2]Department of Pharmacology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka State, India; [3]Department of Paediatrics, Kasturba Medical College, Manipal, Manipal Academy of Higher, Manipal, Karnataka State, India

Background: Neonatal sepsis is an important cause of mortality among neonates in developing countries accounting for 30-50% of total deaths each year and is major public health challenge. Mortality from neonatal sepsis may be as high as 50% for infants who are not treated and even among treated there may be several maternal and neonatal factors influence poor outcomes.

Objectives: Objective of the study was to find out in-hospital neonatal sepsis rate, associated motility and identify the risk factors associated with mortality.

Methods: A retrospective observational study was conducted among neonates admitted to neonatal intensive care unit (NICU), in a tertiary care teaching hospital. Institutional ethics committee approval was obtained prior to the study. Neonates with culture positive sepsis, admitted during January 2012 to December 2016 at the level 3 NICU were identified using ICD 10 Code P36.0-9 from inpatient medical records, based on the inclusion and exclusion criteria. Data on demography, birth weight, mode of delivery, gestation age, maternal comorbid conditions, maternal surgical procedures done, maternal drug use, neonatal outcomes were collected from the patient medical records. Multiple logistic regression was used to identify the factors associated with mortality and calculation of adjusted odds ratio (AOR).

Results: A total of 613 neonates were identified with culture positive sepsis from the 4690 neonates admitted in NICU during the study period. Total rate of sepsis in the NICU was 13.07 per 100 neonates and mortality rate was found to be 25.4%. Multiple logistic regression analysis showed, extremely low birth weight (AOR: 6.17; CI: 3.47-10.96; p<0.001), extreme preterm (AOR: 5.76; CI: 2.61-12.71; p<0.001), very pre-term (AOR: 2.55; CI: 1.61-4.04; p<0.001), maternal steroid prophylaxis (AOR: 1.64; CI: 1.04-2.58; p<0.033) and pregnancy induced hypertension (AOR: 1.67; CI: 1.09-2.56; p<0.018), were statistically significant independent risk factors associated with mortality. However, breast feeding (AOR: 0.3; CI: 0.18-0.49; p<0.001) has shown statistically significant protective effect.

Conclusions: Both maternal and neonatal factors were associated with increased mortality in neonatal sepsis. Therefore, varied strategies should be implemented for better management of the disease.

70 | The impact of socioeconomic status on the risk of total hip arthroplasty during 1995 to 2017 in Denmark

Nina M. Edwards[1], Claus Varnum[2,3], Søren Overgaard[3,4] and Alma B. Pedersen[1]

[1]Aarhus University Hospital, Aarhus, Denmark; [2]Vejle Hospital, Vejle, Denmark; [3]University of Southern Denmark, Odense, Denmark; [4]Odense University Hospital, Odense, Denmark

Background: People are widely affected by their socioeconomic status (SES) even in health care, where low SES is associated with higher risk of developing osteoarthritis (OA). Total hip arthroplasty (THA) is an effective procedure for reducing pain and improving function and quality of life in patients suffering from disabling OA. Thus, it is plausible to expect an increased need of THA among individuals with low SES. One previous study examined the use of THA in relation to SES in four European countries finding pro-rich-area inequality. However, the study has several limitations including missing data on the individual level measures of SES. Our hypothesis is therefore, that there is a socioeconomic inequality in THA utilization in Denmark.

Objectives: Examine the association between SES and the risk of THA and whether the association is age- or time-dependent.

Methods: This is a population based case-control study, where we included all patients undergoing primary THA due to OA (cases) in Denmark from the 1st of January 1995 to the 31st of December 2017 using the Danish Hip Arthroplasty Register. Using the Danish Civil Registration System each case was matched on sex, region of residence and surgery date with 5 controls from the background population. We retrieved individual-level data on SES markers (education, cohabitation, income and liquid assets). We performed logistic regression to estimate adjusted odds ratios (aOR) with 95% confidence intervals for THA, adjusting for SES markers and comorbidity according to Charlson.

Results: A total of 108,946 THA cases and 544,730 population controls were identified. The aOR for the risk of THA with the lowest education vs. highest education was 1.42 (1.32-1.53) for the age group 45-55. The association between education and THA decreased with increasing age. The aOR for the risk of THA for patients who lived alone vs. lived with a partner was OR 0.93 (CI: 0.91-0.96). The aOR for the age group 45-55 with the lowest vs. highest income was 1.12 (1.02-1.23) and was 0.75 (0.70-0.80) for those with the lowest vs. highest liquid assets. The aOR for the risk of THA with the lowest education vs. highest was 1.23 (1.15-1.31) in the years 1995-2000 and decreased to 1.01 (0.97-1.05) in the years 2013-2017. For the lowest income vs. the highest the aOR was 1.22 (1.12-1.32) in 1995-2000 and decreased to 0.84 (0.80-0.89) in 2013-2017.

Conclusions: The association between lower level of education, lower level of income, and living alone and the high risk of THA was age dependent. The inequality seen in the risk of THA by education decreased over time suggesting a time trend towards less socioeconomic inequality.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

92 | Association between dietary diversity and all-cause mortality among Chinese adults 65 years of age or older, a community-based cohort study

Liyuan Tao, Lin Zeng, Nan Li, Yanyan Shi, Hua Zhang, Xiaoxiao Wang, Hongling Chu, Lin Zhuo, Kaiwen Ni and Xiaoli Liu
Peking University Third Hospital, Beijing, China

Background: Diet is a well-established major modifiable risk factor for multiple chronic disease and mortality, but few studies have evaluated the association of dietary diversity and mortality in older adults.
Objectives: We aimed to examine the prospective association between dietary diversity and the risk of all-cause mortality in a community-based cohort study of older Chinese adults.
Methods: In this prospective cohort study, we invsetigated the association between dietary diversity and all-cause mortality among 17949 community-based participants aged 65 years or old in China. The consumption on the frequencies of food groups was collected at baseline, and a dietary diversity score (DDS) was calculated. Survival status and date of death were collected during the follow-up survey. We used univariate and multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals for all-cause mortality with higher DDS (score: 8-9) versus lowest DDS (score 0-1).
Results: We identified 8445 death events over 57,685 person-years of follow up. Compared with participants in the lowest DDS group (score 0-1), higher DDS was associated with lower mortality risk in the univariate models. After adjusting for potential confounders, participants in the higher DDS group had a 9%-30% lower risk in all-cause mortality (p trend<0.001) compared to participants in the lowest DDS group. The inverse relationship between diet diversity score and all-cause mortality was also statistically significant in four food groups (vegetables, fish, fruits, and nuts). We observed similar results after including different confounders in model 2 and model 3 in the sensitivity analyses.
Conclusions: Dietary diversity is inversely associated with all-cause mortality among the Chinese elderly, especially in the oldest old and men. These findings suggest that increasing dietary diversity may lower mortality rates in older population and that tailored interventions on improving dietary diversity may improve health and increase survival in this population.

95 | Evaluation of reporting quality for prediction models of HBV-related hepatocellular carcinoma by tripod statement

Liyuan Tao, Lin Zeng, Nan Li, Yanyan Si, Hua Zhang, Xiaoxiao Wang, Hongling Chu, Kaiwen Ni, Xiaoli Liu, Siyan Zhan and Lin Zhuo
Peking University Third Hospital, Beijing, China

Background: The design, conduct, analysis, and reporting of risk prediction model studies should be complete, transparent, and accurate. To improve the reporting quality, a guideline for the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) with a checklist of 22 items was developed and published in 2015, and previous studies showed that quality of reporting of prediction model studies is poor. However, none of them assessed the reporting quality in viral hepatitis domains.
Objectives: To assess reporting quality of predication models for viral hepatitis using the TRIPOD checklist.
Methods: We searched PubMed, Embase, and Web of science from inception to 1 June 2019, to identify potentially relevant scientific papers reporting original research. We assessed the reporting quality of eligible articles according to the TRIPOD checklist.
Results: A total of 38 papers were included in the final analysis. Only 10 (26.32%) papers completed reporting for >75% items per publication. Among all the TRIPOD items, the poor reporting items were title (26.32% [10/38]), descriptions of outcome (24.24% [8/33]), predictors (15.15% [5/33]), sample size (0.00% [0/38]), missing data (i2.63% [1/38]), and risk groups (36.00% [9/25]) in the methods. The median proportion of completeness of reporting per publication was 70.56% (IQR: 63.33%-75.86%). Completeness of reporting per publication did not statistically significant in different year of publication, type of study, and study design. In the multivariate model, after adjustment of potential confounders, impact factor of published journal (OR=10.14, 95% CI: 1.66-61.84) and sample size (OR=22.77, 95% CI: 1.10-472.57) was independently associated with sufficient reporting.
Conclusions: The reporting quality of the overall and some key items were not sufficient in studies focusing on developing and external validation of prediction models for HBV-related HCC development or prognosis. More attentions should be paid on the complete and transparent reporting.

2352 | Elevated risk of hospitalization for infection in anemic patients in Japan at the beginning of impaired renal function

Tomomi Kimura[1], Satoshi Onozawa[2], Masataka Morita[2], Osamu Yamamoto[2] and Tadao Akizawa[3]
[1]Astellas Pharma US Inc., Northbrook, IL; [2]Astellas Pharma Inc., Tokyo, Japan; [3]Showa University, Shinagawa City, Japan

Background: Anemia in chronic kidney disease (CKD) is known to be associated with an increased risk of renal and/or cardiovascular outcomes, as well as higher mortality. Anemia is also associated with chronic infection, but the association with acute, severe infection at early stage CKD has not yet been elucidated in the Japanese population.
Objectives: To descriptively compare the incidence and hazard ratio of the hospitalization for infection between anemic and non-anemic patients with early stages of impaired renal function.
Methods: This was a retrospective cohort study using annual health checkup data and insurance claims between 2008 and 2019 for employees and their dependents aged 74 years or younger, provided by JMDC. Subjects aged 18 years or older who had an estimated glomerular filtration rate (eGFR) of ≥60 ml/min/1.73m^2 at the previous checkup, and first experienced an eGFR <60, were enrolled and followed until hospitalization for infection or end of data period

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(including death). Anemia was defined with baseline hemoglobin value, age, and sex according to Japanese guidelines for Renal Anemia in Chronic Kidney Disease, regardless of treatment for anemia. Hospitalization for infection was defined as those with an anti-infective prescription on the admission date and infectious disease-related diagnosis codes on the inpatient claims. Propensity score for anemia (or non-anemia) at baseline was estimated and the stabilized inverse-probability-weighted Kaplan-Meier estimates were calculated. Hazard ratio was estimated using the Cox proportional hazard model adjusted for baseline age, sex, eGFR, proteinuria, Charlson comorbidity index score, HbA1c, systemic blood pressure, and current smoking status.

Results: In total, 32,870 subjects were enrolled and followed-up in an average of 4.1 years. At baseline, 1,396 (4.2%) of the subjects were anemic. The crude incidence rates per 1000 person-years (95% confidence interval [CI]) were 7.64 (5.55-10.26) in anemic group vs 2.30 (2.05-2.58) in the non-anemic group. Unweighted and weighted 5-year Kaplan-Meier survival estimates (95% CI) of time to first hospitalization for infection in the anemic and non-anemic groups were 96.5 (95.2-97.5) vs 98.9 (98.8-99.1) and 97.6 (95.7-98.7) vs. 98.9 (98.8-99.0), respectively. The adjusted hazard ratio (95% CI) was 2.349 (1.672-3.301).

Conclusions: Anemia in very early stage CKD was associated with elevated risk of hospitalization for infection, independent of the level of renal impairment.

2370 | Doxycycline adherence scale: The impact on the incidence of leptospirosis among flood affected South Indian population

Jose J. Kochuparambil[1] and Aleena Issac[2]
[1]*St. Joseph's College of Pharmacy, Cherthala, Alappey, India;* [2]*Nirmala College of Pharmacy, Muvattupuzha, India*

Background: Leptospirosis is a zoonotic disease caused by *Leptospira* after flood or heavy rain. Doxycycline is the most commonly used prophylactic antibiotic for the prevention of leptospirosis. Adherence to doxycycline is crucial in case of moderate to severe exposure to contaminated water. Non-adherence and unawareness towards chemoprophylaxis after the flooding in the Indian state of Kerala on the year 2018 contributed towards an epidemic. This incident pointed towards the need of developing and implementing a scale to assess adherence towards doxycycline.

Objectives: To develop and implement a scale to measure adherence to the administration of doxycycline.

Methods: A five-item doxycycline adherence scale was prepared based on the leptospirosis policy statement of the health ministry and insights from the past incidence of leptospirosis. This prospective, interventional study included 200 flood victims aged 18 years and older, displaced from the home and staying in the rescue homes. They were interviewed for basic demographic details and the doxycycline adherence scale was given to them for the next 5 weeks on a weekly basis by 5 different interviewers. Half of the study sample was provided with counseling on rational use of doxycycline. The impact of counseling and adherence to therapy in reducing the incidence of leptospirosis was analyzed by comparing the response from infected to the non-infected responders with chi-square method with p value < 0.05 to be significant.

Results: 161 (80.5%) people were adherent to the doxycycline chemoprophylaxis and 17 cases of leptospirosis (9.5%) were reported among the cohort by the health workers. The number of cases of leptospirosis reported among the adherents vs non-adherents (3% vs 31%, $p < 0.001$) and among the population that received counseling vs no counseling (2% vs 15%, $p < 0.001$) showed statistically significant results.

Conclusions: Proper adherence and providing counseling regarding the rational use of medicines and health habits can decrease the incidence of leptospirosis. Implementation of doxycycline adherence scale can help to monitor the patients and provide corrective intervention regarding non-adherence.

2467 | Clinical characteristics of sepsis patients by survival status: An analysis of electronic medical records

Brian Buysse[1], Claire Le Nguyen[1] and Jessica Albano[2]
[1]*Syneos Health, Farnborough, United Kingdom;* [2]*Syneos Health, Morrisville, NC*

Background: Sepsis-related mortality is estimated to be 20% globally. There is lack of understanding characteristics of patients with fatal sepsis.

Objectives: To describe clinical characteristics of sepsis deaths and of those who survived sepsis using a US database of electronic medical records (EMRs).

Methods: EMR data of patients with newly diagnosed sepsis within 12 months (ICD-10 codes included A40 and A41) in the past 5 years was analyzed in TriNetX Analytics (TriNetX, Cambridge, US; January 2020), a live database of ~60M US patients. Disease diagnoses, microbiological investigations and antimicrobial therapy were assessed in two cohorts, one of patients who had died within 1 month of sepsis diagnosis (deceased) and one of patients who had lived for at least 6 months (survived).

Results: Included were 21,241 deceased and 90,304 surviving patients. Deceased patients were older at sepsis diagnosis than surviving patients (mean 69.3 and 57.4 yrs, respectively) and had greater prevalence of chronic conditions recorded in the year before sepsis. For instance, metastatic cancer was 4 times more frequent in deceased than in surviving patients. Microbiological investigations within 7 days before and including day of sepsis were done in only 34% of deceased and 38% of surviving patients. About 25% of both cohorts received antimicrobials within 30 days before sepsis. Antibiotics were given to ~80% of both cohorts in the 7 days following and including day of sepsis diagnosis, and this was higher in patients with microbiological investigations (87% in both cohorts). In deceased patients, vancomycin plus piperacillin-tazobactam was the most common first-line (15% of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients) and second-line (10%) therapy. In contrast, ceftriaxone monotherapy was the most common first-line antibiotic therapy in surviving patients (13%)—only 7% received vancomycin plus piperacillin-tazobactam as first-line therapy. The two most common second-line therapies in surviving patients were levofloxacin (7%) and amoxicillin (7%); only 2% of deceased patients took levofloxacin and only 1% amoxicillin. Antifungal therapy following sepsis diagnosis was higher in deceased (16%) than in surviving patients (3%).

Conclusions: These results lay bare differences between patients who survive and succumb to sepsis in the US. The apparent low use of blood culture tests indicates that most patients receive empirical antimicrobial treatment. Differences in antimicrobial treatment between deceased and surviving patients may be explained by sepsis cause and severity. Sepsis and death are known to undercoded in EMRs, so results are approximate.

2484 | Comorbidities analysis of patients with atopic dermatitis on non-biologic systemic drug therapy using optum electronic health records databases

Huifang Liang[1], Varinder Singh[2], Dongmu Zhang[1], Jianzhong Liu[1], Philip Sugerman[1], Colleen Wegzyn[1] and Ryan D. Kilpatrick[1]
[1]AbbVie Inc., North Chicago, IL; [2]Syneos Health, Morrisville, NC

Background: Managing comorbid conditions may improve treatment outcomes in patients with atopic dermatitis (AD). Limited data exist on comorbidities in AD patients who are on non-biologic systemic drug therapy.

Objectives: To describe comorbidities in AD patients who are on non-biologic systemic drug therapy.

Methods: A retrospective cohort study was performed to identify patients with AD in the Optum™ Electronic Health Records Databases from 2008-2018 based on the algorithm of Silverberg et al. The algorithm uses two diagnoses of AD, or the combination of (i) one diagnosis of eczema or rash and nonspecific skin eruption and (ii) ≥2 historic codes for asthma, food allergies or allergic rhinitis. Patients were eligible if they were in the integrated data network and had ≥1 year of activity before the index date (or the first date of receiving non-biologic systemic drug therapy after the diagnosis date). Prespecified thirteen comorbidities of interest were assessed using data within one year before the index date. Descriptive statistics were generated for overall and pediatric and adult populations separately.

Results: A total of 286,941 patients were included. Their mean age was 37.1 ± 26.9 years, with children and adults being 34.4% and 65.6%, respectively. Overall, females were predominant (73.3%) among adults; however, males were predominant among children (56.4%). The majority of non-biologic systemic immunosuppressants were corticosteroids (97.6%). The use of the index systemic immunosuppressants was higher in adults than children (3.3% vs 0.64%). Among patients with AD who were on non-biologic systemic drug therapy, over 75% of adults and over 20% of children had at least one comorbidity. More females than males had comorbidities (73.8% vs 63.4%). Asthma was the most common allergic comorbidity in both adults (33.3%) and children (39.1%). Several neuropsychiatric disorders were also common in all patients: sleep disturbances (adults vs children: 20.2% vs 5.2%), anxiety (24.3% vs 2.6%), depression (24.0% vs 1.1%), and attention-deficit/hyperactivity disorder (ADHD) (2.6% vs 4.0% in children). In addition, common non-allergic comorbidities in adults included hypertension 47.2%, hyperlipidemia 42.1%, and diabetes 18.8%.

Conclusions: In patients with AD on non-biologic systemic drug therapy, asthma is the most common allergic comorbidity; common non-allergic comorbidities include sleep disturbances, depression and anxiety. Screening and intervening on atopic and nonatopic comorbidities are essential to alleviating the burden for patients with AD.

2512 | Comorbidities and characteristics in a cohort of patients with NAFLD/NASH from the Netherlands

Jetty A. Overbeek[1], Marieke Krol[2], Kelly Mulder[2], Marina Bakker[1], Ger H. Koek[3] and Ron M.C. Herings[1,4]
[1]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands; [2]IQVIA, Amsterdam, Netherlands; [3]Maastricht UMC, Maastricht, Netherlands; [4]VU University Medical Center, Amsterdam, Netherlands

Background: The burden of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) is increasing. However, limited real-world information is available regarding patients with NAFLD/NASH in Europe.

Objectives: To create a dynamic cohort of patients suffering from NAFLD and/or NASH with detailed information to study the safety and effectiveness of future treatment options.

Methods: All patients with a diagnosis of hepatic steatosis in the General Practitioner (GP) Database of the PHARMO Database Network in the period 2009-2018 were selected. The date of first recorded diagnosis was defined as the index date. All patients were followed from index date until end of study period, data availability or death, whichever occurred first. Patients were characterised in terms of demographics, laboratory measurements, comorbidities and medication use.

Results: In total, 9,050 patients were included. Of these patients 54% was male and the mean age (±SD) was 55 (±14) years. The mean (±SD) BMI at index date was 31 (±5) kg/m^2 and 43% was current or former smoker. The median (IQR) ALAT, ASAT and bilirubin value at index date were 51 (33-76) U/l, 35 (26-50) U/l, and 9 (7-12) μmol/L, respectively. The mean (±SD) lipid values at index date were 5.2 ± 1.2 mmol/l (total cholesterol), 3.0 ± 1.0 mmol/l (LDL), 1.2 ± 0.4 mmol/l (HDL), and 2.2 ± 1.5 mmol/l (triglycerides). The most common comorbidities were uncomplicated hypertension (2.9%) and type 2 diabetes (2.7%). In the year before the index date the most frequent reasons for GP visits were general complaints, such as abdominal pain (6%) and weakness/

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

tiredness (6%). The most frequently prescribed drugs were omeprazole (26%), diclofenac (16%) and simvastatin (15%).

Conclusions: This study from PHARMO's GP database gave insight in the characteristics of a real-world cohort of NAFLD/NASH patients from the Netherlands. At index the majority of patients were obese and had elevated ALAT levels. Further criteria are needed to distinguish between NAFLD and NASH. This cohort makes it possible to study patients with NAFLD/NASH in a real-world setting.

2518 | Risk of hospitalisation due to infection in patients with psoriasis: A population-based cohort study using the United Kingdom clinical practice research datalink

Zenas Z.N. Yiu[1], Rosa Parisi[1], Mark Lunt[1], Richard B. Warren[1], Christopher E.M. Griffiths[1], Sinéad M. Langan[2] and Darren M. Ashcroft[1]

[1]*University of Manchester, UK, Manchester, United Kingdom;* [2]*London School of Hygiene and Tropical Medicine, London, United Kingdom*

Background: Psoriasis is associated with multiple comorbidities and treated with systemic therapies that may increase the risk of serious infections. The relationship between psoriasis and serious infection, however, is as yet unclear.

Objectives: The primary objective was to determine whether patients with psoriasis have a higher risk of hospitalisation due to infection; the secondary objective was to determine whether patients with psoriasis have a higher risk of death due to infection compared with matched patients without psoriasis from primary care.

Methods: We performed a cohort study of adult patients (≥18 years of age) with psoriasis delineated from the UK Clinical Practice Research Datalink (CPRD GOLD) and linked to Hospital Episode Statistics (HES) and national mortality records between 01/04/2003 and 31/12/2016. Each patient with psoriasis was matched to up to 6 individuals without psoriasis on age, sex, and primary care practice. Hospitalisation due to infection was ascertained in the linked HES records. Unadjusted and adjusted stratified Cox proportional hazard models were estimated, with the adjusted model inclusive of potential confounders such as lifestyle factors and comorbid conditions.

Results: 69,312 patients with psoriasis and 338,598 comparison patients were followed up for a median (inter-quartile range [IQR]) of 4.9 (5.9) and 5.1 (6.3) years respectively. Patients with psoriasis had a higher incidence rate of serious infection (20.5/1000 person-years, 95% CI 20.0-21.0, n=7629) compared with those without psoriasis (16.1/1000 person-years, 95% CI 15.9-16.3, n=30756). The unadjusted hazard ratio for serious infection in patients with psoriasis was 1.46 (95% CI 1.42-1.50), and the fully adjusted hazard ratio was 1.36 (95% CI 1.31-1.40). The unadjusted hazard ratio for death due to infection in patients with psoriasis was 1.30 (95% CI 1.18-1.43), and the fully adjusted hazard ratio was 1.33 (95% CI 1.08-1.63).

Conclusions: Psoriasis is associated with a small increase in the risk of serious infection. Further research is needed to understand the mechanism by which psoriasis predisposes to a higher risk of infection.

2561 | 40-year mortality among patients hospital-diagnosed with overweight or obesity

Sigrid B. Gribsholt[1,2], Dóra K. Farkas[1], Reimar W. Thomsen[1], Bjørn Richelsen[1] and Henrik T. Sørensen[1]

[1]*Aarhus University, Aarhus N, Denmark;* [2]*Aarhus University Hospital, Aarhus N, Denmark*

Background: Obesity is a risk factor for several chronic diseases with an elevated mortality risk compared to the general population. Data on long-term mortality among persons with hospital-diagnosed obesity are limited.

Objectives: To examine 40-year mortality among patients with hospital-diagnosed overweight or obesity.

Methods: We used national registries covering the entire Danish population of 8,846,452 residents and all Danish hospitals between 1979 and 2018. We identified all Danes with a first incident hospital-based overweight or obesity diagnosis (median age 45 years), and constructed an age-, gender-, and index date-matched general population comparison cohort. We computed mortality risk and mortality rate ratios (MRRs) with 95% confidence intervals (CIs), using Cox regression.

Results: We observed 68,506 deaths among 322,130 persons (2,987,320 person years) with a hospital diagnosis of overweight or obesity, and 253,897 deaths among 1,610,596 persons (16,316,670 person years) in the comparison cohort, corresponding to an all-time MRR of 2.02 (95% CI: 2.01-2.04). The mortality risk for patients with overweight or obesity was increased in the first year (2.5% versus 0.4% in comparisons, MRR=6.58 (95% CI: 6.37-6.79)) of follow up. Mortality risk then remained approximately doubled throughout follow-up (1-10y MRR=1.80 (95% CI: 1.78-1.82); 11-20y MRR=1.92 (95% CI: 1.89-1.96); 21-30y MRR=2.05 (95% CI: 2.00-2.11), and 31-40y MRR=2.12 (95% CI: 2.00-2.24)). Patients with overweight or obesity had markedly higher all-time mortality due to diabetes and other endocrine diseases (MRR=4.99 (95% CI: 4.80-5.19)) and cardiovascular diseases (MRR=2.67 (95% CI: 2.63-2.72)), but also due to respiratory diseases (MRR=2.30 (95% CI: 2.24-2.36)), infectious diseases (MRR=1.83 (95% CI: 1.79-1.88), and cancer (MRR=1.48 (95% CI: 1.44-1.53)). The 1-10-year MRR associated with overweight or obesity decreased over calendar time: from 2.02 (95% CI; 1.98-2.06) in 1977-1989 to 1.63 (95% CI; 1.59-1.68) in 2010-2018.

Conclusions: Patients with hospital-diagnosed overweight or obesity had a two-fold increased long-term mortality, compared with the general population. Our data suggest an improved prognosis in patients with overweight or obesity over the last decades.

2569 | Incidence of anemia in patients with chronic kidney disease - A population-based cohort study

Søren V. Vestergaard[1], Uffe Heide-Jørgensen[1], Heleen van Haalen[2], Glen James[3], Katarina Hedman[2], Henrik Birn[4], Reimar W. Thomsen[1] and Christian F. Christiansen[1]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Aarhus University Hospital, Aarhus, Denmark; [2]AstraZeneca, Gothenburg, Sweden; [3]AstraZeneca, Cambridge, United Kingdom; [4]Aarhus University, Aarhus, Denmark

Background: Anemia is common in patients with advanced chronic kidney disease (CKD) and is associated with increased mortality risk.
Objectives: We conducted a population-based cohort study to clarify the incidence of anemia in patients with newly progressed CKD stages 3-5.
Methods: Using a population-based registry with complete laboratory test results available for the entire population of Northern Denmark (~1.9 million people) during 2009-2016, we identified cohorts of patients with newly progressed CKD (stages 3-5). CKD was defined by two creatinine tests ≥90 days apart both revealing an estimated glomerular filtration rate (eGFR, MDRD) <60 mL/min/1.73 m2. Patients entered a higher CKD stage cohort if their CKD deteriorated during the study period. We followed patients for incident anemia [hemoglobin (Hb) level <12 g/dl in women and <13 g/dl in men] and for incident events of mild (Hb >10 g/dL), moderate (Hb 8-10 g/dL), or severe (Hb <8 g/dL) anemia. We computed cumulative incidence proportions (risks) of anemia by CKD stage, examined anemia trajectories and calculated adjusted hazard ratios (HRs) of anemia by CKD stage, using multivariable Cox regressions with a robust sandwich estimator.
Results: We identified 55,940 individuals with newly progressed CKD in stages 3-5, who over time contributed to CKD stage cohorts [n=41,958 patients in 3a, n=17,875 in 3b, n=5,182 in 4, and n=931 in 5]. Within 1 year 36.1% (95% CI: 35.7 - 36.6) of patients with CKD 3a developed anemia, increasing to 62.3% (95% CI: 61.7 - 62.9) within 5 years. Anemia risks were higher in higher CKD stages, as 80.8% (95% CI: 80.1 - 81.5) of CKD 3b patients, 90.6% (95% CI: 89.6 - 91.5) of CKD 4 patients, and 98.8% (95% CI: 97.8 - 99.4) of CKD 5 patients developed anemia within 5 years. Cox regression showed increases in anemia hazards with increasing CKD stage [adjusted HRs of 1.55 (95% CI: 1.52 - 1.58) in CKD 3b; 2.38 (95% CI: 2.30 - 2.47) in CKD 4; and 5.42 (95% CI: 5.09 - 5.77) in CKD 5, compared to CKD 3a. One in five patients with any CKD stage 3-5, and half of all patients with CKD 5 experienced severe anemia (Hb <8 g/dL) during total 8 years of follow-up.
Conclusions: A substantial proportion of patients with newly progressed CKD develop anemia during the subsequent year, with increasing anemia risk at higher CKD stages. Clinicians should be aware of the high risk of anemia in patients with CKD stage 3-5 in everyday clinical care and exercise vigilance about associated complications.

2610 | Probabilistic linkage of the French cystic fibrosis patient registry with the French national health data system

Manon Belhassen[1], Deborah Walther[1], Lydie Lemonnier[2], Marjorie Bérard[1], Faustine Dalon[1], Isabelle Durieu[3] and Eric Van Ganse[1]
[1]PELyon, Lyon, France; [2]Association Vaincre la Mucoviscidose, Paris, France; [3]HESPER 7425, Health Services and Performance Research, Université Claude Bernard Lyon 1; Centre de Référence Adulte de la Mucoviscidose, Service de Médecine Interne, Hospices Civils de Lyon, Lyon, France

Background: To efficiently assess the management of the cystic fibrosis (CF), the French Cystic Fibrosis Patient Registry was linked to the SNDS (French Claims Data System, with information on health care utilization of the national population).
Objectives: The aim of this linkage was to build a complete dataset that will open up new perspectives of research on CF patients, such as the changes in healthcare consumption, and to relate it to the epidemiological transformation of CF.
Methods: The records of CF patients included between 2006 and 2016 in the French CF Registry were linked by probabilistic method to their corresponding SNDS data. To perform this linkage, a scoring system was developed with variables available in both data sources, ranging from the least (sex, month and year of birth, region of residence) to the most specific ones (dates of spirometry, dates of transplant, and sweat test). Next, a decision algorithm was developed. In a last step, to allocate remaining patients, "comorbidities" (e.g. diabetes, aspergillosis or pancreatic insufficiency) were used. Sensitivity analyses were performed using other scoring systems, to test the validity of the linkage.
Results: Of the 7,671 patients included in the French CF Patient Registry between 2006 and 2016, 6,186 patients (80.6%) could be linked to the SNDS. Non-linked patients were mainly children younger than 10 who had little or no spirometry data. The sensitivity analyses validated the linkage.
Conclusions: We performed one of the first linkages between a French registry and the SNDS. These two data sets include robust and complementary data, leading to an exhaustive database and opening new prospective to study the management of CF patients.

2674 | Characterization of women with adenomyosis identified in a large U.S electronic health record database with and without hysterectomy

Stephanie E. Chiuve[1], Anita M. Loughlin[2], Stacey A. Missmer[3], Michael C. Snabes[1], Keith Gordon[1], Gally Reznor[2], Michael C. Doherty[2] and Cheryl Enger[2]
[1]AbbVie, Inc, North Chicago, IL; [2]Optum, Boston, MA; [3]Michigan State University, Grand Rapids, MI

Background: Adenomyosis is the growth of endometrial tissue into the myometrium. Data on symptoms and comorbidities of adenomyosis have been limited primarily to women diagnosed via uterine histology after a hysterectomy. Although "endometriosis of the uterus" may be used as a surrogate for documentation, emerging hallmarks of adenomyosis do not overlap with endometriosis, and the lack of an ICD code for adenomyosis has limited studies of women living with adenomyosis.
Objectives: To characterize symptoms and comorbidities of women with affirmed adenomyosis, stratified by timing of hysterectomy

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: Women aged 18-55 years for whom adenomyosis was mentioned within clinical notes from 2014-2018 were identified using natural language processing of the Optum Electronic Health Record (EHR) database. The anchor date was the date of first affirmed mention of adenomyosis. Covariates were assessed in the 12 months prior to anchor date (baseline period).

Results: Among the 19,503 women with an affirmed mention of adenomyosis, 27% had an ICD code for "endometriosis of the uterus". Among these women, 84% were ≥36 years old, 68% were white, and 45% were obese. In the baseline period, 50% of women had a transvaginal ultrasound, 6% had a pelvic MRI, and 52% had a hysterectomy. Of women who had a hysterectomy, 31% occurred prior to, 56% occurred on and 23% occurred after the anchor date. Gynecologic comorbidities among women without hysterectomy, or women with hysterectomy timed prior to, at, or after anchor date, respectively, were endometriosis (19%, 72%, 32% and 28%), uterine fibroids (18%, 59%, 42% and 26%) and gynecologic cancer (7%, 16%, 10% and 7%). Gynecologic symptoms among women without hysterectomy, or women with hysterectomy timed prior to, at, or after anchor date, respectively, were heavy menstrual bleeding (47%, 78%, 70% and 66%), anemia (19%, 31%, 24% and 21%), pelvic pain (31% 50%, 35% and 42%), dysmenorrhea (18%, 38%, 33% and 30%), and dyspareunia (7%, 14%, 10% and 11%).

Conclusions: While symptoms and comorbidities of adenomyosis may be documented more consistently when diagnosis was made at or after hysterectomy, the ICD code for "endometriosis of the uterus" was documented for <1/3 of women with affirmed adenomyosis, missing 2/3 of diagnosed adenomyosis cases. This suggests that ICD-driven discovery is subject to misclassification and potential selection bias. Natural language processed clinical notes enabled the characterization of women living with adenomyosis that had not been studied previously.

2685 | Applying machine learning to define phenotypes of women with endometriosis undergoing laparoscopic surgery

Andrea K. Chomistek[1,2], Cheryl Enger[1,2], Stacey A. Missmer[3], Stephanie J. Estes[4], Jenna F. Calderbank[1,2], Michael C. Doherty[1,2] and Stephanie E. Chiuve[5]

[1]Optum, Boston, MA; [2]Optum, Ann Arbor, MI; [3]Michigan State University, Grand Rapids, MI; [4]Penn State Health, Hershey, PA; [5]AbbVie, Inc., North Chicago, IL

Background: Endometriosis is an often chronic, inflammatory gynecologic condition; endometriosis-related pain, dysmenorrhea (DYSM), and dyspareunia (DYSP) can impair quality of life. Laparoscopic surgery is used as first-line therapy to remove or ablate endometriosis to relieve pain or performed after failure of medical therapy.

Objectives: To identify phenotypes of women who have had laparoscopic surgery to treat endometriosis defined by patterns of clinical covariates.

Methods: This study was conducted in the Optum Research Database, a claims database from a large U.S. health insurer. Women aged 18-55 years who had a laparoscopic surgery (LS) within the abdomen or pelvic cavity (excluding hysterectomy and oophorectomy), in conjunction with an ICD-10 code for endometriosis within 30 days of surgery, between July 2016 and June 2018 were identified. Machine learning using an agglomerative hierarchical clustering analysis identified subgroups based on comorbidities, procedures, and medications within the 6 months prior to LS and a phenotype was defined for each subgroup based on clinical characteristics.

Results: The cohort included 4,878 women with LS with a mean age of 34 (SD: 8) years. Pain (pelvic, abdominal, lower back) was the most prevalent symptom (81%) and opioid analgesics (52%) and prescription nonsteroidal anti-inflammatory drugs (46%) were the most prevalent medications.

An 8-cluster solution was identified based on cluster statistics and covariate distributions. Among the 8 clusters, one cluster predominantly had endometriosis of the ovary, along with low frequency of pain medication, pain and mental health conditions (6%). Four clusters predominantly had endometriosis of the pelvic peritoneum and the phenotypes identified were: 1) low medication use, DYSM, DYSP, pain comorbidities and mental health conditions (11%); 2) high DYSM and DYSP but low pain medication (14%); 3) infertility and DYSM (5%); and 4) high DYSM, DYSP, pain comorbidities, pain medication, and mental health conditions (11%). Finally, 3 clusters had endometriosis of multiple sites and the phenotypes identified were: 1) high cardiometabolic comorbidities and pain medication use, but low DYSM and DYSP (11%); 2) high DYSM, DYSP, pain comorbidities, pain medication and poor mental health (21%); and 3) heavy menstrual bleeding and leiomyoma (21%).

Conclusions: Among patients with endometriosis who underwent laparoscopic surgery, we identified several phenotypes based on varying patterns of clinical covariates. Future studies might consider whether unmet needs for surgical avoidance differ by patient phenotype.

3695 | Occurrence of metabolic risk factors stratified by psoriasis severity: A Swedish population-based matched cohort study

David Hägg[1], Marie Linder[1], Mohammadhossein Hajiebrahimi[1], Ci Song[2], Therese M.-L. Andersson[3] and Reginald Villacorta[4]

[1]Karolinska Institutet, Centre for Pharmacoepidemiology, Stockholm, Sweden; [2]Janssen-Cilag, Stockholm, Sweden; [3]Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden; [4]Janssen Research & Development, LLC, Horsham, PA

Background: Psoriasis is a chronic immune-mediated inflammatory disease which can affect up to 8% of the population in Nordic countries. Patients with psoriasis experience an increased risk of developing metabolic risk factors such as diabetes mellitus (DM), hypertension (HTN) or hypercholesterolemia. Understanding whether patients with psoriasis are being actively managed regarding metabolic risk factors is a research gap in the literature. Based on prior work that demonstrated an increased risk of HTN and DM among Swedish

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients with severe psoriasis during a one-year period before anti-psoriasis drug prescription, the current study aims to understand the time to occurrence of metabolic risk factors such as DM, HTN and hypercholesterolemia.

Objectives: To assess relative risk of metabolic risk factors in patients stratified by psoriasis severity compared with population controls.

Methods: Retrospective cohort study conducted using national Swedish registers. Adult patients with psoriasis were selected if they had a dispensing of anti-psoriasis prescription (2007-2013) and at least one diagnosis within 5 years before the dispensing date. The patients with psoriasis were matched 1:10 to controls from the general population on birthyear, sex and county. The cohort was further divided into three disease severity groups (mild, moderate or severe) based on their dispensed anti-psoriasis medication. We applied flexible parametric modelling to understand the risks of the incident comorbidities HTN, hypercholesterolemia and DM among patients with psoriasis from 6 months through 10 years. Hazard ratios and predicted risk of comorbidities are reported.

Results: The hazard of HTN, hypercholesterolemia and DM is higher among psoriasis patients compared with population controls, and the hazard ratio increased following the psoriasis severity. For example, HRs of HTN for patients with mild, moderate and severe psoriasis are 1.29 (95% CI: 1.27-1.32), 1.35 (95% CI: 1.32-1.38) and 1.73 (95% CI: 1.64-1.82), respectively. The predicted risk of HTN, hypercholesterolemia, and DM among patients with severe psoriasis at year ten was 0.58 (95% CI: 0.56, 0.59), and 0.22 (95% CI: 0.21, 0.24) respectively while it was 0.42 (95% CI: 0.41, 0.43), 0.30 (95% CI: 0.30, 0.30), 0.11 (95% CI: 0.10, 0.11) among controls, respectively. The predicted risk at year ten was similar among patients with mild or moderate psoriasis.

Conclusions: The HRs and the predicted risks of metabolic risk factors are higher among patient with psoriasis compared with matched controls, and more prominent among the severe psoriasis group.

3722 | Identifying adenomyosis and undiagnosed adenomyosis within natural language processed clinical notes of an electronic health record database

Anita M. Loughlin[1], Gally Reznor[1], Michael Doherty[1], Stacey A. Missmer[2], Stephanie E. Chiuve[3] and Cheryl Enger[4]
[1]*Optum, Boston, MA;* [2]*Michigan State University, Grand Rapids, MI;* [3]*AbbVie Inc., North Chicago, IL;* [4]*Optum, Ann Arbor, MI*

Background: Often diagnosed at hysterectomy, adenomyosis is the presence of endometrial tissue within the myometrium. The prevalence of identified adenomyosis is low (0.17%) due to diagnostic challenges and lack of a specific ICD code.

Objectives: To identify women with adenomyosis using NLP data in the Optum EHR database and to estimate the prevalence of potentially undiagnosed adenomyosis (PUA).

Methods: Adenomyosis cases were identified from a population of 11,456,347 women aged 18-55 years with NLP data in the EHR (2014-2018). Adenomyosis mentions were scored by applying a rank to sentiments (-1 to +2) and modifiers (-2 to +1); range of total possible scores was +3 to -3. An affirmed adenomyosis mention had a score of +2 or +3. The anchor date was set at the date of first affirmed adenomyosis mention. Baseline characteristics were assessed in the 12 months prior to the anchor date. Characteristics common to adenomyosis cases were used to select a suitable pool from the underlying population among whom undiagnosed adenomyosis might exist. Adenomyosis cases were compared to a sample of the suitable pool (comparators) using logistic regression, and we determined the predictive probability (PP) of being an adenomyosis case. The proportion of the comparators having a PP > 0.1 was considered PUA; 75% of adenomyosis cases and 7% of comparators had PP > 0.1. We extrapolated the proportion of PUA in the comparators to calculate the prevalence of PUA in the underlying population.

Results: There were 19,503 women with affirmed adenomyosis. Of the 332,583 comparators, we identified 22,696 women with PUA. The PUA prevalence estimate was 19.1 per 1,000 women aged 18-55 years. The majority of women with adenomyosis and PUA, respectively, were aged 36-55 years (84%, 86%) and white (69%, 66%). The frequency of transvaginal ultrasound, pelvic MRI, and hysterectomy, respectively, was 50%, 6%, and 16% in adenomyosis cases and 46%, 5% and 5% in PUA cases. Women with adenomyosis and PUA, respectively, had similar frequency of heavy bleeding (60%, 60%), pelvic pain (36%, 36%) and dysmenorrhea (26%, 22%). Gynecologic comorbidities appeared higher in adenomyosis cases relative to PUA: endometriosis (31%, 11%) and uterine fibroids (31%, 25%).

Conclusions: Using NLP and considering PUA, the prevalence of adenomyosis may be up to 10x higher than prior estimates. Identification of adenomyosis in real world data may improve disease characterization and assessment of treatment effectiveness. Increased diagnostic suspicion and early detection may facilitate better management among symptomatic women.

3735 | Treatment, healthcare resource utilization, and healthcare costs for medicare patients with generalized pustular psoriasis and palmoplantar pustulosis

Allison A. Petrilla, Sudeepti Pahuja, Shambhavi Kumar and Courtney R. Jaeger
Avalere Health, Washington, DC

Background: Generalized Pustular Psoriasis (GPP) and Palmoplantar Pustulosis (PPP) are rare and severe distinct disease entities from plaque psoriasis; however, the burden of illness for these patients is unknown.

Objectives: To characterize treatment patterns, healthcare utilization (HCRU) and costs for a cohort of GPP and PPP patients in the US Medicare Fee-for-Service population.

Methods: GPP and PPP patients were identified by ≥ 1 inpatient or ≥ 2 outpatient diagnoses (at least 30 days apart) in a 100% sample of Medicare FFS beneficiaries between January 1, 2016 and December

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

31, 2017. Patients were required to have ≥ 6 months of continuous medical and pharmacy coverage prior to the date of diagnosis (baseline period) and ≥ 12 months of the same continuous coverage following the diagnosis (follow-up period). Demographics, comorbidities, and treatment patterns were captured during the baseline period. Treatment patterns, all cause HCRU, and total direct healthcare costs were measured during the follow-up period in 6-month increments using descriptive statistics.

Results: 1,818 GPP and 1,968 PPP patients were identified. GPP and PPP patients were primarily Caucasian (GPP: 86%; PPP: 85%) and female (GPP: 74%; PPP: 66%) with a mean age of 68 at index diagnosis. 39.4% of GPP and 34.2% of PPP patients originally qualified for Medicare benefits due to disability rather than age. Hyperlipidemia (GPP: 90%; PPP: 87%), Type 2 Diabetes Mellitus (GPP: 56%; PPP: 46%), and other psoriasis conditions (GPP: 54%; PPP: 41%) were the most common comorbidities. Patients with GPP and PPP were mostly treated with steroids or biologics; adalimumab was the most commonly used biologic. At 12-month follow-up, mean counts of hospitalizations, ER visits, and outpatient visits were (GPP: 2.0; PPP: 1.6), (GPP: 2.4; PPP: 2.0), and (GPP: 41.6; PPP: 36.1), respectively. Median costs for GPP and PPP patients were (GPP: $4,205.10; PPP: $2,954.71) at baseline, (GPP: $5,253.20; PPP: $3,294.35) at 6 months, and (GPP: $10,646.87; PPP: $7,005.84) at 12 months of follow-up.

Conclusions: Medicare beneficiaries with GPP and PPP frequently treated with steroids and biologics incur high costs associated with HCRU. Future research should examine long term HCRU and economic burden across different payer types.

3741 | The spectrum of adenomyosis identified in a large US electronic health record database

Anita M. Loughlin[1], Gally Reznor[1], Michael Doherty[1], Stephanie E. Chiuve[2] and Cheryl Enger[3]

[1]Optum, Boston, MA; [2]AbbVie Inc, North Chicago, IL; [3]Optum, Ann Arbor, MI

Background: Adenomyosis, the presence of endometrial tissue within the myometrium, can co-exist conditions such as endometriosis and leiomyomas that have symptoms in common; thus it is difficult to delineate of symptom profiles specific to adenomyosis. Until recently, a definitive diagnosis was made by hysterectomy, recently use of MRI and transvaginal ultrasound allow for non-surgical diagnosis.

Objectives: To examine the spectrum of the clinical presentation of adenomyosis.

Methods: Characteristics of women aged 18-55 years, with an affirmed mention of adenomyosis, identified in the natural language processed clinical notes of the Optum EHR database (2014-2018) were assessed. An anchor date was set as date of first qualifying adenomyosis mention. Baseline characteristics were identified in the 12 months prior to anchor date. A predictive probability (PP) model compared adenomyosis cases to a sample of symptomatic women aged 18-55 years without an affirmed adenomyosis mention. Adenomyosis cases were stratified by PP, and baseline characteristics were assessed across strata.

Results: 19,503 women with adenomyosis were stratified from highest to lowest PP, specifically, 3,336 (PP, ≥ 0.9); 3,651 (PP, 0.6-0.8); 3,523 (PP, 0.3-0.5); 3,857 (PP, 0.1-0.2); and 5,136 (PP, <0.1). Women in the highest PP strata were proportionally more likely to be 35+ years of age (93%, 90%, 88%, 83%, and 71%) and to have been pregnant (74%, 65%, 64%, 56%, and 32%), relative to women in the lowest PP strata. Likewise, women in the highest PP strata were more symptomatic–heavy menstrual bleeding (HMB) (87%, 78%, 74%, 56%, and 23%), pelvic pain (52%, 44%, 39%, 33%, and 22%), dysmenorrhea (46%, 36%, 29%, 19%, and 10%), and gastrointestinal (GI) symptoms (51%, 47%, 44%, 41%, and 38%). General symptoms were predominant symptoms among women in lowest PP stratum, i.e., abdomen/ lower back pain (41%) and GI (38%), while the prevailing symptoms in women in higher PP strata were HMB (87%) and pelvic pain (52%). Women in the highest PP strata had more gynecologic comorbidities–endometriosis (93%, 47%, 18%, 10% and 5%), leiomyomas (57%, 46%, 34%, 22%, and 8%), uterine polyps (13%, 8%, 5%, 4%, and 1%) and hysterectomy (51%, 23%, 11%, 5%, and 2%), relative to those in the lower PP strata.

Conclusions: Using PP stratification of the cases, we show that the adenomyosis clinical presentation can ranged from mildly symptomatic to severely symptomatic, making recognition of disease and management of adenomyosis often difficult. Understanding symptom profiles may improve diagnostic suspicion, early detection, and lead to more treatment options for women with adenomyosis.

3742 | Dopamine agonists and risk of lung cancer

Maria P. Hernandez-Con[1], Justine Shults[1,2], Allison Willis[1] and Yu-Xiao Yang[1]

[1]University of Pennsylvania, Philadelphia, PA; [2]Children's Hospital of Pennsylvania, Philadelphia, PA

Background: There is a clinical need to identify novel chemopreventive and therapeutic targets for lung cancer because it remains the leading cause of cancer deaths worldwide despite newer treatment options. Preclinical evidence suggests that dopamine receptor activation induces apoptosis and inhibits cancer cell proliferation in lung cancer. Dopamine agonists (DAs) are commonly used in Parkinson's disease (PD) and restless leg syndrome (RLS).

Objectives: To determine the association between long-term DA use and the risk of lung cancer.

Methods: We conducted a population-based retrospective cohort study using private insurance administrative claims data from Optum®ClinformaticsTMData Mart (1/2006 - 12/2016). The study population included all adults ≥ 40 years who had ≥ 1 outpatient or inpatient ICD-9 or ICD-10 diagnosis for RLS recorded during the study period. We excluded PD patients because PD itself is associated with a lower overall risk of cancer. Cohort follow-up started on the date of first RLS diagnosis and ended on the earliest of the following: incident diagnosis of lung cancer, end of enrollment in the database or

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

end of study period. The exposure of interest was cumulative duration (i.e., no use or ≤1 year [reference group], 1- 3 years and > 3 years) of DA (i.e., pramipexole, ropinirole or rotigotine) use, measured in a time-varying manner. The outcome was time to incident lung cancer. We constructed a multivariable Cox regression model to estimate the HRs and 95% CIs for lung cancer associated with cumulative durations of dopamine agonist use. The model was adjusted for the following covariates: age, gender, race/ethnicity, area of residence, chronic obstructive pulmonary disease (COPD), tobacco use and interstitial lung disease (ILD).

Results: Over the 11-year study period, we identified 303,079 eligible patients with a diagnosis of RLS. The mean age of the study population was 62.9; 66.3% were women and 82.3% were white. The prevalence of any DA exposure in the study population was 48.2%. Compared to the reference exposure group, the crude HRs for lung cancer were 1.16 (95%CI 1.03 -1.3) and1.33 (95% CI 1.09 -1.62) for 1-3 years and > 3 years of cumulative DA use, respectively. In multivariable Cox regression analysis, the adjusted HR for lung cancer was 1.00 (95% CI 0.89-1.13) for 1-3 years of cumulative DA use and 1.09 (95% CI 0.89-1.34) for > 3 years of cumulative DA use.

Conclusions: At doses typical for the clinical management of RLS, long-term DA use was not associated with the risk of lung cancer. Future studies are needed to determine whether there is a clinically apparent anti-cancer effect of DA exposure at higher doses as those used in animal experiments.

3834 | 21-year trends in first hospitalization for acute urinary retention and subsequent mortality in the Danish male population: A nationwide cohort study

Maria B. Bengtsen[1], Uffe Heide-Joergensen[1], Michael Borre[2] and Mette Nørgaard[1]

[1]*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark*; [2]*Department of Urology, Aarhus University Hospital, Aarhus N, Denmark*

Background: Acute urinary retention (AUR) is a severe complication to benign prostatic hyperplasia associated with high mortality among men in all ages. Limited data exist on trends in incidence and mortality after hospitalization for AUR after the introduction of medical therapy for benign prostatic hyperplasia in the mid 1990's.

Objectives: To investigate trends in AUR incidence and mortality after the introduction of medical therapy for benign prostatic hyperplasia.

Methods: We conducted a nationwide registry-based study in Denmark of all men aged above 50 years with a first hospital (inpatient, outpatient or emergency room) diagnosis of AUR between 1997 and 2017. We used the Danish National Patient Registry and the Danish National Prescription Registry to compute baseline characteristics and proportion of men who redeemed prescription of drugs associated with AUR within 90 days before AUR diagnosis. We computed the standardized incidence rate and the standardized 3-month and 1-year mortality rate after first diagnosis of AUR. Using the Kaplan Meier method, we estimated mortality overall and according to age and Charlson Comorbidity Index (CCI) Score.

Results: We identified 77,047 men above 50 years with a first hospital diagnosis of AUR. The median age was 76 (interquartile range: 68-83) years and 54 % had moderate to severe comorbidity (CCI score ≥1). At time of first AUR diagnosis, about half (49 %) had previous benign prostatic hyperplasia/lower urinary tract symptoms; 11 % had urogenital cancer; 16 % had diabetes and 12 % had chronic pulmonary disease. Within 90 days before AUR diagnosis, 18 % had redeemed a prescription for opioids, 17 % benzodiazepines and 19 % antipsychotics. The standardized incidence rate increased with 30 % during 1997-2017; from 3.1 (95 % CI: 3.0-3.2) per 1000 person-years in 1997 to 4.0 (95 % CI: 3.9-4.7) in 2017. The increase in incidence occurred during 1997-2004, and then remained stable during 2005-2017. The 3-month standardized mortality rate decreased from 10.9 % (95 % CI: 9.5-12.2) in 1997 to 7.9 % (95 % CI: 7.0-8.7) in 2017, and 1-year mortality from 23.7 % (95 % CI: 21.7-25.7) in 1997 to 18.1 (95 % CI: 16.8-19.4) in 2017.

Conclusions: The standardized incidence rate of AUR has increased with 30 % since the introduction of medical therapy, but has remained stable since 2005. Despite a slight decrease in mortality, men hospitalized for AUR remains to have a high mortality.

3837 | Prevalence of contraindication in chronic kidney disease according to eCrCl and eGFR equations and patient related risk factors

Susanne Stolpe and Cornelia Blume

Institute of Technical Chemistry, Leibniz University, Hannover, Germany

Background: Contraindicated (CI) medications in patients with chronic kidney disease (=CKD, glomerular filtration rate (GFR) <60ml/min) negatively impact patients health outcomes. Drug safety information for medications is derived from analyses of kidney function using creatinine clearance (CrCl), in diagnosis, prognosis and treatment of CKD equations normalized on body surface are used to estimate GFR (eGFR).

Objectives: To estimate prevalence of CI medication in non-institutionalized CKD patients using CrCl and eGFR equations and to identify patient groups at higher risk for CI

Methods: We analysed information of 13.338 patients (aged 18-99 years) using baseline data collected in 2010 from the German ",Kern-database." The database comprises patients from five German cohort studies and registries dealing with CKD and related comorbidities (GCKD, 4C, CADRef, DiabCore, BIS). Potential CI medications were identified using PRISCUS-list, BEERS list, START/STOPP-criteria and from literature. eGFR-was calculated with CKD-Epi and the Modification of Diet in Renal Disease (MDRD) equation, CrCl was estimated using the Cockcroft-Gault equation (CG). Prevalence of CKD and of CI was estimated with these equations.

Results: Prevalence of CKD differed by equation: 34% [95%CI: 33%-35%] using CG, 47% [46%-47%] with CKD-Epi and even 49% [48%-

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

50%] with MDRD. Prevalence of CKD4+ (=eGFR <30ml/min) was 2.2% [1.9%-2.4%] with CG, 5.2% [4.8%-5.5%] using CKD-Epi and 5.4% [5.0-5.8] with MDRD equation. Number of drugs taken increased with CKD -stage, but not with age.

Proportion of CI was about 3.4% in CKD3 using any equation. In CKD4, proportion of CI was distinctly higher and depending on GFR equation used: 38% [35%-42%] (MDRD), 41% [37%-44%] (CKD-Epi), and 45% [39%-51%] with CG. Risk for CI increased with number of drugs taken and with risk of kidney failure -calculated with the Kidney-failure-risk-equation. Women (RR=1.3 [1.1-1.5]) and patients unaware of their disease (CKD3: 1.3 [0.9-1.8], CKD4: RR 1.8 [1.5-2.2]) were at higher risk for CI medication. Most CI medications were anti-hypertensive or anti-diabetic drugs. CIs identified by CG only concerned patients in higher ages, relating to hydrochlorothiazide.

Conclusions: The variety of equations for estimating renal function limits comparability of prevalence information for CKD. Precise identification of CIs is aggravated. CI medication is highly prevalent in CKD4 patients. Especial attention to prevent CI medication should be given to female CKD-patients and to patients with polymedication and at higher risk for kidney failure.

3920 | Participant engagement in an arthritispower real-world study to capture smartwatch and patient-reported outcome data among rheumatoid arthritis patients

Jeffrey R. Curtis[1], W. Benjamin Nowell[2], Fenglong Xie[1], Hong Zhao[1], David Curtis[2], Kelly Gavigan[2], Shilpa Venkatachalam[2], Laura Stradford[2], Jessica Boles[2], Justin K. Owensby[1], Cassie Clinton[1], Ilya Lipkovich[3], Amy Calvin[3] and Virginia S. Haynes[3]

[1]University of Alabama at Birmingham, Birmingham, AL; [2]Global Healthy Living Foundation, Upper Nyack, NY; [3]Eli Lilly and Company, Indianapolis, IN

Background: Clear characterization of how different types of patient-generated data reflect patient experience is needed to guide integration of electronic patient-reported outcome (ePRO) measures and biometrics in generating real-word evidence (RWE) related to rheumatoid arthritis (RA).

Objectives: To characterize the level of participant (pt) engagement/adherence and data completeness in an ongoing study of 250 RA pts enrolled in the Digital Tracking of Arthritis Longitudinally (DIGITAL) study of the ArthritisPower (AP) real-world registry.

Methods: AP pts with RA joined a digital RWE study with 14-day lead-in and 12-week main study period. Pts who completed the lead-in received a smartwatch (Fitbit Versa) and study materials. The smartwatch collected activity, heart rate, and sleep duration/quality biosensor data; a study-specific customization of the AP mobile application collected ePROs. The main study period included automated and manual reminders/prompts to complete ePROs, wear the smartwatch, and sync regularly. Study coordinators monitored pt data and contacted pts via email, text and/or phone to resolve adherence issues based on pre-determined rules triggering pt contact. Pts were considered adherent if providing (1) daily ePROs for ≥5 of 7 days/week, (2) weekly ePROs and (3) ≥80% of synced activity data for ≥5 of 7 days/week.

Results: As of December 2019, 170 AP members had enrolled and completed at least 30 days of the main study period; 92.9% female with mean (SD) age 52.5 (10.7) and 10.5 (10.4) years since diagnosis. The overall conversion rate from initial interest to successful completion of the lead-in period was 49.0%. Pts who advanced to the main study were significantly more likely to be employed (52.9%) and on a biologic DMARD monotherapy (64.7%). Overall, daily ePRO data had the lowest adherence (70.0% of pts providing >70% of requested data) across the first 30 days of the study period. Composite adherence was met by 66.5% of pts. Activity data had the highest adherence and persistence, with 92.9% of pts providing 80% or more of activity data for each 24-hour period in the first 30 days. Observed weekly adherence did not decline over time.

Conclusions: RWE studies involving passive data collection in RA require pt-centric implementation and design to minimize pt burden, promote longitudinal engagement, and maximize adherence. Passive data capture via activity trackers such as smartwatches, along with regular contact such as automated reminders, may facilitate greater pt adherence in providing longitudinal data for clinical trials.

3985 | Incidence of opioid abuse, dependence, and overdose in osteoarthritis patients prescribed opioids in the United States - A retrospective cohort study

Xiaofeng Zhou[1], Qing Liu[1], Rongjun Shen[1], Charles Wentworth[1], Richard Gong[1] and Leo Russo[2]

[1]Pfizer Inc., NYC, NY; [2]Pfizer Inc., Collegeville, PA

Background: Osteoarthritis (OA) is a common joint disorder and a leading cause of pain and disability among adults, especially the elderly. Prescription opioids are one treatment option, with another being NSAIDs/COX 2 inhibitors. Although opioid addiction is a known concern, few studies have investigated the incidence of opioid abuse, dependence (OAD) and overdose in OA patients.

Objectives: To estimate the incidence rates (IRs) of 3 endpoints among OA patients with moderate to severe pain who were prescription opioid naive:1) OAD from any medical setting; 2) opioid overdose during a hospitalization or emergency department visit (i.e. in facility); and 3) opioid overdose linked with death in facility

Methods: A retrospective cohort study using 2006-2018 OPTUM claims data was conducted. Adult patients (≥18 years) diagnosed with OA who had used at least 2 different non-opioid analgesic medications (as proxy measure for moderate to severe OA pain) in the 24 months of continuous enrollment prior to the index date, and met study inclusion/exclusion criteria, were included. OA was defined by ICD-9/10-CM codes. Drugs were defined by NDC and procedure drug codes. Index date was the dispensing date of the first opioid prescription. IRs and 95% confidence interval (CI) of the 3 endpoints were calculated.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: A total of 81,909 OA patients with moderate to severe pain who were opioid naïve were identified. The majority of patients were female (63%), aged 65 years and older (54%), and had a history of hypertension (69%). IRs per 1,000 PY for OAD from all settings, opioid overdose in facility, and opioid overdoses linked with in‐facility death were 3.37 [95%CI: 3.13, 3.62], 1.66 [95%CI: 1.49, 1.84], and 0.10 [95%CI: 0.06, 0.15] respectively. Older patients (65+ years) had higher IRs per 1000 PY compared to those aged 18-<65 years: 3.88 [95% CI: 3.55, 4.23] vs. 2.61 [95%CI: 2.30, 2.98] for OAD from all settings; 2.20 [95%CI: 1.96, 2.47] vs. 0.86 [95%CI: 0.68, 1.07] for opioid overdose in-facility; and 0.15 [95%CI: 0.10, 0.24] vs. 0.01 [95%CI: 0.00, 0.08] for opioid overdoses associated with in‐facility death.

Conclusions: Using a large US Claims database, we estimated the real-world IRs of medically diagnosed OAD and overdose among OA patients with moderate to severe pain who were prescription opioid naïve. The risk of opioid addiction appears to be higher among those aged 65 and above. These data in OA patients were not previously available in the medical research literature. Future analyses may benefit from confounder adjustment, medical chart review, and estimation using other databases.

3989 | Potential utility of a novel aggregated US electronic medical record database: Renal transplant pilot

Rachel E. Sobel[1], Robert J. Taylor[2], Stacey N. Purinton[2] and Aaron Berger[3]

[1]United Biosource Corp (UBC), Blue Bell, PA; [2]Cerner Corporation, Kansas City, MO; [3]United Biosource Corp (UBC), Kansas City, MO

Background: Electronic medical records (EMR) have many advantages over typical insurance claims data, such as lab tests, vital signs, and information captured during clinical care. Use of EMR data for rare diseases, exposures, or outcomes has been hampered by multiple proprietary EMR systems that historically lack continuity, resulting in small sample sizes. We sought to identify a rare outcome, renal transplant (RT), in a large novel aggregated US EMR system to describe clinical and population characteristics.

Objectives: To conduct a feasibility pilot to describe the proportion of RT patients with select lab tests, diagnoses, and medications by examining a national US EMR database (DB).

Methods: A retrospective cohort study was conducted using Cerner Real World Data (CRWD), a national de-identified research DB that aggregates Cerner and other EMR systems; data were analyzed with the Cerner "*HealtheDataLab*" tool. The DB contains healthcare data from 80M pts with 652M encounters from >46 health systems.

Patients were identified using first relevant procedure code for RT (CPT, ICD10 PCS, ICD9 CM, MEDCIN, SNOMED CT, NCI, or Read Code) during the study period (01Jan15-31Dec19). Cohort was analyzed for the proportion of patients with lab test orders and/or results for renal function ([RFs]; eg., BUN, eGFR), urinary protein, electrolytes, comorbidities, and outcomes such as dyslipidemia, opportunistic infections, and transplant rejection, as defined by appropriate LOINC procedure codes, ICD10 diagnostic codes, and NDC or DNUM codes for immunosuppressant drugs.

Results: Of >30.3M individuals in the DB during the study period, there were 1302 patients with RT (0.004%; 56.4% male; mean age=48.7 y, range 2-81 y; mean time since RT=1040 d). Post-RT, 1.5% had a subsequent transplant rejection diagnosis, 10.2% had cardiac disease, 9.2% had anemia, and 0.9% had opportunistic infection; 52.7% had record of immunosuppressant medication use. During the entire study period (pre and post RT), 86.6% of patients had >=1 RF test (n=186,603 tests, or 143.3 RFs/pt). Testing frequency ranged from 23 tests/pt (urinary protein) to 504 entries/pt (blood pressure [BP]). Of these tests, electronic results' availability ranged from 95.6% for RFs to 99.9% (BP, serum calcium, phosphorus).

Conclusions: While additional work is needed to better understand the data and explore the comparability of this RT population to existing statistics, this pilot suggests over the 5-yr study period, there may be adequate sample sizes, longitudinality, and key clinical data in this aggregated EMR DB to study certain rare diseases and outcomes such as RT.

4095 | Using self-reported outcomes to detect new-onset flare in a real-world study of participants with rheumatoid arthritis - Interim results from the digital tracking of arthritis longitudinally (DIGITAL) study

Jeffrey R. Curtis[1], Virginia S. Haynes[2], Fenglong Xie[1], Ilya Lipkovich[2], Hong Zhao[1], Carol Kannowski[2], Jiat L. Poon[2], Kelly Gavigan[3], David Curtis[3], Sandra Nolot[1] and W. Benjamin Nowell[3]

[1]University of Alabama at Birmingham, Birmingham, AL; [2]Eli Lilly and Company, Indianapolis, IN; [3]Global Healthy Living Foundation, Upper Nyack, NY

Background: Patients with rheumatoid arthritis (RA) experience fluctuating symptoms between visits to clinicians. Digital Tracking of Arthritis Longitudinally (DIGITAL) study is evaluating electronically captured patient-reported outcomes (ePRO) and passive data collection from a Fitbit device to identify disease worsening in a real-world study participants (pts) with RA.

Objectives: Evaluate agreement between self-reported new-onset flare and ePROs in an interim analysis from DIGITAL using a classification model.

Methods: Members of the ArthritisPower (AP) registry with RA participated in DIGITAL. Pts who completed the lead-in wore a smartwatch, and provided daily and weekly ePROs, including OMERACT RA Flare Questionnaire (FLARE) and PROMIS measures. A "Yes" response to the FLARE question identified a flare. For modeling association between new-onset flare and ePRO, we split the dataset into training (first 30 days) and test data (Day 31+). Repeated binary outcomes (Flare/No Flare) per pt were defined each week. To focus on new-onset flare, we excluded outcomes for patient weeks in which flare was present in previous week. Candidate variables for the model included baseline and current FLARE score (0-50 scale) and each of its

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5 items, daily pain, daily fatigue, and several PROMIS weekly instruments and their lagged values (last week or last 6 days for daily). 'Baseline' was calculated in non-flare weeks. Training data was used for logistic regression model selection combining clinical expertise with backward elimination. Performance of the final model was evaluated using test data.

Results: The training data was composed of outcomes from 128 pts who reported 388 weekly flare. Of pts in the training dataset, 92.2% were female, 87.5% white, mean age (SD) 52.7 (11.0), and years since RA diagnosis 10.4 (10.3); 62.5% were on a biologic. Among those in the training dataset, 58 flare outcomes occurred in 50 (39.1%) unique pts. The best-performing model in training data included the current and baseline FLARE question, current daily pain, and baseline daily pain average and standard deviation. In test data, this model had an area under the receiver operator curve of 0.81. At a cut point requiring specificity to be ≥0.80, sensitivity to detect flare was 0.62 and overall accuracy was 0.78.

Conclusions: Evaluation of passive data as proxy for self-reported new-onset flare is ongoing using machine learning methods

4105 | Two machines are better than one: Using multi-agent reinforcement in machine learning to simulate a clinical second opinion

Cao Xiao[1], Junyi Gao[1], Lucas Glass[2], Jimeng Sun[3] and Christina Mack[4]
[1]IQVIA, Cambridge, MA; [2]IQVIA, Plymouth Meeting, PA; [3]UIUC, Champaign, IL; [4]IQVIA, Durham, NC

Background: When it comes to patient health, a second opinion is often a wise and needed choice. Accurate diagnoses and appropriate treatment selection based on patient risk can be difficult, especially for complex or rare diseases. Multi-agent reinforcement learning is a novel sub-field within machine learning and has shown great success in the realm of Markov Decision Problems (MDPs) including medical decision making.

Objectives: Simulate the practice of seeking a second opinion for diagnosis, prognosis and risk of morbidity and mortality by training 2 reinforcement learning (RL) agents using a different focus for each: a) the primary agent ("first doctor"), which studies the most recent visit of the patient to learn the current health status; b) a "second-opinion" agent, which considers the entire patient history to obtain a more global view.

Methods: Two RL agents were trained on electronic health records (EHR) within the Medical Information Mart for Intensive Care database (2001-12) to simulate second-opinion situation using a) patient's current health condition and b) summary of the patient's historical data. Performance was compared against clinical predictive models across 4 clinical tasks: (1) In-hospital mortality prediction, (2) Acute care phenotype classification, (3) Physiologic Decompensation prediction, (4) Forecasted length of hospital stay. Knowledge of disease progression was provided via long-term reward function; the model was further customized with patient demographics. Dynamic skip-connection was used to focus on relevant information over time, while baseline models made current-time medical decisions based only on last-visit information (Markovian assumption).

Results: Multi-agent reinforcement consistently outperformed models using only a single agent across all 4 clinical outcomes and medical tasks for all metrics. Specifically, it achieved 16% higher area under the precision-recall curve (AUPRC) and 15% lower mean squared error (MSE) and mean absolute percentage error (MAPE) than the best-performing baseline model (SAnD; Simply Attend and Diagnose) and was also superior to a time-aware LSTM model.

Conclusions: Multi-agent reinforcement learning is a cutting edge ML approach that, while typically used in video game environments, is highly applicable to the complex setting of diagnoses and healthcare decision making. The two-agent machine was able to model long-term dependencies of patients' health status while considering patients' demographics and achieve better prediction performance across clinical prediction tasks.

4106 | Agreement between administrative database and medical chart review for the prediction of chronic kidney disease stage

Sylvie Perreault[1], Louise Roy[1], Michael Zappitelli[2], Brian White-Guay[1], Jean-Philippe Lafrance[1] and Marc Dorais[3]
[1]University of Montreal, Montreal, QC, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]Statsciences Inc, Montreal, QC, Canada

Background: Chronic kidney disease (CKD) is a major health issue. Validity assessment of administrative data for the detection of CKD in research on drug benefit and risk using real-world data is important.

Objectives: To validate a CKD predictive algorithm using the administrative databases of Quebec compared to medical chart review as a reference standard in patients with estimated glomerular filtration rate (eGFR).

Methods: Study design: Three administrative databases from RAMQ database and Quebec Health Ministry Database were linked and provided information on demographics and clinical characteristics for 434 patients with normal and abnormal kidney function. **Setting:** All patients 23 years and older received follow-up care in one of these clinics, with at least two serum creatinine measures (up to 1 year apart) between 2013 and 2015. Medical file data were collected by trained nurses in 3 community medical centers in Quebec. We collected the administrative records of hospitalization and medical services in the 5-year period prior to the cohort entry, and the pharmaceutical files in the 2-year period prior to cohort entry. Algorithms were developed to measure eGFR using administrative data. **Main outcome:** We estimated eGFR using the CKD Epidemiological Collaboration, using retrospectively collected variables including variables like age, sex, and serum creatinine measurement. **Statistical:** To estimate the sensitivity, specificity, positive predictive, and negative predictive values of diagnosis code of CKD, medication used, and medical visits for nephrology using administrative databases. Validity

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

indices were estimated for each case definition combination using laboratory data as the reference standard.

Results: The validity of eGFR < 30 mL/min/1.73m^2 was assessed with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity ranged from 82.5% to 99.4%. Specificity ranged from 76.1% to 98.9% with PPV and NPV ranging from 69.5% to 97.7% and 91.1% to 99.5%, respectively. The subsequent validation with literature data and different cohorts of patients emphasized the accurate prediction of the proportion of patients with eGFR < 30 mL/min/1.73m^2.

Conclusions: The case definition of eGFR < 30 mL/min/1.73m^2 derived from an algorithm using diagnosis code, drug use, and nephrologist visits from administrative databases seems to be a valid algorithm compared to medical chart reviews for older adults with CKD.

4125 | Real world evidence of graft survival in four types of transplants: Fifteen years analysis in Brazil

Ludmila P. Gargano[1,2], Túlio T.R. Sarmento[2], Natália C.C. Freitas[1], Guilherme F. Nascimento[1], Rosângela M. Gomes[1], Lucas L. Torres[2], Carolina M.F. Ferreira[2], Carolina Z. Dias[1,2], Isabella F. Zuppo[1,2], Francisco A. Acúrcio[1,2], Juliana Álvares-Teodoro[1,2] and Augusto A. Guerra[1,2]

[1]*Postgraduate Program in Medicines and Pharmaceutical Assistance - Faculty of Pharmacy - UFMG, Belo Horizonte, Brazil;* [2]*SUS Collaborating Centre Technology Assessment and Excellence in Health, Belo Horizonte, Brazil*

Background: Transplantation could be an alternative to increase the patient survival and improve their quality of life. In Brazil, the National Health System (SUS) is responsible for almost 96% of all transplants made in the country. The SUS is a universal, integral, equalitarian and free system of health care. Immunosuppressive treatment is dispensed to transplanted patients on a monthly basis.

Objectives: To assess graft survival in kidney (TxK), liver (TxL), heart (TxH), and lung (TxP) transplantation performed by SUS from 2000 to 2015.

Methods: Cohort study using linkage of 3 SUS administrative databases through deterministic-probabilistic matching: the Hospital Information System (SIH), the Outpatient Information System (SIA), and the Information System of Mortality (SIM). Patients who have undergone kidney, liver, heart or lung transplantation in SUS between January 1, 2000 to December 31, 2014 were included. The survival analysis (SA) was performed using the Kaplan-Meier estimator to determine the cumulative graft survival probability of patients from all four types of transplant. The event considered was graft loss or death.

Results: A total of 63,316 patients were included. 75.6% of patients were submitted to TxK, 20.1% to TxL, 3.5% to TxH and 0.9% to TxP. The SA indicates that the survival rate at the end of the first year was 91.1% (95%IC 90.9 - 91.4%) for TxK, 72.6% (95%CI 71.8%-73.4%) for TxL, 71.1% (69.2%-73.1%) for TxH, and 75.7% (95%CI 71.9%-79.6%) for TxP. At the end of the 15th year of follow-up, the survival rate decreased to 40.9% (95%CI 39.3%-42.6%) for TxK, 45.2% (95%CI 42.2%-48.5%) for TxL, 30.5% (25.2%-37.0%) for TxH, and 20.3% (95%CI 10.4%-39.6%) for TxP. The median survival was 143 months for TxK, 145 months for TxL, 103 months for TxH. and 63 months for TxP.

Conclusions: This research shows an overview of different transplants performed by the Brazilian National Health System and provides information that could support studies of comparative effectiveness of immunosuppressive treatment. Also, this database focused on the individual will allow researchers to perform other clinical, epidemiological and economic studies, in addition to allowing better decision-making for the Brazilian Health System.

4136 | Weight gain following antiretroviral therapy (ART) initiation in ART-naive participants in the current treatment era

Stephanie Ruderman[1], Heidi Crane[1], Robin Nance[1], Bridget Whitney[1], Barbara Harding[1], Kenneth Mayer[2], Richard Moore[3], Joseph Eron[4], William Mathews[5], Benigno Rodriguez[6], Michael Saag[7], Amanda Willig[7], Sara Lindstrom[1], Brian Wood[1], Ann Collier[1], Greer Burkholder[7], Mari Kitahata[1] and Joseph Delaney[8]

[1]*University of Washington, Seattle, WA;* [2]*Harvard Medical School, Fenway Institute, Boston, MA;* [3]*Johns Hopkins, Baltimore, MD;* [4]*University of North Carolina, Chapel Hill, NC;* [5]*University of California San Diego, San Diego, CA;* [6]*Case Western University, Cleveland, OH;* [7]*University of Alabama Birmingham, Birmingham, AL;* [8]*University of Manitoba, Winnipeg, MB, Canada*

Background: People living with HIV (PLWH) who initiate integrase inhibitor (INSTI)-based antiretroviral therapy (ART) may increase body weight more quickly than those initiating other ART regimens.

Objectives: We evaluated weight change among PLWH initiating ART in the current treatment era.

Methods: Between 2012-2019, across 8 Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites, we identified 3156 ART-naïve PLWH initiating ART, including efavirenz (EFV), rilpivirine (RPV), atazanavir (ATV), darunavir (DRV), raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), or bictegravir (BIC), with tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF) or abacavir (ABC) and emtricitabine or lamivudine (standard 3+ drug combination regimens for initial ART). Weight change was examined during all follow-up time on regimen (excluded newer regimens with limited mean follow-up e.g., containing TAF) and short-term (6 month; including all regimens) using linear mixed models adjusted for time on regimen, interaction between time and regimen, age, sex, race, hepatitis B or C coinfection, nadir CD4, smoking, diabetes, antipsychotic medication use, and site.

Results: Mean follow-up on initial ART regimen was 1.8 years. In analyses including all follow-up, compared with EFV/TDF, DTG/ABC was associated with a 0.8 kg (95%CI:0.4-1.1) per 6-months greater weight gain while DTG/TDF was associated with a 0.6 kg (95%CI:0.1-1.2) per

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

6-months greater weight gain. Other INSTI-based regimens showed less weight gain. Weight gain on DTG/ABC was greater than EFV/TDF, RPV/TDF, and EVG/TDF, but not DRV/TDF (1.1 kg per 6-months, 95%CI:0.5-1.6). In short-term (6 month) analyses, compared with EFV/TDF, BIC/TAF (5.0 kg (95%CI:2.5-7.4)) and DTG/TAF (4.9 kg (95%CI:2.2-7.6)) were associated with the greatest weight gain per 6 months, followed by DRV/TDF (4.1 kg (95%CI:2.3-5.9)) and DTG/TDF (3.1 kg (95%CI:1.5-4.7)).

Conclusions: DTG users showed greater weight gain than RAL or EVG users, although differences decreased with longer follow-up. DRV/TDF users showed the greatest weight gain in the long-term, while DTG/TAF- and BIC/TAF-based regimens showed the greatest gain in the first 6 months. For ART-naïve PLWH, potential weight gain should be considered in conjunction with the benefits of viral suppression when comparing ART regimens.

4142 | Defining phenotypes of women with endometriosis undergoing hysterectomy or oophorectomy using machine learning

Andrea K. Chomistek[1,2], Cheryl Enger[1,2], Stacey A. Missmer[3], Stephanie J. Estes[4], Jenna F. Calderbank[1,2], Michael C. Doherty[1,2] and Stephanie E. Chiuve[5]

[1]Optum, Boston, MA; [2]Optum, Ann Arbor, MI; [3]Michigan State University, Grand Rapids, MI; [4]Penn State Health, Hershey, PA; [5]AbbVie, Inc., North Chicago, IL

Background: Endometriosis is an often chronic and painful, inflammatory gynecological disorder. Current treatment for management of pelvic pain includes medical therapies and surgery. If medical treatment and conservative surgery have been ineffective, a hysterectomy (with or without oophorectomy) is considered when childbearing is complete.

Objectives: To identify phenotypes of women with endometriosis who have had a hysterectomy or bilateral oophorectomy based on clinical covariates.

Methods: This study was conducted in the Optum Research Database, a claims database from a large U.S. health insurer. Women aged 18-55 years with a hysterectomy or bilateral oophorectomy (HYBO), combined with an ICD-10 code for endometriosis within 30 days of surgery, between July 2016 and June 2018 were identified. Machine learning using an agglomerative hierarchical clustering analysis was performed to identify subgroups of patients among those with HYBO based on clinical characteristics documented within the 6 months prior to surgery. A phenotype for each subgroup was defined by patterns of comorbidities, procedures, and medications.

Results: The cohort included 7,005 women with HYBO with mean age 44 (SD: 6) years. Sixty-three percent of women had pain in the pelvis, abdomen, or lower back, while 38% and 11% had dysmenorrhea and dyspareunia, respectively. Frequently used medications included opioid analgesics (53%) and prescription nonsteroidal anti-inflammatory drugs (47%). An 8-cluster solution was identified based on cluster statistics and covariate distributions; 4 clusters were characterized by high frequency of uterine fibroids (UF) (≥70%), 3 by moderate UF (60-70%), and one by low UF (<40%). The 4 clusters with high UF were defined as: 1) low pain (22%); 2) low pain but poor mental health (7%); 3) high pain medication use (11%); and 4) high endometriosis-related pain, pain comorbidities, digestive and cardiometabolic disorders (15%). The 3 clusters with moderate UF were defined as: 1) high endometriosis-related pain but low pain medication use (11%); 2) high pain comorbidities and pain medication use (10%); and 3) endometriosis outside the uterus (i.e. ovary, fallopian tubes, pelvic peritoneum) (12%). The final cluster was defined by low UF, high endometriosis-related pain, pain comorbidities, pain medication use, and prior laparoscopic surgery (13%).

Conclusions: Among patients with endometriosis who underwent HYBO, we identified several phenotypes based on patterns of clinical covariates. Future studies might consider whether unmet needs for surgical avoidance differ by patient phenotype.

4225 | Incidence of community-acquired pneumonia in China: A nationwide claims database analysis

Yixin Sun[1], Yinchu Cheng[2] and Siyan Zhan[1]

[1]Peking University, Beijing, China; [2]Peking University Third Hospital, Beijing, China

Background: Community-acquired pneumonia (CAP) is one of the major global health problems and among the top 10 causes of death worldwide. However, the epidemiological information of CAP is limited in China.

Objectives: To estimate the incidence rate of CAP and describe the epidemiologic characteristics among Chinese population.

Methods: We conducted a retrospective analysis on CAP incidence using the Chinese Urban Basic Medical Insurance database of 23 provinces in 2016, which covered 427·52 million urban beneficiaries of all age groups in Mainland China. CAP episodes were identified using diagnosis-term-derived algorithm, and multiple CAP records of one single person within 90 continuous days were considered as one single episode. The incidence rates were calculated and described by sex, age, region, and season.

Results: A total of 1·42 million patients were identified as having one or more CAP episodes, and finally a sum of 1·48 million CAP episodes were counted. The overall incidence of CAP was 7·13 (95% CI: 6·11-8·15) per 1000 person-years, in males 7·32 (95% CI: 6·28-8·35) and females 6·93 (95% CI: 5·92-7·94) per 1000 person-years, respectively. The incidence varied by age with a U-shaped curve peaking in children aged < 5 years old [65·80 (95% CI: 62·52-69·08)] and elderly population aged ≥ 80 years old [14·98 (95% CI: 13·63-16·34)]. The incidence varied markedly by regions. Furthermore, the rate showed a clear seasonal trend, which peaked in spring, decreased in summer and autumn, and re-ascended in winter.

Conclusions: This study reveals a relatively high level of CAP incidence in China. These findings provide baseline data for establishing effective prevention strategies, targeted at susceptible population, regions and seasons in China.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4266 | Changes in serum creatinine values during and after pregnancy in a cohort of women with or without pre-existing chronic kidney disease

Carole Marxer[1,2], Katrina W. Hagberg[3], Rishi J. Desai[4,5], Julie M. Paik[4,5], Susan S. Jick[3,6], Christoph R. Meier[1,2,3] and Julia Spoendlin[1,2]

[1]University Hospital Basel, Basel, Switzerland; [2]University of Basel, Basel, Switzerland; [3]Boston Collaborative Drug Surveillance Program, Lexington, MA; [4]Brigham and Women's Hospital, Boston, MA; [5]Harvard Medical School, Boston, MA; [6]Boston University School of Public Health, Boston, MA

Background: Chronic kidney disease (CKD) occurs in up to 3% of women of childbearing age. Impaired kidneys may not sufficiently adapt to physiological changes during pregnancy, which may result in accelerated CKD progression.

Objectives: To describe changes in renal filtration during/after pregnancy in women with or without CKD.

Methods: We performed a longitudinal descriptive study using data from the UK-based Clinical Practice Research Datalink (2000-2018). We included pregnancies ending in live birth if they had ≥ 1 serum creatinine (SCr) value recorded during a 1-year baseline period before the estimated last menstrual period or during trimester 1. Pregnancies were categorized into 3 groups based on the mean estimated glomerular filtration rate (eGFR [ml/min/1.73m^2], CKD-EPI formula) during baseline/trimester 1: no CKD (eGFR ≥ 90), mild CKD (eGFR 60-90), moderate-severe CKD (GFR < 60). We captured demographics and risk factors for CKD and calculated percentage changes of mean SCr levels (group means) as a proxy for renal filtration in 3-month intervals during and until 1 year after pregnancy. We quantified the difference between the mean baseline eGFR and mean eGFR 6-12 months after delivery.

Results: Of 169'855 pregnancies, maternal moderate-severe CKD was present in 981 (0.6%), mild CKD in 29'433 (17.3%), and no CKD in 139'441 (82.1%) pregnancies. Pre-existing hypertension, diabetes, and/or obesity was recorded in 37% in moderate-severe CKD, and in 30% in the other 2 groups. Autoimmune diseases pre-existed in 3-4% in all groups. Mean reduction in SCr levels were larger between baseline and the end of trimester 2 in women without CKD (-22%) and with mild CKD (-24%) than in women with moderate-severe CKD (-14%). Thereafter, mean SCr levels increased, to level off around 6 months after delivery. In women without CKD, mean eGFR levels 6-12 months after delivery (118 ml/min, SD 15) were comparable to baseline SCr levels (119 ml/min, SD 13). Women with mild CKD revealed an increased eGFR (97 ml/min, SD 18) after delivery (baseline eGFR 88 ml/min, SD 9). In women with moderate-severe CKD, the post-pregnancy eGFR (55 ml/min, SD 23) was similar to the baseline eGFR (50 ml/min, SD 14), but sample size was small (incomplete lab data).

Conclusions: Our results suggest that kidneys of women with moderate-severe CKD adapted to a lesser degree to physiological changes during pregnancy, but sample size was small. Renal filtration was not decreased within 1 year after delivery in all groups. The increased post-pregnancy eGFR in women with mild CKD may reflect continued hyperfiltration or random variability.

4274 | Utilising mobile and web-based technology for capturing patient specific information: Methods from the DISCOVER CKD program

Glen James[1], Juan Jesus Carrero[2], Jenny Wei[3], Gary Curhan[4], Eric Wittbrodt[5], Steven Fishbane[6], Carol Moreno Quinn[1], Hiddo Heerspink[7], Katarina Hedman[8], Eiichiro Kanda[9], Tony Chen[5], Naoki Kashihara[9], Björn Holmqvist[8], Mikhail Kosiborod[10], Peter Fenici[1], Mitja Lainscak[11], Jennie Medin[8], Carolyn Lam[12,13], Roberto Pecoits-Filho[14,15], Carol Pollock[16], Peter Stenvinkel[17] and David Wheeler[18]

[1]AstraZeneca, Cambridge, United Kingdom; [2]Karolinska Institutet, Stockholm, Sweden; [3]AstraZeneca, Shanghai, China; [4]Harvard Medical School, Boston, MA; [5]AstraZeneca, Gaithersburg, MD; [6]Northwell, New York, NY; [7]University of Groningen, Groningen, Netherlands; [8]AstraZeneca, Gothenburg, Sweden; [9]Kawasaki Medical School, Okayama, Japan; [10]University of Missouri-Kansas City, Kansas City, MO; [11]University of Ljubljana, Ljubljana, Slovenia; [12]National Heart Centre, Singapore, Singapore; [13]Duke NUS, Singapore, Singapore; [14]Pontifícia Universidade Católica do Paraná, Parana, Brazil; [15]Arbor Research, Ann Arbor, MI; [16]University of Sydney, Sydney, Australia; [17]Karolinska Institutet, Stockholm, Sweden; [18]University College London, London, United Kingdom

Background: Chronic kidney disease (CKD) is a global health problem associated with cardiovascular complications, impaired health-related quality of life (HRQoL) and high mortality. New ways of capturing patient experiences and burden of disease in settings outside of the clinic through mobile or web-based technology are becoming more widely used, but not within CKD real-world data.

Objectives: Utilising mobile and web-based technology to capture patient specific information.

Methods: DISCOVER CKD is an enriched hybrid observational study utilising a novel cloud-based IT platform to integrate retrospective and prospective data from patients with estimated glomerular filtration rate (eGFR) less than 75 ml/min/1.73 m^2 through to end stage kidney disease from the UK, US, Italy, Sweden, China and Japan. Prospective data will be captured over a 3-year period from >1,000 CKD patients. Data collected by validated instruments including HRQoL (SF-36), physical activity (RAPA), work productivity (WPAI), diet (food diary), and other patient-reported outcomes will be captured in a bespoke mobile/web-based application to be completed by the patient before, during or after their routine clinical visit. The application will be available, validated and user-tested in multiple languages.

Results: Capturing patient-reported information outside of the clinic setting provides an innovative patient-centric approach for understanding the burden and journey of CKD from a patients' perspective. Initial results are anticipated later in 2020.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Utilising mobile/web-based technology to collect patient experiences has the potential to increase the understanding of a disease, with easier communication, minimising burden of data collection in the clinic from a patient, physician and eCRF perspective while improving the consistency and validity of data that patients enter.

4377 | Population trends in the 10-year prevalence and incidence of psoriasis and psoriatic arthritis in Taiwan: A nationwide, population-based cohort study

Ireny Y.K. Iskandar[1], Teng-Chou Chen[1], Li-Chia Chen[1], Meng-Sui Lee[2], K. Arnold Chan[3], Christopher E.M. Griffiths[4] and Darren M. Ashcroft[1]

[1]Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optmetry, University of Manchester, Manchester, United Kingdom; [2]Department of Dermatology, National Yang-Ming University, Taipei, Taiwan; [3]Health Data Research Center, National Taiwan University, Taipei, Taiwan; [4]NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom

Background: The burden of psoriasis and psoriatic arthritis across many world regions is high, but there is limited information on the incidence and prevalence of these long-term diseases from Asian countries.

Objectives: To estimate the prevalence and incidence of psoriasis and psoriatic arthritis on the basis of age and gender, and to explore temporal trends in their epidemiology in Taiwan over a 10-year period.

Methods: Population-based cohort study using the Taiwan National Health Insurance claims records, which covered 99.9% of Taiwan's population between 2006 and 2017. The International Classification of Diseases, 9th and 10th edition diagnosis codes were used to identify patients with ≥1 diagnostic code for psoriasis or psoriatic arthritis with the diagnosis made by either a dermatologist or rheumatologist. A sensitivity analysis using ≥2 diagnostic codes made by any medical speciality was also conducted.

Results: The overall prevalence (per 100,000 population) for psoriasis and/or psoriatic arthritis increased steadily from 0.19% (194 cases per 100,000) in 2006 to 0.94% (936 cases per 100,000) in 2017. Specifically, the prevalence increased from 0.18% (180 cases per 100,000) to 0.86% (855 cases per 100,000) for psoriasis; and from 0.01% (8 cases per 100,000) to 0.08% (77 cases per 100,000) for psoriatic arthritis. The incidence rates for psoriasis and/or psoriatic arthritis, however, remained stable over time. Overall, the prevalence and incidence of psoriasis were higher in males compared to females. However, the prevalence and incidence rates for psoriatic arthritis were found to be similar between the genders. The incidence data showed a clear bimodal age pattern in psoriasis onset, with the first and second peak at around 30-39 and 70-79 years of age, respectively, characteristic of early-onset and late-onset psoriasis. The prevalence data showed an increasing trend with age until around 90 years of age, after which it decreased. Results from the sensitivity analyses were consistent with the main findings.

Conclusions: The steady increase in the prevalence of psoriasis and psoriatic arthritis over the last decade has important implications for healthcare service delivery and for resource allocation. This increase in the prevalence which does not appear to be attributable to increasing incidence rates, suggests that improvements in life expectancy are likely to be the key determinant to this increase.

4390 | Assessing comorbid inflammatory arthritis conditions and swollen to tender joint count ratios in a real world systemic lupus erythematosus cohort

Cristi Cavanaugh, Greg Donadio, Kathryn Starzyk, Kathleen Mortimer, Michael Behling, Gary Curhan and Rich Gliklich

OM1, Inc., Boston, MA

Background: Joint swelling and tenderness are common in patients with systemic lupus erythematosus (SLE) and other inflammatory arthritis conditions such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Swollen to tender 28-joint count ratio (STR) is an index proposed in RA to assess joint involvement with a higher score indicating greater likelihood of treatment response. Given the prevalence of joint involvement in SLE, STR has potential application in this patient population.

Objectives: To assess the overlap of SLE and other inflammatory arthritis conditions in a real-world cohort and characterize patients based on joint involvement, as defined by STR.

Methods: The OM1 SLE Registry (OM1, Boston, MA) follows more than 37,000 SLE patients longitudinally with deep clinical data, including laboratory, patient-reported and disease activity information, and linked administrative claims starting from 2013. Patients with swollen and tender 28-joint counts assessed at the same encounter were included. Patient cohorts were defined as SLE+ (RA, PsA or AS) vs. SLE alone. STRs were calculated by inserting 1 if the denominator was 0. Patients were categorized as low (STR <0.5), moderate (0.5 ≤ STR ≤ 1.0) or high (STR >1.0), based on first observed STR. Clinical characteristics were summarized by cohort and STR group.

Results: The study included 9,919 patients (92.1% female) with ≥1 STR available in the OM1 SLE Registry. Of the 17.0% of patients in the SLE+ cohort, 94.8% had RA, 6.7% PsA and 1.6% AS. SLE+ patients were older at 57.1 years (standard deviation [SD]: 13.1) compared to 51.1 (SD:14.9) for SLE alone. Comorbid osteoarthritis was more common in the SLE+ cohort (46.3% vs. 26.0%). The SLE+ cohort also had higher STRs: low (69.3%), moderate (19.3%), high (11.4%) compared to 82.6%, 10.8% and 6.7%, respectively, in the SLE cohort. For SLE+, immunosuppressant use increased with higher STR from 44.5% (low STR) to 54.2% (high STR). For SLE alone, immunosuppressant use was lower overall (26.5%) with similar use among STR groups. Select disease-modifying antirheumatic drug (DMARD) use was higher among SLE+ patients (33.9% vs. 3.9%) with highest use in the moderate STR group (39.2%). Use of belimumab or rituximab was higher

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

among SLE+ (13.7% vs. 7.5%) with highest use in the low STR group (14.3%).

Conclusions: Higher STR and differences in treatment patterns were observed in the SLE+ cohort. Additional research is needed to assess the relationship between STR and treatment response in SLE and relevant subphenotypes.

4413 | Description of COPD patients treated with multiple inhaler triple therapies (MITT) using the CPRD GOLD and CPRD aurum electronic health record (EHR) databases

Gema Requena[1], Leah Sansbury[2], Achim Wolf[3], Rachael Williams[3], Jennifer Quint[4], Daniel Dedman[3] and Jeanne M. Pimenta[1]
[1]*GlaxoSmithKline, London, United Kingdom;* [2]*GlaxoSmithKline, Collegeville, PA;* [3]*Medicines and Healthcare Products Regulatory Agency, London, United Kingdom;* [4]*Imperial College, London, United Kingdom*

Background: The Clinical Practice Research Datalink (CPRD) GOLD has been previously used for observational respiratory research however, limited research has additionally used CPRD Aurum. To better understand this new database, we aim to compare key clinical variables related to COPD patients in the CPRD Aurum with the CPRD GOLD database. Recent guidelines (*GOLD 2019*) recommend the use of MITT in COPD patients and we used this population as an example to assess differences.

Objectives: Identify and describe COPD patients treated with MITT in CPRD GOLD and CPRD Aurum to assess whether patients and data differ between databases.

Methods: Patients with a GP recorded COPD diagnosis, aged ≥35 years, registered for ≥1 year and receiving MITT prescriptions continuously for at least 3 months at index date (December 31, 2017) were included. Patient characteristics were described at index, disease severity and healthcare resource use (HCRU) were described 1-year prior index date and comorbidities at any time in the patient's history.

Results: 3,600 COPD patients in CPRD GOLD and 8,981 in CPRD Aurum were treated with MITT at index. Patients characteristics were comparable across CPRD GOLD and CPRD Aurum respectively: median age (70, 71 years), proportions male (55, 54%), most deprived (52, 58%) and overweight/obese (59, 63%). Current smoking was more prevalent in CPRD Aurum (37, 47%). Proportions of patients with a history of asthma (59, 57%), "severe/very severe airway limitation" (35, 41%), median FEV1/FVC (57, 60), and moderate COPD exacerbations, mean (2.0, 1.6 per person-year) were comparable. However, pneumonia (12, 21%) and mMRC scores 3-5 (47, 66%), were higher in CPRD Aurum. Other comorbidities were similar across databases. In terms of HCRU, the number of all-cause hospitalisations was higher in CPRD Aurum (mean 1.0, 2.1); GP visits were similar; and nurse visits were higher in CPRD GOLD (mean 4.5, 2.4).

Conclusions: Patients and data from the two databases were comparable across key aspects of a COPD population. When interpreting results from both databases, researchers should consider the impact of differences in geographical distribution of practices, and the completeness of recording for specific variables. CPRD Aurum significantly increased the patient pool, illustrating suitability for respiratory research and potentially utility to investigate uncommon events.

4417 | Enhancing model interpretability and accuracy for disease progression prediction via phenotype-based patient similarity learning

Christina Mack[1], Yue Wang[2], Fan Zhang[3], Corey M. Benedum[4], Yunlong Wang[2] and Emily Zhao[2]
[1]*IQVIA, Durham, NC;* [2]*IQVIA, Plymouth Meeting, PA;* [3]*IQVIA, Plymouth, NC;* [4]*IQVIA, Cambridge, MA*

Background: Recent growth of longitudinal claims data has enabled the use of machine learning (ML) to help clinicians find undiagnosed patients and understand what clinical factors are related to specific diseases. This information is often used to examine market share or support trial enrollment, but the real patient impact in the clinical setting remains unrealized. Enabling ML to move beyond finding predictors (identifying variables correlated with a disease or outcome) to making predictions (predicting the diagnosis of patients with an outcome of interest) will bring the value of ML to the patient. One challenge is that clinicians remain skeptical of models they do not fully understand. Non-negative matrix factorization (NMF), an ML approach that emphasizes interpretability, can address this gap by creating informative model predictors by grouping patients into *phenotypes* based on clinical data. Phenotype membership is defined by patterns in observed factors; allowing the end-user to observe factors relevant to each phenotype.

Objectives: Using a clinical setting of chronic lymphocytic leukemia (CLL), develop ML models incorporating NMF. Evaluate the ability to enhance model interpretability and accuracy, enabling greater utility for clinicians.

Methods: We used NMF to group patients according to frequently observed claims codes. Clinical experts described each phenotype to understand commonalities between the most frequently observed clinical codes. We then developed ML models to predict the diagnosis of CLL. Model predictors included demographic and clinical service predictors, and with or without phenotype predictors. We used Precision-Recall and Area Under the Curve (PR-AUC) and F1 score to assess model accuracy.

Results: NMF clustered patients into 3 phenotypes, defined by codes related to: 1) respiratory disease and pain, 2) blood related clinical services/anemia, 3) infections. Inclusion of phenotype predictors increased CLL prediction for each tested model by an average of 2 percentage points for PR-AUC. All models which included phenotype predictors generally had higher F1 scores.

Conclusions: These results suggest that inclusion of phenotype predictors enhanced each model's interpretability and accuracy of CLL predictions. NMF extracts more detail from claims data, enabling the model to attain highly explanatory predictors indicative of the targeted disease. We envision that clinical phenotypes can be used to

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

improve model interpretability and accuracy for rare disease detection or pairing patients with well-matched clinicians and medications.

4420 | The incidence of acute pancreatitis in the United States: Identification of cases in an electronic healthcare database with supportive laboratory evidence

Usha Gungabissoon[1], Megan Delgado[2], Selin Cooper[3], Liyuan Ma[4] and Iain Uings[3]
[1]GSK, London, United Kingdom; [2]University of North Carolina, Chapel Hill, NC; [3]GSK, Stevenage, United Kingdom; [4]GSK, Philadelphia, PA

Background: Despite acute pancreatitis (AP) being one of the most common causes of gastrointestinal disease hospitalizations in the United States (US), few robust US epidemiological studies exist to quantify its incidence. Most published estimates in the US are higher than reported elsewhere, whether this reflects a true difference remains unclear. A diagnosis of AP is made on the basis on clinical symptoms and laboratory evidence. In most studies, there is a lack confirmatory evidence from laboratory testing or imaging meaning that individuals with clinically suspected AP whose diagnosis is subsequently ruled could be included, thus overestimating the incidence of AP.
Objectives: To estimate the incidence of AP using an ICD code alone, to compare with published estimates, or in combination with laboratory evidence to obtain a more accurate estimate of incidence.
Methods: Data from the Cerner Corporation's Health Facts® (HF) electronic health record database were used to identify AP cases in 2015. Cases were classified as "possible AP" or "probable AP" based on the presence of an ICD code alone or in combination with laboratory evidence, respectively. Possible AP was defined as an inpatient or emergency admission with the presence of an ICD code for AP in the primary position. Probable AP was defined as the presence of an ICD code for AP in any position and laboratory evidence (defined as amylase and/or lipase values three times the upper limit of normal) during the hospital admission. The incidence of AP (per 100,000 population) was estimated using two denominators; the study population and nationally inflated estimates to the 2015 United States population.
Results: Of the 4,684,825 individuals with at least one encounter in 2015, a total of 8,833 individuals had an AP ICD code at any position. Of these, 5,732 (64.9%) and 3,739 (42.3%) met the criteria for possible AP and probable AP, respectively. Across AP definitions (probable and possible AP), sex, age, and etiology were comparable. Using the study population as the denominator, the incidence of possible and probable AP was 122.4 (95% Confidence Interval [CI]: 119.2, 125.5) and 79.8 (95% CI: 77.2, 82.4) per 100,000 population, respectively. Inflation to national estimates yielded lower incidence estimates of 46.5 (95% CI: 46.3, 46.8) and 29.4 (95% CI: 29.2, 29.6), respectively.
Conclusions: Our results indicate that AP could be less common in the US than previously reported. Estimates of incidence from our study are similar to those reported using a similar approach in Europe.

4439 | Incidence of acute pancreatitis among US adolescents and adults diagnosed with atopic dermatitis, asthma, or chronic rhinosinusitis with nasal polyposis, 2014-2018

Andrea F. Marcus[1], Cherise Wong[1], Sarah-Jo Sinnott[2], Anna Coleman[1], Faisal Khokhar[1], John D. Huber[1], David Lederer[1] and Steve Gao[1]
[1]Regeneron Pharmaceuticals, Tarrytown, NY; [2]Sanofi, Cambridge, MA

Background: The incidence of acute pancreatitis (AP) among individuals with type-2 inflammatory diseases is not well documented.
Objectives: To estimate the incidence of AP among individuals with a diagnosis of atopic dermatitis (AD), asthma, or chronic rhinosinusitis with nasal polyposis (CRSwNP), stratified by age.
Methods: The study period for this retrospective cohort study spanned January 1, 2014 - September 30, 2018. Three cohorts were identified from Truven MarketScan data and defined as individuals aged ≥12 years with diagnosis codes as follows: 1) AD (ICD-9 code: 691.8/ ICD-10 codes: L20.0, L20.81, L20.82, L20.84, L20.89, L20.9), 2) asthma (at least one inpatient or at least 2 outpatient diagnosis codes for asthma (ICD-9: 493.xx/ICD-10: J45.*), or 3) CRSwNP (at least one inpatient or at least 2 outpatient diagnosis codes for nasal polyps (ICD-9: 471.*/ICD-10: J33.*). The index date was defined as the first date of AD, asthma, or CRSwNP diagnosis. The outcome was defined as the presence of one inpatient diagnosis code for AP (ICD-9: 577.0/ICD-10: K85.9*). Patients with an AP diagnosis on the index date or within the past 3 months of it were excluded. Incidence rates (IRs) were calculated by dividing the number of AP diagnoses by total number of person-years (PY= AP diagnosis or end of study minus the index date).
Results: Overall, the AD cohort included n=85,051 individuals, the asthma cohort n=995,055, and the CRSwNP cohort n= 34,929. In all three cohorts, a large proportion of individuals were >40 years old (ranging from 50.7-74.0%). There were more females in the AD (62.4%) and asthma (65.3%) cohorts than males, but less females in the CRSwNP cohort (40.7%). The crude IRs (per 10,000 PY) for AP were 7.6 (95% CI: 6.4, 9.1) in the AD cohort, 14.2 (13.7, 14.7) for the asthma cohort, and 8.5 (6.6,11.0) for the CRSwNP cohort. IRs increased with age for AD (ages 12-17 years=1.17; 18-39=4.25; 40 +=12.15 per 10,000 PY) and asthma (ages 12-17=3.16; 18-39=10.06; 40+=17.79 per 10,000 PY), but not CRSwNP (ages 12-17=8.38; 18-39=4.21; 40+=9.64 per 10,000 PY).
Conclusions: Our findings indicate that AP occurs among populations with AD, asthma, or CRSwNP, and that age-adjusted AP rates increased with age for AD and asthma, but not CRSwNP. The crude IRs for the AD and CRSwNP cohort are comparable to unadjusted rates of AP in the general population, however, the asthma cohort IR was substantially higher. Further study evaluating risk factors associated with AP development is needed.

4442 | Stigma as a barrier to the hepatitis C virus continuum of care in the era of direct-acting antiviral therapies

M. Elle Saine[1,2], Julia E. Szymczak[1], Frances K. Barg[1] and Vincent Lo Re, III[1]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Perleman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [2]University of Pennsylvania, Philadelphia, PA

Background: The number of patients with Hepatitis C virus (HCV) infection has tripled in the past decade. Despite highly curative all-oral direct-acting antiviral therapies, most patients remain undiagnosed, are not linked into care, and do not receive antiviral treatment. Stigma is an important and understudied barrier to HCV treatment and elimination, but the extent to which stigma interferes with HCV diagnosis, linkage to care, and treatment initiation remains unknown.

Objectives: We conducted an exploratory mixed-methods study evaluating the impact of stigma at each step along the HCV Continuum of Care, a healthcare framework for identifying gaps in HCV diagnosis (Step 1), linkage to care (Step 2), treatment (Step 3), and antiviral adherence/cure (Step 4).

Methods: We conducted cross-sectional surveys among HCV-infected patients in Philadelphia, PA, USA using the HCV-stigma scale, a validated 33-item questionnaire that measures HCV-related stigma. Qualitative data were collected via a free-response question within the survey instrument and semi-structured interviews among a purposive subsample of 22 participants who completed the survey instrument. Associations between HCV-related stigma and stage of treatment were evaluated by multivariable linear regression. Survey responses were linked to narrative data on patient's lived experiences with HCV at each stage of care.

Results: Among 265 participants, the median stigma score was 75.57 (SD, 19.13). Although scores did not differ significantly between each step along the HCV Care Continuum (P=0.204), most participants (95.5%) experienced some degree of HCV-related stigma. Experiences of HCV-related stigma posed barriers to each of the steps along the Continuum of Care: 1) Diagnosis: injection drug use history interfered with HCV testing; 2) Linkage to Care/Treatment: stigma from healthcare providers, particularly refusal of services, was a barrier to linkage to care and antiviral treatment initiation; 3) Antiviral Adherence/Cure: experiences of social distancing, being treated as "dirty" for having HCV, and reluctance to disclose diagnosis to family/friends adversely affected antiviral adherence and cure.

Conclusions: Participants described HCV-related stigma as an important barrier in access to care. Importantly, stigma from healthcare providers creates significant barriers to medical care and antiviral treatment among patients with HCV. Addressing HCV-related stigma may increase HCV diagnosis, linkage to care, and treatment uptake and improve health-related quality of life.

4444 | Prevalence, mortality, disease progression and associated comorbidities of chronic obstructive pulmonary disease in the United States: A literature review

Anil Dasari[1], Salman Hussain[2] and Pradeep Basa[3]
[1]Independent Researcher, Delhi, India; [2]Jamia Hamdard, Hamdard University, Delhi, India; [3]Independent Researcher, Bangalore, India

Background: Chronic Obstructive Pulmonary Disease (COPD) is the major component of chronic lower respiratory diseases and characterized by obstruction to airflow that interferes with normal breathing. COPD is the fourth leading cause of death in the United States (US). It is out-most important to review the morbidity and mortality of COPD in the US to make better healthcare decisions.

Objectives: To evaluate the prevalence, mortality, disease progression and associated co-morbidities of COPD in the US.

Methods: A comprehensive literature search was conducted in PubMed and Cochrane Library by combination of MeSH terms & keywords from May 2017 to May 2018. Google & Google Scholar was also searched for additional publications. The quality of included studies was assessed by Newcastle-Ottawa-Scale.

Results: The age-adjusted diagnosed COPD prevalence rate among adults aged ≥18-years was 5.9% (95% CI 5.8–6.0) in 2015. It was highly prevalent in West-Virginia (12.0%) & lower in Utah (3.8%). Age-standardised COPD mortality rate was 45.1 & 40.3 per 100,000 populations in 2014 and 2015, respectively and it was increased between 1980 and 2014 (34.5-to-45.1 deaths per 100,000 populations). Older age (β=0.03058), lower BMI (β=-0.0569), airway disease axis (β=0.64179), and CT intensity variability/noise (β=0.30924) were significantly (p<0.0001) associated with higher mortality. Almost half (49%; N=1105) of the COPD patients had at least one acute exacerbation. 7% & 2% of patients had at least one & ≥2 acute exacerbation each year, respectively. Mean number of overall & severe exacerbations were 1.5 & 0.48, respectively. COPD patients with previous exacerbations (5.22), ≥2-exacerbations in the year preceding enrolment (3.03), lower baseline FEV1 (0.93), younger-age (0.69) and higher CAT-score (1.11) significantly (p<0.001) higher odds to have at least one-exacerbation. Very commonly reported co-morbidities in COPD patients were hypertension (46-63.2%), diabetes (28.3-31%), affective disorders (27%), congestive heart failure (26.9%), and fluid and electrolyte disorder (23.4%).

Conclusions: COPD is highly prevalent and associated with significant morbidity, and mortality in the US.

4456 | Estimating chronic obstructive pulmonary disease prevalence in Portugal using pharmacy sales data

António T. Rodrigues[1], Rúben Pereira[1], Mariana Romão[1], Peter Heudtlass[1], José Guerreiro[1] and José Alves[2]
[1]Associação Nacional das Farmácias (ANF), Lisbon, Portugal; [2]Fundação Portuguesa do Pulmão (FPP), Lisbon, Portugal

Background: The prevalence of a disease is among the most fundamental measures in epidemiology. Though estimation methods based on primary sources are the gold standard for assessing prevalence, these are resource intensive and consequently limit reproducibility and periodicity. Recent estimations of prevalence of Chronic Obstructive Pulmonary Disease (COPD) in Portugal date from 2014 (assessed by self-reporting: 5,8% of the population) and 2016 (assessed using BOLD methodology: 14,2% of the individuals over 40 years living in

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Lisbon). However, discussion on whether the estimates are overvalued still resides among healthcare practitioners as only 132.000 COPD diagnosed patients were referenced to the national health service.

Objectives: The present study aims to estimate the prevalence of patients on medication for COPD in Portugal based on sampled data from medical prescriptions and on dispenses in community pharmacies nationally.

Methods: The average medication used for a 12-months period, at the patient level, was extrapolated from prescribed therapeutic regimens comprising at least one specific medication for COPD. This estimate considered average daily dosage, treatment duration, and class-specific Medication Possession Ratio (MPR) as reported in the literature. The prevalence in the population was estimated by distributing the total of dispenses of any COPD medication, nationally and per region, considering the calculated average medication used per patient in each therapeutic regimen.

Results: The estimated prevalence of treated COPD in Portugal in the 12-month period from Sep'18 to Aug'19 was 2,05% (≈210.700 patients). Attending to gender specific prescriptions and population distribution, we estimate this prevalence to be 2,80% in men (≈136.000 pts) whereas in women the prevalence is approximately half (1,38%, ≈74.700 pts). Estimates at the regional level range from 0,79% in Beja (≈1.125 pts) and 4,80% in Santarém (≈20.700 pts).

Conclusions: The number of treated COPD patients presented supports the underdiagnosis of COPD in Portugal, when compared to the prevalence estimates based on the gold standard for diagnosis. This suggests only individuals under treatment are likely to be known to the national health service. This study reinforces the role of the data available from community pharmacies on the assessment of the real burden of diseases. The presented estimation method retains national and regional representativity of the data used, enables stratified estimates and continuous monitoring of the number of individuals treated for COPD and may be applicable to other diseases.

4647 | Adverse events after acute kidney injury admission: A cohort study in the UK clinical practice research datalink

Patrick Bidulka, Kathryn Mansfield, Viyaasan Mahalingasivam, Dorothea Nitsch and Laurie Tomlinson

London School of Hygiene & Tropical Medicine, London, United Kingdom

Background: There is ongoing intense debate on how to best treat people discharged following acute kidney injury (AKI), particularly in those taking angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocking (ARB) drugs. In order to understand key differences between the ACEI/ARB users and all individuals admitted for AKI (that may limit generalisability of any findings within the ACEI/ARB subgroup) it is important to describe the overall population admitted for AKI compared to a sub-group of ACEI/ARB users.

Objectives: To describe an overall UK population admitted to hospital with AKI and the sub-population who are prescribed ACEI/ARB in terms of baseline characteristics, death or dialysis during and after AKI hospitalisation, prescribing patterns before and after AKI admission, and subsequent readmissions.

Methods: We conducted a cohort study using linked UK primary and secondary care data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES). Participants were admitted to hospital for AKI (2010-2016), without a history of previous AKI, end-stage renal disease, or dialysis. Main outcome measures were ACEI/ARB prescription after discharge following AKI, mortality, and re-admissions (overall and cause-specific [heart failure, AKI, stroke]). We described the incidence of outcomes in the overall cohort admitted for AKI, as well as ACEI/ARB users using absolute rates stratified by follow-up period, Kaplan-Meier curves, and mean and median length of admissions.

Results: In the overall cohort (n=18,034) admitted for AKI, mean age was 77 (SD 14) with 48% female. 48% had chronic kidney disease (CKD) stage 3 or worse, 25% heart failure, and 52% were ACEI/ARB users. During the AKI hospitalisation, 679 (4%) received dialysis and 2524 (14%) died. Of those discharged (n=15510), 76% were readmitted within 2 years. The most common readmission primary diagnoses were AKI (7%), urinary tract infections (6%), pneumonia (5%), heart failure (3%), and chronic obstructive pulmonary disease (COPD) (1.6%). ACEI/ARB users had the same pattern of readmissions following initial AKI admission.

Conclusions: Infections and further AKI are among the most common causes of re-admission following AKI hospitalisation. Overall readmission and mortality rates are high in both the overall and ACEI/ARB users cohorts. Further research should investigate why infections are so common in people discharged after AKI hospitalisation.

4667 | Prevalence and baseline characteristics of dialysis and non-dialysis dependent CKD patients with and without anemia: A US cohort from DISCOVER-CKD

Eric Wittbrodt[1], Juan Jesus Carrero[2], Glen James[3], Steven Fishbane[4], Supriya Kumar[1], Roberto Pecoits-Filho[5,6], Juan Jose Garcia Sanchez[3], Carol Pollock[7], James Sloand[1], Katarina Hedman[8] and David Wheeler[9]

[1]AstraZeneca, Gaithersburg, MD; [2]Karolinska Institutet, Stockholm, Sweden; [3]AstraZeneca, Cambridge, United Kingdom; [4]Northwell, New York, NY; [5]Pontifical Catholic University of Parana, Curitiba, Brazil; [6]Arbor Research, Ann Arbor, MI; [7]University of Sydney, Sydney, Australia; [8]AstraZeneca, Gothenburg, Sweden; [9]University College London, London, United Kingdom

Background: Anemia is a frequent complication of chronic kidney disease (CKD), with prevalence increasing as kidney function declines and is associated with adverse clinical outcomes and reduced quality of life.

Objectives: To describe prevalence and baseline characteristics of CKD patients with and without anemia in a US cohort from DISCOVER CKD.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: DISCOVER-CKD is an international observational study in patients with CKD. The DISCOVER-CKD retrospective US cohort of patients was extracted using real world data from the integrated Limited Claims and Electronic Health Record data (IBM Health, Armonk, NY). The study cohort included patients aged greater than 18 years with diagnostic CKD code (stage3A through end stage renal disease or renal replacement therapy (RRT)) or 2 estimate glomerular filtration rate (eGFR) measures less than 75 mL/min/1.73m^2 at least 90 days apart between 1st January 2008 and September 2018. The index date was the first hemoglobin (Hb) measure on or up to 1-year after any of the following: the first diagnostic code for CKD or RRT, or initial eGFR; all patients require a second confirmatory eGFR which qualifies the patient to be part of the DISCOVER CKD cohort. Exclusion criteria was: less than 1-year registration/medical history prior to index, active bleeding in the 30 days preceding and inclusive of index and no Hb measure within a year after CKD diagnosis. Descriptive analyses were used to summarize prevalence and patient characteristics according to World Health Organization anemia categories.

Results: Of the 55495 CKD patients meeting our I/E criteria, 43700 (78.7%) where not anemic at baseline (Hb (g/dL) greater than 12/13 (female/male)). In anemic patients: 9743 (17.6%), 1665 (3.0%) and 387 (0.7%) had a baseline Hb of 10-12/13 (female/male), 8-10 and less than 8, respectively. Compared to non-anemic patients: anemic patients at baseline were older (68-70 years vs 63 years), more likely female (50-60% vs 56%), more likely to have comorbidities including hypertension (55-62% vs 47%), heart failure (15-28% vs 5%), type 2 diabetes (26-32% vs 16%), had more advanced CKD (mean eGFR 48-56 vs 64) and were more likely to be prescribed medications. Patients with more severe anemia (Hb less than 8) were more likely to receive iron (10%) or blood transfusions (15%) but not ESAs (0.3%).

Conclusions: In routine clinical care, the presence and severity of anemia increases as CKD advances. Patients with anemia have a higher comorbidity burden, lack of transfusion history and treatment for anemia at baseline was rare and almost absent in patients with Hb less than 10.

4686 | Using over-the-counter medication sales and the moving epidemic method for flu surveillance in Portugal (2016-2020)

Peter Heudtlass[1], Nuno Rodrigues[2], António T. Rodrigues[1], Rúben Pereira[1] and Zilda Mendes[1]

[1]Associação Nacional das Farmácias, Lisboa, Portugal; [2]Agrupamento de Centros de Saúde Oeste Sul, Torres Vedras, Portugal

Background: Most patients with influenza-like illness (ILI) do not see seek medical attention immediately, if at all. This potentially leads to a lag in detecting the start of flu epidemics and in predicting their peak, when using primary care case load data for surveillance.

Objectives: To model seasonal influenza with the Moving Epidemic Method (MEM) using over-the-counter (OTC) sales instead of health care case load data and to estimate the sensitivity and specificity of this model. To test whether our data can detect beginning and peak of the 2019/2020 influenza epidemic earlier than models based on primary care data.

Methods: Using a time-warping algorithm and time series correlations, we define a basket of OTC products that explains best the variation in ILI cases reported by primary care units in the health zone Oeste Sul, north of Lisbon, Portugal, during five previous flu seasons (2014-2019). We fit a MEM model with the total Portuguese sales of these products in the same period and estimate the model's sensitivity and specificity. Using this model and OTC sales of the influenza season 2019/2020 in Portugal, we estimate beginning and peak of the 2019/2020 epidemic and compare this to primary care case load data.

Results: We estimate that the MEM model calibrated with OTC data from 2014-2019 has a sensitivity of 80.4% and a specificity of 83%. Using the fitted model for surveillance, it allows us to detect the beginning and the peak of the 2019/2020 before they are observable in the primary care case.

Conclusions: Data from OTC sales in community pharmacies can complement and strengthen flu surveillance in Portugal.

4702 | Mortality in preterm infants with bronchopulmonary dysplasia associated pulmonary hypertension: A systematic literature review

Laura Downham, Sofija Cerovic, Catherine Lesage and Sandrine Leroy

Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Background: Pulmonary hypertension (PH) is a common complication of bronchopulmonary dysplasia (BPD) in preterm infants and worsens outcomes in these patients with other competing mortality risk related to multiple comorbidities (cerebral palsy, infections, enterocolitis). Mortality estimates are unclear in the literature, and its relationship to BPD-PH specifically.

Objectives: To provide an up-to-date overview of mortality in infants with BPD-PH through a systematic literature review.

Methods: A systematic literature search of Medline and Embase was conducted and included observational studies in paediatric BPD-PH patients and mortality data. Mortality proportion (MP; rate of death over the study sample size) was explored in regards with all available factors to better explore its heterogeneity across studies.

Results: 25 studies (n=2179 BPD-PH patients) were included, 84% were retrospective, and 76% were conducted in North America. PH diagnosis was based on a combination of echocardiographic criteria in 96% of the studies. When reported, all studies included preterm infants with gestational age (GA) <28 weeks. The MP ranged from 4.0% to 52.8% (median: 13.0%) while the 2-year survival estimate (n=5 studies) ranged from 35.0% to 80.0% with a steep decrease in survival between 6 months and 1 year, then stabilisation. In studies with follow-up ≥1 year, median MP was of 20.8%, ranging from 11.1% to 28.0%; studies with shorter follow-up offered more heterogeneity. Independently of the time of follow-up, the median MP was higher in the studies where PAH was diagnosed later than 40 weeks GA, likely due to an immortal bias leading to inclusion of only

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

surviving infants with a high all-causes mortality in their first weeks of life. As expected, there was an inverse relation between MP and birthweight that reflected the degree of immaturity of pulmonary and vascular tracts leading to severe BPD-PAH disease. Causes of death were reported in 52.0% of the studies, and were not clearly related to PAH, highlighting the multiplicity of factors that lead to the high mortality rate observed. The methodological quality of the included studies was acceptable (STROBE median score of 14.8- Q1, Q3: 13.7, 16.2).

Conclusions: This systematic literature review demonstrated that mortality estimates were highly heterogeneous, due to immortal bias, follow-up duration, GA limit to define BPD-PH, and birth weight. Registries with standardised definitions, longer follow-up would be of interest to better estimate mortality, and its direct relationship to BPD-PH in preterm infants.

4707 | Identifying chronic kidney disease in a laboratory database: Setting does matter

Uffe Heide-Jørgensen[1], Christian F. Christiansen[1], Henrik Birn[1,2], Reimar W. Thomsen[1] and Søren V. Vestergaard[1]

[1]Aarhus University Hospital, Aarhus, Denmark; [2]Aarhus University, Aarhus, Denmark

Background: Chronic kidney disease (CKD) is usually diagnosed based on the glomerular filtration rate (GFR). Estimated GFR (eGFR) can be assessed from serum creatinine, making laboratory databases an excellent data source for patient identification in pharmacoepidemiological studies of CKD. However, during hospitalization and emergency room visits eGFR may not correctly reflect the patient's normal GFR due to acute illness.

Objectives: To investigate differences between CKD patient cohorts identified using serum creatinine tests from outpatient settings only, compared with using all tests regardless of setting.

Methods: We conducted this cohort study in 2009-2016, using a population based laboratory database containing results from all creatinine blood tests from primary, secondary and tertiary care in Northern Denmark. Tests taken on days where a person was hospitalized or visited an emergency room (ER) were flagged. We identified patients with CKD as anyone with at least two tests showing eGFR < 60 mL/min/1.73m^2 at least 90 days apart, with the second being the index date. We did this using only unflagged blood tests (outpatient), and using all tests (total), resulting in two cohorts. We followed patients until death or emigration using the Civil Registration System. For both cohorts, we described baseline characteristics and estimated mortality using the Kaplan Meier approach. In sensitivity analyses we required just one test tests showing eGFR < 60 mL/min/1.73m^2 to define CKD.

Results: The outpatient and total cohorts included 84,688 and 95,213 patients, and the median age was 74 years in both. The median (interquartile range) time from first to second CKD defining blood test was 13 (6-35) months in the outpatient and 15 (6-41) months in the total cohort. The 1-year mortality was 8.2% (95% confidence interval [CI] 8.0-8.3) in the outpatient cohort and 12% (95% CI 11-12) in the total cohort. The difference in mortality between the outpatent and total cohorts attenuated over time, after 8 years the corresponding mortalities were 45% (95% CI 44-46) and 46% (95% CI 45-47). In the sensitivity analyses, we identified 103,435 and 123,841 patients with median ages of 71 and 70 years in the outpatient and total cohorts. The cohorts were similar with respect to baseline characteristics but the difference in mortality was more pronounced than in the main analyses.

Conclusions: The distribution of baseline characteristics in CKD patient cohorts was not affected much by the in- or exclusion of creatinine blood tests from inpatient or ER settings. However, inclusion of all tests increased both the number and mortality of patients included in the cohorts.

4774 | Development of novel algorithms to identify cases of focal segmental glomerulosclerosis in a large electronic medical record database

Irene Cosmatos[1], Cynthina de Luise[2], J. Brian Copley[2], Daniel I. Levy[2], Nihad Tamimi[2], Stephen Berasi[3], Donal Gorman[4], Michael Bulgrien[1] and Gretchen Dieck[1]

[1]UBC, Blue Bell, PA; [2]Pfizer, New York City, NY; [3]Pfizer, Cambridge, MA; [4]Pfizer, Cambridge, United Kingdom

Background: Health authorities are increasingly accepting real world data (RWD) to support regulatory decision-making. Access to large, clinically rich, geographically representative electronic medical record (EMR) databases and other RWD enable the conduct of real world studies to inform natural history of disease and assess disease prevalence.

Objectives: To develop laboratory-based computer algorithms to identify cases of focal segmental glomerulosclerosis (FSGS), a rare kidney disease with clinically diverse etiology, in Humedica, a national level EMR database reflecting the age, gender, geographic, and racial diversity of the United States population.

Methods: The prevalent 2017-2018 glomerulonephritis (GN) disease population in Humedica, of which FSGS is a subset, was assessed to gain insight into relevant diagnoses (e.g., nephrotic syndrome), procedures (e.g., kidney biopsy), laboratory tests, and demographics needed to identify potential cases of primary and secondary FSGS. Next, a team of expert nephrologists conducted an in-depth clinical review of detailed EMR-generated profiles of patients who broadly qualified as potential cases of FSGS based on a combination of relevant lab results, diagnoses, and procedures. Key factors that influenced the determination of FSGS case status included age, evidence of nephrotic range proteinuria, FSGS ICD-10 codes, evidence of a kidney biopsy, and exclusions due to comorbidities related to nephrotic range proteinuria (e.g., diabetes).

Results: Among >30,000 patients with diagnoses of GN, the distribution of GN subtype by race demonstrated an increased frequency of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

nephrotic syndrome diagnoses in general, and FSGS in particular, among African-Americans vs. Caucasians and Asians. Expert nephrologists established a set of computer algorithms to identify primary and secondary FSGS cases in Humedica, with the likelihood of case status ranging from 'definite' to 'uncertain.' Only patients with a documented kidney biopsy could be classified as 'definite', based on laboratory results and the frequency and timing of FSGS diagnoses. Algorithms were specific to age group (<10 yrs vs. ≥10 yrs), as the disease presents differently in children.

Conclusions: These original algorithms represent the first opportunity to create FSGS diagnostic groups of increasing levels of certainty depending on available evidence in a patient's EMR data. Upper and lower ranges of primary and secondary FSGS prevalence can then be estimated in a representative US population according to important disease risk factors of age, gender, and race.

4799 | The association between the use of long-term antibiotics used to treat acne vulgaris and subsequent infection sequelae and antimicrobial resistance: A systematic review

Ketaki Bhate[1], Liang-Yu Lin[1], John Barbieri[2], Sarah-Jo Sinnott[1], Rohini Mathur[1] and Sinead Langan[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]University of Pennsylvania, Philadelphia, PA

Background: Antimicrobial resistance (AMR) is a global health priority. Acne vulgaris is a highly prevalent skin condition predominantly of adolescence and antibiotics are widely used in its treatment. Average antibiotic use for acne ranges from a few months to years of daily exposure.

Objectives: To systemically search for and synthesise evidence on the role of long-term oral antibiotic use for acne in increased risk of infections unrelated to acne or other outcomes suggestive of AMR.

Methods: The following databases were searched: Embase, MEDLINE, Cochrane and Web of Science, using MeSH, EMTREE or other relevant terms. Search strategies were developed in collaboration with a librarian and run in July 2019. All searches date from database inception. Inclusion criteria: Randomised controlled trials, cohort or case control studies investigating oral antibiotics of any class for a minimum of 28 days in individuals over 8 years old, compared to people with acne not treated with oral antibiotics, or the general population. Exclusion criteria: Ecological studies and studies that did not assess temporality. Studies investigating topical antibiotics or Cutibacterium acnes. The primary outcome was antibiotic treatment failure or infection caused by a resistant organism. The secondary outcome was the detection of resistant organisms without an infection, rate of infection, or changes to flora. Three reviewers independently screened the search results based on title and abstract. Full-text papers were assessed independently using a standardised pilot-tested data extraction form. ROBINS-I was used to assess the risk of bias and GRADE was used to make an overall assessment of quality of evidence.

Results: 6996 records were identified for title and abstract screening. 73 full-text articles were shortlisted for full review, of which five articles were included. Two investigated infection rates and three identified resistance or changes to microbial flora; all were cohort studies from high income western countries. Three studies had 35 or fewer participants (range 20-118,496). Given heterogeneity, meta-analysis was not possible. Three studies had a 'serious' risk of bias and two a 'moderate' risk of bias. Findings suggest there may be an association with an increased rate of upper respiratory tract infections and pharyngitis.

Conclusions: There is an outstanding gap in our understanding of the relationship between oral antibiotics used to treat acne and infectious sequelae and AMR. This needs to be urgently addressed with rigorously conducted studies.

4894 | Digitization of physical behaviors

Marie Mc Carthy, Paul Nolan, Antonio Lampasi, Jialiang Chen and Michal Skackov

ICON PLC, Dublin, Ireland

Background: This study looks at the feasibility of extracting clinically relevant digital data from wearables. This data has significant potential as real world data particularly as they evolve to more robust and reliable sources of data with many manufacturers pursuing regulatory pathways.

Objectives: To architect a cloud based platform to facilitate the storage of large datasets from wearables and advanced analysis of the ingested data. T

Methods: Employees who own a Fitbit were recruited by email, 10 consented and were sent a link to the authorization application (app). An analysis of clinical trials.gov to identify endpoints from studies where wearable data had supported outcomes. The platform was built with a multi-cloud strategy. Microsoft's Azure cloud platform hosted the app used to authorize participants data collection. Amazon Web Services Cloud (AWS) was used to implement the backend data collection, processing and analytics. Serverless technologies were deployed in AWS resulting in a highly scalable architecture. Data generated was pushed into Microsoft's Power BI cloud to enable analytics and visualizations to reflect the endpoints identified.

Results: Fitbit were used in 276 of the 361 studies identified. Outcome measures mapped to broad categories; Physical Activity, Sleep, Heart Rate and Wear Compliance each category consisting of a variety of individual endpoints. Over an 87 day period 54048 steps, 9595 sleep and 541421 heart-rate data points were captured. Analytics were developed to map to the identified endpoints. The average steps/day was 4,396, this figure was consistent for weekday and weekends. There was a 30% reduction in steps over the period December 25th and 26th. There was a corresponding decrease in Moderate and Vigorous physical activity with 0 hr recorded on the 25th of December. There was a similar reduction in the percentage time spent in the cardio range of heart rate patterns going from

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

0.65% to 0.34% on that day. The sleep pattern showed a reduction in REM sleep as a percentage of the overall sleep pattern.

Conclusions: The growing availability of wearables among the general population, is an untapped digital data resource. A BYOD model is feasible to track physiological changes using advanced analytics to convert large data streams into clinically meaningful endpoints. Currently the BYOD model pertains only to devices from a single vendor as aggregating data from different wearables is challenging as manufactures use different accelerometers, sampling rates and algorithms to generate physical activity, sleep data. In addition it is likely an RWE study would require a mix model with both provisioned and a BYOD approach.

4987 | People living with HIV with higher CD4+ lymphocyte counts rated their own health as good

Cristiane A. Menezes de Pádua[1], Letícia P. Braga[2], Isabel N. Santos[2], Letícia F. Silva[2], Bianca R. Guerra[2], Joyce C.M. Faria[1] and Cassia C.P. Mendicino[1]

[1]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [2]Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

Background: Antiretroviral therapy has markedly contributed to the increase of life expectancy and quality of life of people living with HIV. Self-rated health is a sensitive measure of easy application, which is related to morbidity and mortality.

Objectives: To assess the factors associated with good self-rated health among people living with HIV on long-term antiretroviral therapy.

Methods: Cross-sectional study with 85 treatment-experienced individuals from Belo Horizonte, Brazil. Self-rated health was obtained through the interview question: "How much are you satisfied with your own health?" based on a 5-point scale (1=very unsatisfied, 2=unsatisfied, 3=satisfied nor unsatisfied, 4=satisfied and 5=very satisfied). Patients were grouped into two categories, according to their responses: good self-rated health (4 or 5) or bad self-rated health (1, 2 or 3). Socio-demographic, behavioural/lifestyle and clinical/laboratory variables were obtained from interviews and review of medical charts. Binary logistic regression was used to assess the association between good self-rated health and exposure variables estimated through odds ratios (OR) with 95% confidence intervals (CI).

Results: Fifty-seven (67.1%) participants rated their health as good. Most patients were men (54.1%), aged 50 years or older (57.7%), had non-white skin colour (84.3%) and reported current consumption of alcohol (70.6%). Approximately 30% of patients were on treatment with lamivudine/tenofovir and efavirenz, 32.9% reported current use of tobacco and 46.5% had regular physical activity in the previous 12 months. The majority of the participants had undetectable (< 50 copies/mL) viral load (81.2%), T-CD4+ count >500 cells/μl (76.5%) and had at least one comorbidity during their HIV/AIDS treatment (62.3%). LT-CD4+ count >500 cells/μl (OR=3.27; CI95%=1.03-10.34) and absence of comorbidity were independently associated with a good self-rated health (OR=6.63, CI95%=1.93-22.71).

Conclusions: The proportion of good self-rated health was similar to that found in other national studies. Characteristics related to the HIV infection appeared to have impact on the self-rated health of the participants rather than behavioural/lifestyle or socio-demographic variables. LT-CD4+ count >500 cells/mm^3 is related to reduced risk of disease progression and death, thus it might contribute to the perception of being healthy. Therefore, the monitoring on immunological response is important to ensure higher life expectancy and better quality of life of people living with HIV.

5003 | Analysis of a large cohort of patients with erythema multiforme majus: Epidemiology, clinical pattern and risk factors

Maja Mockenhaupt, Susanne Martin and Maren Paulmann

Medical Center - University of Freiburg, Freiburg, Germany

Background: Erythema multiforme majus (EMM) is a severe reaction affecting skin and mucous membranes. For decades EMM has erroneously been considered to be the same as Stevens-Johnson syndrome (SJS), leading to false conclusions in terms of etiology. However, a consensus definition (Bastuji-Garin et al, 1993), which was further specified (Schröder et al, 1999), allows to separate EMM from SJS, and differentiate between a typical and atypical form of EMM.

Objectives: Demographic data, clinical pattern and risk factors of EMM are investigated in a large cohort of validated cases, and compared to those seen in SJS.

Methods: Since 1990 the German Registry has ascertained hospitalized cases of severe skin reactions including EMM. From Jan 2003 these cases entered the multinational RegiSCAR-study. For this analysis all potential cases of EMM collected from this time onwards until Aug 2017 were investigated. They were clinically reviewed by an expert committee blinded for potential causes based on the definitions referenced above.

Results: Of 312 EMM-cases 219 were validated as "definite", 72 as "probable", 21 as "possible. Of these, 192 cases were typical EMM, 119 atypical EMM; 1 case could not be determined. Men were much more often affected than women (204 vs. 108). Children and adolescents <18 yrs accounted for 65% of cases, 2/3 of them were male. Cases occurred throughout the year but clustered Nov - Feb. No death was observed in this EMM-cohort. In all cases at least 1 mucous membrane was affected by hemorrhagic erosions. On average, 4 mucosal sites were erosive, most frequently oral cavity (99%), lips (98%) and genital mucosa (86%). In 33% of patients, severe conjunctivitis was diagnosed. The type of lesions could be analyzed in 309 cases: 85% had typical targets, 39% atypical raised targets. In cases of typical EMM the average amount of skin involvement was 4%, with <2% of detachment. In contrast, the amount of skin involvement in atypical EMM was much higher with up to 40% and detachment with up to 10%. In 81% of definite and probably cases (n=291) the reaction was preceded by an infection. Most frequently this was a

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

respiratory infection, and in 55% of patients, mycoplasma pneumoniae was identified. In 18% of the cases a herpes simplex-eruption took place before EMM. Medications with a high risk to induce SJS and toxic epidermal necrolysis (TEN) could only be identified in 1 patient, who suffered from an infection that was treated with sulfamethoxazole.

Conclusions: These data clearly demonstrate that EMM must be differentiated from SJS/TEN and should be viewed as an infection-induced condition, and not as a drug eruption.

5038 | Prevalence of eosinophilia in the United States

Hoa V. Le[1], Chi H.H. Le[2], Phuong H.U. Le[3] and Chi T.L. Truong[4]
[1]*Bristol-Myers Squibb, Berkeley Heights, NJ;* [2]*School of Medicine, Vanderbilt University, Nashville, TN;* [3]*University of Toronto, Mississauga, ON, Canada;* [4]*MedCodeWorld, Chapel Hill, NC*

Background: An accumulation of eosinophils in the blood is observed in certain disease states such as atopy, allergy or parasitic infections. Due to tissue infiltration and subsequent inflammation and fibrosis, a marked rise in eosinophils has been associated with critical organ-damage. However, there is a paucity of data examining eosinophilia in the general population.

Objectives: To determine the prevalence of eosinophilia and hypereosinophilia in a nationally representative sample of the U.S. population.

Methods: Eosinophilia and hypereosinophilia cases, defined as individuals with eosinophil count over 500/uL and 1500/uL respectively, were identified in the National Health and Nutrition Examination Survey (NHANES) 2015-2016. Prevalence and 95% CIs were analyzed in the overall sample and by age groups, sex, and race/ethnicity. Multivariate logistic regression was performed to compare prevalence among different subgroups. Statistical analyses accounted for complex survey design with examination sample weights and adjusted for nonresponse. Sensitivity analyses included unadjusted, gender- and age-adjusted modeling. Statistical significance was determined by 2-sided p value of 0.05.

Results: Among 8,116 U.S. individuals from 2015-2016, the overall prevalence of eosinophilia and was hypereosinophilia were 8.2% (95% CI: 7.2-9.2%) and 0.14% (95% CI: 0.07-0.21%), respectively. Rates of eosinophilia were significantly higher in men than in women 10.3% (95% CI: 8.7-12%) vs. 6.2% (95% CI: 5.3-7%), $p < 0.0001$. Among different age groups, eosinophilia was observed at significantly higher rate in children aged ≤ 11 years (17.3%, 95% CI: 15.4-19.3). Sensitivity analyses adjusted for age- and/or gender- showed similar trends. Moreover, non-Hispanic blacks had lower rates of eosinophilia in comparison non-Hispanic whites (7.2% vs. 8.3%, p=0.048). Among the study population, the mean, median and IQR of eosinophil count were 214/uL, 120/uL and 51-219/uL, respectively.

Conclusions: These findings provided an updated depiction of the prevalence of eosinophilia and hypereosinophilia in the general US population. In addition to known comorbidities, our study identifies potential high-risk groups for eosinophilia including men and children ≤ 11 years old.

5063 | Use of administrative health databases to estimate incidence and prevalence of rheumatic arthritis in the general population

Francesco Barone-Adesi, Andrealuna Ucciero, Gianmarco Cotrupi and Antonio Isabella
University of Eastern Piedmont, Novara, Italy

Background: Unrecognized and untreated Rheumatic Arthritis (RA) leads to serious clinical complications with adverse outcomes for patients and increasing costs for the health care system. Hence, adequate knowledge of the epidemiological features of such a condition is desirable to plan effective interventions. However, currently available information is mainly derived from data collected in specialized referral centers, whose catchment areas may not cover the whole population.

Objectives: The aim of our study was to use administrative data sources to estimate incidence and prevalence of RA in the general population of a large Italian region.

Methods: A retrospective cohort study was conducted using Administrative Health Databases of Piedmont, an Italian Region with a population of 4.3 million inhabitants, during the period 2012-2018. RA cases were defined as the subjects who had at least one of the following claims: i) Hospital discharge records with RA diagnosis code; ii) Exemption from co-payment for RA; iii) Prescription of one of the following medications: tocilizumab, abatacept, leflunomide, sodium aurothiomalate, sodium aurotiosulfate, auranofin. Prevalence was calculated by dividing the number of prevalent cases of RA (i.e., those with RA-related claims at any time during the period 2012-2018) by the total number of residents in Piedmont. Incidence was calculated by dividing the number of new RA cases (i.e., no evidence of RA during the 3 years prior to the index claim) by the size of the population total time at risk during the period 2015-2018. Clopper-Pearson and Byar methods were used to estimate the 95% confidence intervals (CI) for prevalence and incidence, respectively.

Results: The overall prevalence was 5.5 per 1000 inhabitants [95% CI 54-56], and the overall incidence 28 per 100,000-person years [95% CI 26-29]. Prevalence and incidence increased with age and were about 2-fold higher among women.

Conclusions: Administrative data source can represent a simple and inexpensive method to monitor patterns of RA in large populations. This study is part of the FOHN project, funded by the Italian Ministry of Education, University and Research.

Drug Effectiveness

94 | Drug survival of secukinumab, ustekinumab, and adalimumab in patients with psoriasis

Zenas Z.N. Yiu and BADBIR Study Group
University of Manchester, UK, Manchester, United Kingdom

Background: Biologic drug survival in the real world is an important proxy measure for effectiveness. Predictors of drug survival may help patients with psoriasis choose the right biologic first time.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: 1. To assess the relative drug survival of adalimumab, secukinumab and ustekinumab in patients with psoriasis; 2. To look for predictors for biologic drug survival in the same cohort.

Methods: The prospective cohort study was performed using data from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), a multicenter longitudinal pharmacovigilance registry of patients with moderate-to-severe psoriasis in the United Kingdom and Republic of Ireland between November 2007 and August 2019. The outcomes were survival functions after 1 and 2 years, separated by discontinuation reason; adjusted hazard ratios (adjHR) for adalimumab and secukinumab compared with ustekinumab; and adjHRs for the effect of the potential predictors of drug discontinuation due to ineffectiveness in a flexible parametric survival model.

Results: 9,652 participants were included in the study, with 5,542 starting on adalimumab (57.4%); 991 on secukinumab (10.3%); and 3118 on ustekinumab (32.3%) after registration. The overall drug survival of adalimumab, secukinumab and ustekinumab was 0.78 (95% CI 0.77-0.79), 0.88 (0.86-0.91) and 0.88 (0.87-0.89) in Year 1 respectively, dropping to 0.66 (0.64-0.67), 0.77 (0.73-0.80), and 0.77 (0.76-0.79) respectively in Year 2. Fourteen covariates were included. The adjHR for discontinuation of adalimumab and secukinumab compared with ustekinumab were 2.11 (1.76-2.54) and 0.67 (0.40-1.11) respectively. Psoriatic arthritis predicted for survival in the adalimumab and secukinumab cohorts (adjHR 0.67 (0.51-0.88); 0.70 (0.40-1.24) respectively) but for discontinuation in the ustekinumab cohort (adjHR 1.42 (1.12-1.81)), while having previous exposure to biologic therapies predicted for discontinuation in the ustekinumab and secukinumab cohorts (adjHR 1.54 (1.26-1.89); 1.49 (0.91-2.45) respectively) and for survival in the adalimumab cohort (adjHR 0.71 (0.55-0.92)).

Conclusions: Secukinumab and ustekinumab have similar sustained drug survival, while adalimumab has a lower drug survival in patients with psoriasis. We identified psoriatic arthritis and previous biologic experience as predictors of drug survival with differential effects between the biologic therapies.

99 | Treatment effectiveness, safety and health related quality of life in multiple myeloma: Evidence from the real world

Mir Mahmood Asrar[1], Dipika Bansal[1] and Deepesh P. Lad[2]
[1]*National Institute of Pharmaceutical Education and Research (NIPER) S.A.S. Nagar, Mohali, India;* [2]*Postgraduate Institute of Medical Education and Research, India, Chandigarh, India*

Background: Recent advances in the treatment of multiple myeloma (MM) have improved prognosis and increased disease-free and overall survival among patients. However, no study has been reported from India.

Objectives: This study aims to describe patients with MM their treatment and clinical outcomes, the comparative tolerability, effectiveness, health-related quality of life (HRQoL) and cost implications among different treatment groups.

Methods: A prospective single-center cohort study was conducted at hematology department, PGIMER Chandigarh, a tertiary care hospital in India. Baseline patient and MM-specific characteristics, diagnosis, comorbidities, and prior therapies, MM management, disease status, safety data, and cost details were recorded at baseline and follow-up based on a review of hospital/clinic records and patient interviews. HRQoL was measured using the Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the MM module (EORTC QLQ-MY20). Kaplan-Meier analysis was performed to determine progression-free and overall survival.

Results: A total of 75 patients were included; 60% were males and the mean age was 60.5±9.0 years. A statistically significant difference was observed in EQ-5D-5L domains like Usual activities and Health Status in patients with different ISS stages ($P<0.05$). A higher Very good partial response (VGPR) of 50% was reported in patients treated with Bortezomib, Lenalidomide, Dexamethasone(VRD) regimen relative to 27.3% receiving Bortezomib, Cycophosphamide, Dexamethasone (VCD). At 6-months follow-up, the significant reduction was reported in mobility [VCD: 2.53±1.02; VRD: 1.58±0.77, $p<0.05$], pain/discomfort [VCD: 2.32±1.11; VRD: 1.63±0.76, $p<0.05$] and health status [VCD: 64.37±22.86; VRD: 76.53±16.84, $p<0.05$]. The overall 6-month survival was comparatively lower in patients with higher albumin levels (3.5g/dL) $\chi 2 = 0.364$, $p = 0.547$. The average cost per cycle on the Cyclophosphamide, Thalidomide, Dexamethasone(CTD) regimen was lower 1339.9±229.6 Indian National Rupees compared to VRD and VCD.

Conclusions: HRQoL among MM patients were very low at diagnosis, but improved substantially after the initiation of novel MM regimens among treatment naïve patients. The rising out- of- the pocket cost of novel MM treatment raises the concern for affordability in developing countries.

105 | Effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis: A population-based cohort study

Tanja Tran[1,2], Deborah Assayag[1], Pierre Ernst[2] and Samy Suissa[1,2]
[1]*McGill University, Montreal, QC, Canada;* [2]*Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada*

Background: Gastroesophageal reflux disease is a common comorbidity in idiopathic pulmonary fibrosis (IPF) and is hypothesized to contribute to its progression. As treatment options for IPF are limited, anti-acid therapy, such as proton pump inhibitors (PPIs), has been conditionally recommended in international treatment guidelines for IPF. However, the evidence is inconsistent, where the observational studies that suggest a benefit are affected by immortal time bias.

Objectives: To assess the association between use of PPIs and all-cause mortality, respiratory-related mortality, and respiratory-related hospitalization in patients with IPF using a large population-based cohort.

Methods: We used the UK Clinical Practice Research Datalink to identify a cohort of patients diagnosed with IPF between 2003 and 2016. The prevalent new-user cohort design was used to match

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients initiating PPIs with non-users using time-based exposure sets and time-conditional propensity scores. Exposure sets were based on the first PPI prescription after IPF diagnosis (±1 month), with non-users having a record of a physician visit within the corresponding exposure set. Matched non-users could receive a PPI later during follow-up, so that their follow-up was censored and the patient could be included as a PPI user from that point onward. All study patients were followed until death or end of observation. Cox models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of death and of a respiratory-related hospitalization, correcting for informative censoring by inverse probability of censoring weighting.

Results: There were 1852 PPI users matched to 1852 non-users identified among the cohort of patients with IPF, with median survival of 2.8 years. The HR of all-cause mortality with PPI use was 1.07 (95% CI 0.94-1.21), relative to non-use. For respiratory-related mortality the HR was 1.10 (95% CI 0.61-1.97) and 1.01 (95% CI 0.87-1.18) for respiratory-related hospitalizations.

Conclusions: In this large study conducted in patients with IPF within a real world setting of clinical practice, PPI use was not associated with lower mortality or hospitalization incidence. PPIs may not be as beneficial in treating IPF as suggested by some observational studies affected by major bias. The conditional recommendations for the use of these medication in treatment guidelines need revision.

2320 | The potential beneficial effects of low-dose aspirin for the primary prevention of gastrointestinal cancers: A population-based cohort study in Hong Kong

Jessica J.P. Shami[1], Jiaxi Zhao[1], Swathi Pathadka[1], Pareen Vora[2], Montse Soriano Gabarró[2], Ian Wong[1] and Esther Chan[1]

[1]The University of Hong Kong, Hong Kong, Hong Kong; [2]Bayer AG, Berlin, Germany

Background: The effects of low-dose aspirin use in gastrointestinal cancers remain unclear in the general Chinese population.

Objectives: To evaluate associations between the use and duration of low-dose aspirin and the risk of colorectal cancer (CRC), gastric cancer (GC), and esophageal cancer (EC) in Hong Kong.

Methods: We conducted a retrospective population-based cohort study, using the Clinical Data Analysis and Reporting System (CDARS), an electronic clinical database managed by the Hong Kong Hospital Authority. Patients prescribed either low-dose (75-300mg/daily) aspirin or paracetamol (reference exposure) between January 2004 and December 2008 were matched (without replacement) by propensity score at a 1:1 ratio with follow-up until December 31, 2017. Potential confounders included age, sex, a list of comorbidities and concurrent medications. The primary outcome was an incident diagnosis of gastrointestinal cancer (either CRC, GC, or EC) identified using ICD-9 codes (International classification of diseases, 9th revision). The follow-up period started from the first prescription of either low-dose aspirin or paracetamol (i.e. index date) until the occurrence of outcome, any cancer diagnosis, death, or end of study period (December 31, 2017) whichever came first. We used competing risk Cox regression with death as the competing risk to generate hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: We included 166,466 low-dose aspirin or paracetamol users. The mean (standard deviation) follow-up was 8.7 (4.2) years for low-dose aspirin users and 9.0 (4.3) years for paracetamol users. The incidence rates of CRC, GC, and EC were 20.4, 5.4, and 2.2 per 10,000 person-years respectively for low-dose aspirin users and 22.9, 6.8, and 2.9 respectively for paracetamol users. Low-dose aspirin (vs. paracetamol) use was associated with a reduced risk of CRC, GC, and EC (CRC: HR = 0.88 [0.82-0.94]; GC: 0.77 [0.68-0.88]; EC: 0.72 [0.59-0.89]). Low-dose aspirin use for ≥3 years was associated with a reduced risk of CRC, GC, and EC (CRC: HR = 0.74 [0.67-0.82]; GC: 0.43 [0.35-0.52]; EC: 0.43 [0.32-0.59]) compared to <3 years low-dose aspirin use.

Conclusions: The use of low-dose aspirin was associated with a significant reduced risk of CRC, GC and EC among the study cohort. The use of low-dose aspirin for more than 3 years was more protective of CRC, GC, and EC compared to less than 3 years low-dose aspirin use.

2353 | Impact of maternal depression during pregnancy and its treatment options on fetal health: A prospective cohort study of 84,000 pregnant women

De-Kun Li[1], Jeannette R. Ferber[1], Roxana Odouli[1], Charles Quesenberry[1], Lyndsay A. Avalos[1], Mason Turner[2] and Tracy Flanagan[3]

[1]Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, CA; [2]Kaiser Permanente Hawaii, Wailuku, HI; [3]Kaiser Permanente, Oakland, CA

Background: Maternal depression during pregnancy is prevalent and its impact on fetal health remains uncertain. The risk-benefit profile of its treatment remains unclear due to a lack of control for the underlying depression in previous studies.

Objectives: To determine the risk of preterm delivery (PTD) associated with untreated depression and risk-benefit profiles of its treatment options, and whether those profiles are impacted by the presence of psychiatric comorbidity.

Methods: To disentangle the contribution of untreated depression from that of its treatments to the risk of PTD, we conducted a prospective cohort study among 84,912 pregnant Kaiser Permanente Northern California members. Clinically diagnosed depression, its treatments, PTD, and confounders were obtained from electronic medical records. A sub-cohort of more than 3,000 women were interviewed to collect additional information on confounders and compliance with use of prescribed antidepressants. The Cox proportional hazards regression was employed to account for PTD at various gestational ages.

Results: After using propensity score methodology to control for confounders and ensure comparability between cohorts, when compared to those without depression, pregnant women with *untreated*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

depression had 41% increased risk of PTD: adjusted hazard ratio (aHR)=1.41, 95% confidence interval (CI)=1.24-1.60. Compared to untreated depression, treating depression with antidepressants during pregnancy was associated with an additional 31% increased risk of PTD: aHR=1.31, 95% CI=1.06-1.61. There was a dose-response relationship with higher PTD risk associated with a longer duration of use. In contrast, mental health counseling was associated with a decreased risk of PTD: aHR=0.82 (0.71-0.96). This mitigating effect also showed a dose-response relationship with more visits being associated with a greater reduction in PTD risk. These associations were consistently observed regardless of the presence of psychiatric comorbidities. Sensitivity analyses, including adjustment for additional factors collected through interview of a sub-cohort, did not change the above observations.

Conclusions: Our results isolate the effect of depression from its treatment, and show that maternal depression during pregnancy, if not treated, increases the risk of PTD. Antidepressant treatment further increases the risk, and, in contrast, mental health counseling reduces the risk of PTD associated with depression. Thus, different treatment approaches during pregnancy could have different risk-benefit profiles.

2395 | Assessment of clinical outcome of twice daily dosing schedule of deferasirox in transfusion dependent paediatric beta thalassemia patients a randomized controlled study

Juny Sebastian, Tirin Babu, George Mathew Panachiyil and Mandyam Dhati Ravi

JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, India

Background: Deferasirox has proven good efficacy and acceptable safety for the management of thalassemia patients. However, some patients are unresponsive or intolerant to once daily administration of deferasirox even at a high dose.

Objectives: To evaluate the efficacy and tolerability of twice daily dosing of deferasirox among transfusion dependent paediatric beta thalassemia patients.

Methods: This prospective randomized single blinded parallel study was conducted at the Pediatric Hematology clinic of a tertiary care hospital over a period of one year. Study enrolled transfusion dependent paediatric beta thalassemia patients prescribed with deferasirox who visited the study site for their regular blood transfusions and follow up. All the eligible subjects were randomized by block randomization method to intervention and control group. Once daily dosing of deferasirox was changed to twice daily dosing with the same total daily dose for the intervention group. Whereas, in the control group, the patients were continued with the once daily deferasirox dosing. Serum ferritin levels were tested at baseline and after 6 months of enrollment to assess the clinical outcome. Statistical analysis was performed using independent t test with the help of SPSS software version 22.

Results: Forty one patients were randomized into intervention (n=20) and control group(n=21). A statistically significant mean decrease in serum ferritin levels was detected in the intervention group (P value 0.011), while, the serum ferritin levels of the control group was significantly increased from baseline (P 0.000). The number of drug related problems was also significantly reduced in intervention group (P 0.031) when compared to control group (P 0.062).

Conclusions: This study concludes that twice daily dosing of deferasirox with the same total daily dose significantly enhances the iron chelation efficacy and tolerability among transfusion dependent paediatric beta thalassemia patients when compared to once daily regimen.

2419 | Endostar continuous versus intermittent intravenous infusion combined with chemotherapy in treating patients with advanced non-small cell lung cancer: A meta-analysis

Lu Xu[1], Bo Wang[2], Limai Mansai[2], Qihuan Li[2], Cheng Jin[2], Siyan Zhan[1,3] and Yi Ning[2]

[1]Peking University, Beijing, China; [2]Meinian Institute of Health, Beijing, China; [3]Research Center of Clinical Epidemiology, Beijing, China

Background: Endostar is a novel recombinant human endostatin approved to treat non-small cell lung cancer (NSCLC) in combination with first-line chemotherapy in China. Both intermittent intravenous (II) infusion and continuous intravenous (CI) infusion of Endostar are widely used currently in clinical practice.

Objectives: To compare the efficacy and safety of CI of Endostar with II.

Methods: We did a systematic review and meta-analysis by searching relevant databases from inception until June 25, 2019. Randomized controlled studies (RCTs), non-randomized controlled trials (NRCTs) and cohort studies compared CI of Endostar with II in combination with chemotherapy in stage III or IV NSCLC patients and reported efficacy or safety outcomes were eligible. Two reviewers independently screened records, extracted data and assessed risk of bias. Pooled risk ratios (RRs) with 95% confidence intervals were calculated using random effects meta-analysis for short-term efficacy and safety outcomes, and hazard ratios (HRs) for survival outcomes. GRADE approach was used to evaluate the quality of evidence in each outcome.

Results: Finally nine studies involving 597 patients were included, including two RCTs, three NRCTs and four cohort studies. For short-term efficacy, moderate quality of evidence showed that there were no significant differences between CI of Endostar and II in objective response rate (ORR; RR 1.34, 95% CI 0.91-1.98, P = 0.14) and disease control rate (DCR; RR 1.11, 95% CI 0.94-1.30, P = 0.21). Low quality of evidence indicated that CI of Endostar significantly improved both overall survival (OS; HR 0.69, 95% CI 0.48-0.99, P = 0.046) and progression-free survival (PFS; HR 0.71, 95% CI 0.55-0.93, P = 0.01) compared with II. As for safety outcomes, high quality evidence found that CI of Endostar significantly substantially reduced the risk of myelosuppression (RR 0.55, 95% CI 0.32-0.96, P = 0.03) and cardiovascular toxicity (RR 0.21, 95% CI 0.06-0.78, P = 0.02) in comparison

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

with II. Low quality of evidence also supported reduced risk of laryngeal hemorrhage in CI compared with II. No significant differences were found for the other adverse events.

Conclusions: In NSCLC patients, compared with II, CI of Endostar had similar short-term efficacy, substantially lower risk of myelosuppression and cardiovascular toxicity. Although insufficient evidence supported the survival benefit of CI compared with II, large RCTs with long follow-up are needed to demonstrate these survival benefits.

2420 | Effects of incretin-based therapies on weight-related indicators among patients with type 2 diabetes: A network meta-analysis

Lu Xu[1], Shuqing Yu[1], Zhirong Yang[2], Sanbao Chai[3], Yuan Zhang[4], Feng Sun[1] and Siyan Zhan[1,5]

[1]Peking University, Beijing, China; [2]University of Cambridge, Cambridge, United Kingdom; [3]Peking University International Hospital, Beijing, China; [4]McMaster University, Hamilton, ON, Canada; [5]Research Center of Clinical Epidemiology, Beijing, China

Background: Nowadays, a new class of anti-diabetic drugs based on incretin including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl-peptidase IV inhibitors (DPP-4Is) have been introduced into clinical practice. Several studies reported that they can help control body weight.

Objectives: To evaluate the effects of incretin-based therapies on body weight, body mass index (BMI) and waist circumference (WC).

Methods: Databases including Medline, Embase, the Cochrane library and clinicaltrials.gov were searched for randomized controlled trials concerning the effects of incretin-based therapies on body weight, BMI and WC from inception to June 23, 2017. Risk of bias tool recommended by Cochrane handbook was used. Subgroup analysis, sensitivity analysis, and GRADE evaluation were performed as well.

Results: A total of 292 RCTs (262 for weight, 191 for BMI and 56 for WC) were included in this study. Nine treatments were involved in this study, including GLP-1 RAs, DPP-4Is, insulin, metformin (Met), sodium-dependent glucose transporters 2 (SGLT-2), sulfonylurea (SU), thiazolidinedione (TZD), α-glycosidase inhibitor (a-Glu) and placebo. A total of 227, 118, 183, 269 and 260 trials were at low risk in terms of random sequence generation, allocation concealment, blinding of outcome assessment, complete outcome data, and selective reporting. As for weight, compared with placebo, DPP-4Is increased weight slightly by 0.31kg (95% CI: 0.05, 0.58) and GLP-1 RAs decreased weight by -1.34kg (95% CI: -1.60, -1.09). As for BMI, GLP-1 RAs decreased BMI by -1.10 (95% CI: -1.42, -0.78) and DPP-4Is had negligible effects on BMI compared with placebo. As for WC, compared with placebo, GLP-1 RAs decreased WC by -1.28cm (95% CI: -1.69, -0.86) and DPP-4Is represented a neutral impact. Subgroup analysis showed that DPP-4Is have no statistically significant effect on reduction of all three indicators compared with placebo, but GLP-1 RAs lowered all three indicators. According to the sensitivity analysis, the main results were robust. According to the ranking results, GLP-1 RAs and DPP-4Is ranked second and sixth respectively in terms of effects on weight loss. Regarding BMI deduction, GLP-1 RAs and DPP-4Is ranked first and fourth respectively. Speaking of WC decrease, GLP-1 RAs and DPP-4Is ranked second and fourth respectively. The evidence quality of ranking of treatments were low, very low and moderate for weight, BMI and WC, respectively.

Conclusions: GLP-1 RAs are better at lowering all three indicators than DPP-4Is. Overall, the effects of GLP-1 RAs on weight, BMI and WC are good.

2432 | Comparative effectiveness of statins and fibrates for primary prevention of cardiovascular disease and mortality: A cohort study

Joseph E. Blais[1], Jiaxi Zhao[1], Stephen Weng[2], Eric Y.F. Yan[1], Vincent K.C. Yan[1], Michael Mok[3], Ian C.K. Wong[1,4] and Esther W. Chan[1]

[1]University of Hong Kong, Pokfulam, Hong Kong; [2]University of Nottingham, Nottingham, United Kingdom; [3]University Hospital Geelong, Geelong, Australia; [4]UCL School of Pharmacy, London, United Kingdom

Background: The role of fibrates and their comparative effectiveness to statins for primary prevention of cardiovascular disease and mortality remains uncertain.

Objectives: To determine whether statins versus fibrates are associated with a reduced risk of mortality and cardiovascular events in individuals without a history of cardiovascular disease.

Methods: Observational, active comparator, new user, cohort study, using the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority. Adults without a history of cardiovascular disease who initiated a statin or a fibrate were enrolled from 2003-2012 and followed-up until the first occurrence of an outcome of interest, death, or 31 December 2017. Outcome measures were all-cause mortality, cardiovascular mortality, and major cardiovascular events, defined as a composite of cardiovascular mortality, myocardial infarction, stroke and transient ischemic attack. Cox-proportional hazards models, with inverse probability of treatment weighting on the estimated propensity score were used to estimate hazard ratios (HR). We performed subgroup analyses stratified by baseline low-density lipoprotein cholesterol concentration, high-density lipoprotein cholesterol concentration, triglyceride level, and diabetes status.

Results: A total of 271 491 participants (mean age 62; 46% men; median follow-up 7.3 years) were treated with a statin (n=213 218) or a fibrate (n=58 273). Compared with fibrates, statins were associated with a reduction in all-cause mortality (HR 0.96, 95% confidence interval (CI) 0.92-1.00), cardiovascular mortality (0.84, 95% CI 0.77-0.92), and major cardiovascular events (0.87, 95% CI 0.83-0.91). With the exception of participants with low high-density lipoprotein cholesterol concentrations (<1.0 mmol/L), statin use was consistently associated with a decreased risk of cardiovascular mortality and major cardiovascular events across subgroups.

Conclusions: Statins were more effective than fibrates at reducing major cardiovascular events and cardiovascular mortality in

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

participants without cardiovascular disease. Our results suggest that statins are preferred as initial treatment in individuals with elevated triglyceride levels or diabetes. However, individuals with low HDL cholesterol concentrations appeared to derive similar benefits from statins and fibrates.

2437 | Sodium-glucose cotransporter-2 inhibitors and the risk of gout - A Danish nationwide symmetry analysis and active comparator new user cohort study

Lars Christian Lund, Kasper Kristensen, Jesper Hallas and Daniel P Henriksen
University of Southern Denmark, Odense, Denmark

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are used as second-line treatment in type 2 diabetes. Recently, they have been associated with lower rates of gout compared to glucagon-like peptide-1 receptor agonists (GLP1-RA).
Objectives: To assess the association of SGLT2i and gout using a case-only study design and a cohort study design. In both designs we used GLP1-RA as an active comparator.
Methods: We used the symmetry analysis (SA) design and an active comparator, new user cohort study design. The SA is easy-to-compute and comprehend, and its greatest strength is the ability to adjust for time-invariant confounders. For the SA, we identified all Danish adults born before 1977 who filled their first prescription of an SGLT2i in the period 2012-2018 and had gout one year prior to or after this date. We repeated the analysis using GLP1-RA. The primary outcome measure was the trend adjusted sequence ratio (SR), which is an estimate of the incidence rate ratio (IRR). The active-comparator adjusted SR for SGLT2i emerged as the ratio of SRs for SGLT2 and GLP1-RA.
In the cohort study, new users of SGLT2i and GLP1-RA were matched in a 1:1 ratio based on a high dimensional propensity score. Individuals were followed according to the intention-to-treat and unadjusted IRRs, incidence rate differences (IRD) and numbers needed to treat for one additional patient to be harmed (NNTH) were obtained.
Results: A total of 208 individuals filled in their first prescription of an SGLT2i and had gout within the time window; 87 patients filled their prescription of SGLT2i prior to gout. The null-effect adjusted SR was 0.70 (95% CI 0.54-0.93). The corresponding SR of the GLP1-RA was 0.96 (0.83-1.07). SRs were effectively unchanged when varying window size (one year and five years). were effectively unchanged when varying window size (one year and five years).
The active comparator-adjusted SR was 0.73, (CI 0.54-0.98)
In the cohort analysis, 28,194 individuals were included contributing 41,576 person years and 264 incident cases of gout. Using GLP1-RA as an active comparator, the IRR was 0.47 (95% CI: 0.36-0.61), corresponding to an IRD of -4.6 cases/1000 person years and a NNTH of 215.
Conclusions: SGLT2 inhibitor use is associated with a decreased risk of gout compared to GLP-1 receptor agonists. This finding is robust towards the choice of study design.

2449 | Comparative effectiveness and safety of systemic treatments for metastatic castration-sensitive prostate cancer: A parametric survival network meta-analysis of randomized controlled trials

Lin Wang[1], Channing Paller[2], Hwanhee Hong[3], Anthony De Felice[2], Otis Brawley[2] and Caleb Alexander[1]
[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [2]*Johns Hopkins School of Medicine, Baltimore, MD;* [3]*Duke University, Baltimore, MD*

Background: Treatment decision-making for metastatic castration-sensitive prostate cancer (mCSPC) is complicated by the unclear comparative effectiveness and widely varying costs of competing strategies.
Objectives: To compare the effectiveness and safety of systemic treatments for mCSPC.
Methods: We searched bibliographic databases, regulatory documents, and trial registries for randomized controlled trials testing active drugs added to androgen deprivation therapy (ADT) for mCSPC. We used Cochrane risk-of-bias tool (version 2) to assess trial quality and Bayesian network meta-analysis (NMA) to estimate the relative effects of competing treatments. In addition to combing published time-invariant hazard ratios (HRs), we reconstructed survival data from Kaplan Meier curves to enable parametric survival NMA that allows time-varying HR.
Results: Seven trials with 7,236 patients were included comparing six treatments. Risk of bias is a concern for trials with open label (N=4), missing data (N=3), or unprespecified analysis (N=3). Ordered from the most to the least effective based on hazard ratios (HRs, 95% credible interval [CI]), treatments significantly improving overall survival (OS) include abiraterone acetate (0.62 [0.54-0.71]), apalutamide (0.67 [0.51-0.88]), and docetaxel (0.80 [0.71-0.89]); treatments significantly improving radiographic progression-free survival (rPFS) include enzalutamide (0.39 [0.30-0.51]), abiraterone (0.45 [0.40-0.51]), apalutamide (0.48 [0.39-0.59]), and docetaxel (0.68 [0.61-0.75]). Allowing time-varying HR produced similar treatment rankings. Serious adverse events (SAE) were substantially increased for docetaxel (odds ratio [OR] 104.17, 95% credible interval [CI] 24.85-1012.32) and slightly increased for abiraterone (OR 1.42, 95% CI 1.11-1.83).
Conclusions: Abiraterone provided the largest OS benefit with slightly increased risk of SAE. Apalutamide offered comparable OS benefit with abiraterone without increasing SAE risk. Although enzalutamide delayed rPFS to the greatest extent, longer follow-up is needed to examine its OS benefit.

2453 | Sodium-glucose cotransporter-2 inhibitors and risk of urolithiasis in patients with type 2 diabetes: A population-based active comparator new user cohort study

Kasper Bruun Kristensen, Daniel Pilsgaard Henriksen, Jesper Hallas and Lars Christian Lund
University of Southern Denmark, Odense, Denmark

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) lower blood glucose levels by increasing urinary glucose secretion. This increases urine osmolality and urinary flow, which reduces the concentration of lithogenic substances and, theoretically, the risk of forming stones in the urinary tract (urolithiasis). Whether this proposed mechanism translates into a clinically relevant reduction of urolithiasis risk is unknown.

Objectives: To examine whether initiation of SGLT2i was associated with a decreased rate of urolithiasis compared to Glucagon-Like-Peptide-1 analogues (GLP-1).

Methods: An active comparator new user cohort study was conducted using the nationwide Danish health registries. We identified all patients without a history of urolithiasis who initiated either SGLT2i or GLP-1 therapy from 2012 and onwards. Patients were followed for 3 years or until death, emigration, urolithiasis, or end of the study period (12-31-2018). High-dimensional propensity scores were calculated and asymmetrical trimming of the propensity score was conducted. Remaining SGLT2i and GLP-1 initiators were matched 1:1 based on the propensity score. We calculated incidence rates and incidence rate ratios with 95% confidence intervals (CI) using an intention-to-treat analysis where patients were considered exposed from cohort entry throughout follow-up.

Results: Results: We included 14,819 new users of SGLT2is and 14,819 new users of GLP-1s after propensity score matching. The median age was 61 years, 48% were female and the mean duration of follow-up was 1.8 years. The incidence rate of urolithiasis was lower in the SGLT-2 cohort (2.6 per 1000 person-years) compared to the GLP-1 cohort (4.5 per 1000 person-years) with an incidence rate ratio of 0.58 (95% CI 0.42 to 0.78) and a rate difference of -1.9 per 1000 person years (95% CI -0.9 to -2.9). Number needed to treat for one year was 533 (95% CI 347 to 1149).

Conclusions: Conclusion: Patients who initiated SGLT-2 inhibitors had an approximately 40% lower risk of developing urolithiasis compared to patients initiating GLP-1 agonists. There are plausible mechanisms through which SGLT2 inhibitors may reduce stone formation in the urinary tract, however, the clinical relevance of this finding is probably limited due to the small absolute risk reduction.

2500 | Comparative effectiveness and safety of SGLT2 inhibitors vs GLP-1 receptor agonists among real-world older adult

Elisabetta Patorno[1], Ajinkya Pawar[1], Lily G. Bessette[1], Dae H. Kim[1], Chintan Dave[2], Robert J. Glynn[1], Medha N. Munshi[3], Sebastian Schneeweiss[1], Deborah J. Wexler[4] and Seoyoung C. Kim[1]

[1]Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [2]Rutgers University, New Brunswick, NJ; [3]Beth Israel Deaconess Medical Center and Joslin Diabetes Center, Harvard Medical School, Boston, MA; [4]Massachusetts General Hospital Diabetes Center and Harvard Medical School, Boston, MA

Background: Both SGLT2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1RA) have shown cardiovascular benefits in randomized controlled trials of patients with type 2 diabetes (T2D) generally younger than 65 years and mostly with cardiovascular disease (CVD). However, the comparative effectiveness and safety of these agents in older adults, who represent most of patients with T2D, remain largely unknown.

Objectives: To evaluate the comparative effectiveness and safety of SGLT2i vs. GLP-1RA in real-world older adults.

Methods: Using U.S. Medicare claims data (4/2013-12/2016), we identified 45,047 pairs of 1:1 propensity score (PS)-matched T2D patients ≥66 years initiating SGLT2i or GLP-1RA. Primary outcomes included major adverse cardiovascular events (MACE, i.e., myocardial infarction, stroke or cardiovascular death) and hospitalization for heart failure (HHF). Individual MACE components and overall mortality were secondary effectiveness outcomes. Safety outcomes were diabetic ketoacidosis (DKA), genital infections (GI), fractures, lower-limb amputations (LLA), acute kidney injury (AKI), and severe urinary tract infections (UTI). Subgroup analyses by baseline CVD were conducted for effectiveness outcomes. We estimated hazard ratios (HR) and rate differences (RD) per 1000 person-years, each with 95% confidence intervals (CI), controlling for 140 baseline covariates.

Results: Compared with PS-matched GLP-1RA initiators, PS-matched SGLT2i initiators had a similar risk of MACE [HR (95% CI)=0.98 (0.87-1.10); RD (95% CI)= -0.38 (-2.48, 1.72)] and a decreased risk of HHF [HR=0.68 (0.57-0.80)]; RD= -3.23 (-4.68, -1.77)], over a mean 8.4-month follow-up. The risk of the individual MACE components and overall mortality was similar between groups. SGLT2i initiators had 0.7 more DKA, 0.9 more LLA, 57.1 more GI, and 5.6 fewer AKI events, vs. GLP-1RA (each $p<0.05$). Among patients with baseline CVD, SGLT2i vs. GLP-1RA initiators had no reduction in MACE but 5.9 fewer HHF, 2.6 fewer cardiovascular deaths and 2.8 fewer overall deaths (each $p<0.05$). Among those without CVD, SGLT2i vs. GLP-1RA initiators had no reduction in MACE, its components, or overall mortality, but had reduced risk of HHF (1.1 fewer events, $p<0.05$), with a benefit of substantially lower magnitude compared to patients with CVD (p for homogeneity<0.001).

Conclusions: Among real-world older adults, SGLT2i had similar risk of MACE, decreased risk of HHF, and increased risk of DKA, LLA, and GI, vs. GLP-1RA. In patients with CVD, SGLT2i had a more favorable risk-benefit profile vs. GLP-1RA, with less benefit in those without CVD.

2554 | Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in extensive disease small cell lung cancer

Christine Cramer[1], Franz Schramel[2], Bas Peters[2], John van Putten[3], Olaf Klungel[4], Harry Groen[5] and Ewoudt van de Garde[4]

[1]Santeon, Utrecht, Netherlands; [2]St. Antonius Hospital, Nieuwegein, Netherlands; [3]Martini Hospital, Groningen, Netherlands; [4]Utrecht University, Utrecht, Netherlands; [5]University Medical Center Groningen, Groningen, Netherlands

Background: The recommendations in treatment standards are conventionally based on clinical trial data, in which patient populations

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

are studied that are not necessarily a reflection of the general population seen in clinical practice. Important patient characteristics predictive for treatment response are often underrepresented in clinical trial populations.

Objectives: The aim of this study is to assess how clinical outcomes in real-world (effectiveness) correspond to the outcomes in clinical trials (efficacy) of systemic treatments for ED SCLC, and to search for patient factors that may explain a gap.

Methods: All patients diagnosed with ED SCLC between 2008 and 2014 in six Dutch large teaching hospitals (Santeon network) were identified and followed-up from date of diagnosis until death or end of data collection. For every patient, an efficacy-effectiveness factor (EE factor) was calculated by dividing individual patients' overall survival (OS) by the pooled median OS assessed from clinical trials with the respective first-line treatment. A multivariable linear regression analysis was applied to study the association between patient and treatment characteristics and the magnitude of the efficacy-effectiveness gap.

Results: From 792 diagnosed patients, 568 (72%) started with first-line treatment. For all studied regimens (carboplatin-etoposide, cisplatin-etoposide, and cyclophosphamide-doxorubicin-etoposide), the median OS in real-world is shorter than the clinical trial reference median OS. Overall, the median EE factor was 0.79 ($p<0.001$ from 1.00). Poor performance status (ECOG≥2) and a higher age at diagnosis (age≥65 years) were independent predictors for a lower EE factor. The EE gap was 43% in patients with both age ≥65 years and ECOG ≥2 (EE factor 0.57). The mean age and the proportion of patients with ECOG≥2 in real-world were different from those in clinical trials (mean age of 66 versus 62 years, and ECOG≥2 25% versus 17%; both $p<0.001$). In patients with ECOG≥2 and aged ≥65 years in real-world, early discontinuation of treatment and no subsequent line of treatment were more prevalent.

Conclusions: Overall survival of patients with ED SCLC treated with systemic therapy in real-world practice is 21% shorter than for patients included in trials. Differences in age at diagnosis and performance status explain this gap.

2566 | The effect of the indicated use of β-blockers on the risk of exacerbations in chronic obstructive pulmonary disease: The Rotterdam study

Leila Karimi[1], Guy Brusselle[2,3,4], Lies Lahousse[3,5], Phebe De Nocker[5], Bruno H. Stricker[3,6] and Katia M.C. Verhamme[1,5]

[1]Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; [3]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands; [4]Department of Respiratory Medicine, Erasmus University Medical Center, Rotterdam, Netherlands; [5]Department of Bioanalysis, Ghent University, Ghent, Belgium; [6]Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands

Background: While several observational studies have reported a reduced risk of exacerbations in COPD patients treated with β-blockers (BB), physicians are reluctant to prescribe BB in patients with cardiovascular disease and concomitant COPD. Recently, the BLOCK COPD randomized clinical trial (RCT) reported an increased risk of COPD exacerbations in metoprolol treated COPD patients without an indication for the use of BB. The current discrepancy between findings of observational studies and the BLOCK COPD RCT might result in further reduction of prescribing BB in COPD patients with a cardiac indication.

Objectives: We investigated whether the association between use of BB and risk of COPD exacerbations differed between patients with and without an indication for treatment with BB.

Methods: Within the Rotterdam Study, a prospective population-based cohort study, we followed COPD subjects until the first COPD exacerbation or end of follow-up. COPD exacerbations were defined as acute episodes of worsening of respiratory symptoms requiring systemic corticosteroids and/or antibiotics or hospitalization. Individuals were considered to have an indication for treatment with BB in case of having hypertension, coronary heart disease, atrial fibrillation, or heart failure at baseline. The association between BB use, as a time-varying variable, and COPD exacerbations was assessed using Cox proportional hazards models adjusted for age, sex, smoking, incident cardiovascular disease (i.e., heart failure, hypertension, atrial fibrillation, and coronary heart disease) during follow-up, respiratory drugs, and nitrates.

Results: In total 1,312 COPD patients with a mean age=69.7±9.2 were included. In patients with an indication for treatment with BB (n=755, mean age=70.4±8.8), current use of cardioselective BB was significantly associated with a reduced risk of COPD exacerbations (Hazard Ratio (HR)=0.69, 95% Confidence Interval (CI): 0.57-0.85). In contrast, in subjects without an indication for treatment with BB (n=557, mean age=68.8±9.7), use of cardioselective BB was not associated with an altered risk of COPD exacerbations (HR=0.94, 95% CI: 0.55-1.62).

Conclusions: In the Rotterdam Study, use of cardioselective BB reduced the risk of exacerbations only in COPD patients with concomitant cardiovascular disease. Our results could explain the discordant findings between the BLOCK COPD RCT (excluding patients with a therapeutic indication for the use of BB) and previous observational studies.

2592 | Effectiveness and safety of vitamin K antagonists in patients with non-valvular atrial fibrillation and renal disease: A cohort study

Antonios Douros[1,2,3], Julien Rousseau[1], Christopher Filliter[4], Brenda Hemmelgarn[5], Samy Suissa[1,2] and Christel Renoux[2,6]

[1]Department of Medicine, McGill University, Montreal, QC, Canada; [2]Department of Epidemiology, McGill University, Montreal, QC, Canada; [3]Charité – Universitätsmedizin Berlin, Berlin, Germany; [4]Lady Davis Institute, Montreal, QC, Canada; [5]University of Alberta, Edmonton, AB, Canada; [6]Department of Neurology, McGill University, Montreal, QC, Canada

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Patients with non-valvular atrial fibrillation (NVAF) and renal impairment are at high risk of both thrombosis and bleeding complicating antithrombotic treatment. However, available clinical evidence on benefits and risks of antithrombotic drugs commonly used in this setting such as vitamin K antagonists (VKAs) or antiplatelet agents is scarce.

Objectives: To assess the effectiveness and safety of VKAs compared to antiplatelet agents in NVAF patients with chronic kidney disease (CKD) or undergoing dialysis.

Methods: We conducted a population-based cohort study using linked administrative healthcare databases from Quebec. We assembled a cohort of patients with incident NVAF from 2000 to 2014 and then constructed three subcohorts based on renal status (dialysis, CKD, no renal disease) at cohort entry. Using a nested case-control approach, we identified all cases with a first-ever diagnosis of ischemic stroke, major bleeding or all-cause mortality (depending on the outcome under study) during follow-up and matched them to 30 controls on age, sex, date of cohort entry, and duration of follow-up in each subcohort. We estimated incidence rate ratios (RRs) and 95% confidence intervals (CIs) of each outcome associated with current use of VKAs compared with current use of antiplatelet agents using conditional logistic regression. Sensitivity analyses accounted for possible exposure and outcome misclassification, restricted to patients with high baseline ischemic or bleeding risk, and explored the potential impact of reverse causality.

Results: Of 231,411 patients with NVAF, 3,613 were undergoing dialysis and 30,608 had CKD. Among dialysis patients, VKAs were associated with a numerically decreased risk of ischemic stroke (RR, 0.79; 95% CI, 0.46 to 1.36), an increased risk of major bleeding (RR, 1.42; 95% CI, 1.04 to 1.93), and a similar risk of all-cause mortality (RR, 0.98; 95% CI, 0.81 to 1.20), compared with antiplatelet agents. Among CKD patients, there was a decreased risk of ischemic stroke (RR, 0.64; 95% CI, 0.56 to 0.73), an increased risk of major bleeding (RR, 1.47; 95% CI, 1.35 to 1.59), and a decreased risk of all-cause mortality (RR, 0.86; 95% CI, 0.81 to 0.90). Sensitivity analyses yielded highly consistent results.

Conclusions: Our results suggest that VKAs could decrease the risk of ischemic stroke in NVAF patients with CKD or undergoing dialysis at the cost of a higher risk of major bleeding. Until data from randomized trials are available, individualized benefit-risk assessment for the antithrombotic management of these vulnerable populations is required.

2638 | Cardiovascular safety of sulfonylureas in type 2 diabetes: Effect modification by obesity?

Karine Suissa[1], Antonios Douros[2], Laurent Azoulay[2], Kristian B. Filion[2] and Sebastian Schneeweiss[1]

[1]*Brigham and Women's Hospital and Harvard Medical School, Boston, MA;* [2]*Jewish General Hospital, Montreal, QC, Canada*

Background: Pharmacokinetic studies suggest that adiposity may modify antidiabetic medication efficacy and safety via altered drug distribution and clearance. While sulfonylureas have been linked to a higher cardiovascular (CV) risk, with inconsistent results, the role of obesity remains unclear.

Objectives: Our main objective was to evaluate the effect of obesity on CV risk with sulfonylureas as first-line therapies for type 2 diabetes in a clinical practice.

Methods: Using the UK's Clinical Practice Research Datalink, we conducted a cohort study of patients initiating antidiabetic treatment. Initiators of sulfonylureas monotherapy were matched with initiators of metformin monotherapy on a high-dimensional propensity score. Patients were censored at the time of discontinuation or addition of another antidiabetic drug. We used Cox proportional hazards models within BMI categories (< 25 kg/m^2 (normal weight; 26%), 25-30 kg/m^2 (overweight; 42%), ≥ 30 kg/m^2 obese; 32%)) to estimate hazard ratios (HR) of major adverse cardiovascular events (MACE), individual components of MACE, and all-cause mortality, comparing sulfonylureas with metformin.

Results: The initial cohort included 94,750 patients with type 2 diabetes initiating sulfonylureas or metformin. We matched 13,999 initiators of sulfonylureas to an equal number of metformin initiators. The overall HR of MACE comparing sulfonylureas with metformin was 1.23 (95% CI: 1.08-1.39); the HR was 1.33 (95% CI: 1.02-1.74) among obese patients, 1.27 (95% CI: 1.04-1.55) for overweight patients, and 0.99 (95% CI: 0.77-1.28) among normal weight patients. Similarly, the risk of all-cause mortality, CV death and ischemic stroke with sulfonylureas was highest in obese individuals, with evidence of interactions for all-cause mortality (p-interaction: <0.0001) and stroke (p-interaction: 0.05).

Conclusions: Sulfonylureas as a first-line monotherapy for type 2 diabetes is associated with a higher risk of MACE compared with metformin. Our data suggest that this effect might be strongest in obese patients, with no increased risk in normal weight patients. To ensure the best response to treatment, BMI level may be considered when choosing metformin over sulfonylureas for first-line treatment.

3749 | Comparative effectiveness of biologics and targeted therapies for psoriatic arthritis

Hanzhe Zhang[1], Jiajun Wen[1], G. Caleb Alexander[1] and Jeffrey R. Curtis[2]

[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [2]*University of Alabama at Birmingham, Birmingham, AL*

Objectives: To quantify comparative effectiveness of interleukin (IL)-12/23 antagonist (ustekinumab), IL-17A antagonists (secukinumab and ixekizumab), PDE4 inhibitor (apremilast), and tumor necrosis factor-alpha (TNF-α) inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab) for psoriatic arthritis (PsA).

Methods: We adapted a de-identified claims-based algorithm validated for inflammatory arthritis treatments to compare treatments among a retrospective cohort of commercially insured and Medicare Advantage beneficiaries with PsA from October 2013 through April 2019 in the OptumLabs® Data Warehouse. Main outcomes include

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(1) Treatment effectiveness, based on: adherence, adding or switching biologic or PDE4, addition of new nonbiologic DMARD, increase in biologic or PDE4 dose or frequency, and glucocorticoid use; (2) percentage of each group fulfilling the effectiveness algorithm. We used Poisson regression with robust variance stratified by prior PsA biologic exposure and adjusted for potential confounders.

Results: Of 2797 individuals with PsA, 334 received IL-12/23, 140 IL-17A's, 634 PDE4 and 1689 TNF-α's. Effectiveness criteria were fulfilled among 63 (18.9%) IL-12/23 recipients, 40 (28.6%) IL-17A recipients, 161 (25.4%) PDE4 recipients, and 545 (32.3%) TNF-α recipients. Among biologic naïve individuals, IL-12/23 was less effective than TNF-α's with fully adjusted relative risk [RR] compared to TNF-α's of 0.61 (95% confidence intervals [CI] 0.43, 0.86). Among biologic experienced individuals, PDE4 recipients were less effective than TNF-α's (adjusted RR 0.66, CI 0.46, 0.94).

Conclusions: TNF-α's appeared more effective than IL-12/23's for biologic naïve individuals, and PDE4's for biologic experienced individuals. These results may help inform treatment choice for individuals with psoriatic arthritis.

3757 | Comparative effectiveness of antipsychotics for risk of attempted or completed suicide among persons with schizophrenia

Heidi Taipale[1], Markku Lähteenvuo[1], Antti Tanskanen[1], Ellenor Mittendorfer-Rutz[2] and Jari Tiihonen[2]

[1]*University of Eastern Finland, Kuopio, Finland;* [2]*Karolinska Institutet, Stockholm, Sweden*

Background: Very little is known about effectiveness of antipsychotics for preventing suicide attempts and completed suicides among patients with schizophrenia.

Objectives: The aim of this study was to investigate comparative effectiveness of antipsychotics for risk of attempted or completed suicide among all patients with schizophrenia in Finland and Sweden.

Methods: Two retrospective nationwide register-based cohort studies were conducted, including all individuals with schizophrenia in Finland (N=61889) and Sweden (N=29823). The main exposure was ten most commonly used antipsychotic monotherapies, and also adjunctive pharmacotherapies including antidepressants, mood stabilizers, benzodiazepines and Z-drugs were investigated. The main outcome measure was attempted or completed suicide which was analyzed with within-individual models by comparing use and non-use periods in the same individual in stratified Cox regression models to minimize selection bias. Sensitivity analyses were conducted by between models, with attempted suicide (hospitalization only) as an outcome, and by censoring the first 30 days from each exposure.

Results: Compared with no use of antipsychotics, clozapine use was the only antipsychotic consistently associated with a decreased risk of suicidal outcomes. Hazard ratios (HRs) and 95% confidence intervals for attempted or completed suicide in clozapine use were 0.64 (0.49-0.84) in the Finnish cohort and 0.66 (0.43-0.99) in the Swedish cohort. No other antipsychotic was associated with a reduced risk of attempted and/or completed suicide. Benzodiazepines and Z-drugs were associated with an increased risk of attempted or completed suicide (HRs 1.29-1.30 for benzodiazepines and 1.33-1.62 for Z-drugs).

Conclusions: Clozapine was the only antipsychotic associated with decreased risk of attempted or completed suicide among patients with schizophrenia, and it should be considered as first-line treatment for high-risk patients.

3764 | Evaluation on therapeutic equivalence of generic and brand-name clopidogrel

Ju-Ling Chen[1,2], Ching-Lan Cheng[1,2] and Yea-Huei Kao Yang[1]

[1]*Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan;* [2]*Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan*

Background: As the increasingly use of generic drugs, concerns about their therapeutic equivalence remain. Because it is unlikely to employ clinical trials to assess therapeutic equivalence between generic and brand-name drugs, claims database and electronic medical records (EMR) are compiled routinely from clinical practice, thus can be used to establish the real-world-evidence in this regard. Meanwhile, persistence and clinical outcomes can be measured with explicit algorithm to assess therapeutic equivalence.

Objectives: To evaluate the therapeutic equivalence of generic and brand clopidogrel.

Methods: A retrospective cohort study with new user design was conducted by using the cohort consisted of two-million peoples, who were randomly sampled from Taiwan National Health Insurance Database (NHID). Patients who were newly hospitalized with an acute coronary syndrome (ACS) from 2008 to 2015, survived at least 7 days after ACS and newly prescribed clopidogrel were eligible for inclusion. Patients were grouped to generic or brand clopidogrel users. The clinical outcome was a composite of recurrent ACS hospitalization, emergency room revascularization and death at 1 year. The non-persistence was defined as an event of treatment change, which included discontinuation, switching study drug to another anti-platelet medication. We followed up patients who incurred treatment change, or up to 9 months, whichever came first. We also conducted sensitivity analysis based on receiving percutaneous coronary intervention (PCI) or not to eliminate confounding by ACS severity. Propensity score (PS) was performed for matching and Cox proportional hazards regression was used to calculate hazard ratios and confidence interval.

Results: There were 7,499 brand and 438 generic users met study criteria. The mean age was 64 years old and hypertension was the most frequent comorbidity among two groups. Compared to brand users, the adjusted hazard ratio for clinical outcome and persistence in generic users were 1.13 [95% CI: 0.9-1.43] and 0.91 [95% CI: 0.8-1.4], respectively. The result from sensitivity analysis was consistent with primary result, implying no significant difference of clinical outcome and treatment change between generic and brand users (HR 1.10 [0.76-1.58], HR 0.98 [0.80-1.20], respectively.)

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: The findings indicate that generic and brand clopidogrel are therapeutic equivalent.

3767 | Early real-world experience with CD19-directed chimeric antigen receptor T-cell therapy (CAR T) among patients with diffuse large B-cell lymphoma (DLBCL)

Jessica J. Jalbert[1], Jon E. Arnason[2], Wenzhen Ge[1], Chieh-I Chen[1], Srikanth Ambati[1], Ning Wu[1] and Aafia Chaudhry[1]

[1]*Regeneron Pharmaceuticals, Inc., Tarrytown, NY;* [2]*Beth Israel Deaconess Medical Center, Boston, MA*

Background: CAR T, approved in the US as of October 2017, impacted the treatment landscape for patients with relapsed or refractory (R/R) DLBCL after ≥2 lines of therapy, but there is little known about real-world (RW) treatment patterns in patients who fail or do not respond to CAR T. No treatments of proven benefits are available after CAR T treatment failure.

Objectives: The objective of this study was to describe RW treatment patterns after CAR T.

Methods: From MarketScan Commercial/Medicare claims databases (2017–2018), we identified adult DLBCL patients who received approved CD19-directed CAR T (treatment date = index date). Eligible patients had ≥6 months continuous health plan enrollment prior to index date (i.e. baseline period) and were followed until plan disenrollment or December 31, 2018. Patients with a diagnosis of acute lymphoblastic leukemia over the baseline period were excluded. We identified the first and second treatments after CAR T with systemic chemotherapy, targeted therapy, immunotherapy, hematopoietic stem cell transplant (SCT), radiation therapy (RT), or a second round of CAR T therapy. Kaplan-Meier estimators were used to estimate risk of subsequent treatment and time to next treatment.

Results: We identified 56 patients with DLBCL treated with CAR T (mean age [SD]: 57.3 years [9.9]; 23.2% female; 80.4% commercially insured). All patients received CAR T in the inpatient setting, median (Q1–Q3) length of stay was 15 days (12–19). Out of 56 patients, 19 initiated a treatment following CAR T; risk of subsequent treatment at 6 months post index was 45.6% (95% CI: 25.4–60.4%) and median days from CAR T to subsequent treatment was 233 days (95% CI: 139–NA). Out of 19 patients, 3 initiated a second treatment following CAR T, within 8–69 days of the first treatment. Over a median (Q1–Q3) follow-up of 139.5 days (90.5–194) following CAR T, of the 19 patients treated after CAR T, 57.9% were treated with immunotherapy, 36.8% with RT, 26.3% with targeted therapy, 21.1% with SCT, 15.8% with chemotherapy, and 0% with a second round of CAR T therapy.

Conclusions: There are few multicenter studies reporting RW treatment patterns in patients who received CAR T. In this study, risk of subsequent treatment at 6 months following CAR T in a RW setting was almost 50%. Although limited by duration of follow-up, our results suggest that additional, effective salvage treatment strategies are needed for patients who do not respond to CAR T or do not achieve a durable response to CAR T.

3773 | Comparing stroke prevention therapy of direct oral anticoagulants and vitamin-K-antagonists in patients with atrial fibrillation: A nationwide retrospective observational study

Lena M. Paschke[1], Maike Schulz[1], Kerstin Klimke[1], Attila Altiner[2] and Dominik von Stillfried[1]

[1]*Central Research Institute of Ambulatory Health Care in Germany, Berlin, Germany;* [2]*University of Rostock, Berlin, Germany*

Background: Direct oral anticoagulants (DOACs) are not only increasingly being used for the initial stroke prevention therapy but progressively also substitute VKA treatment in patients with non-valvular atrial fibrillation (AF). DOACs have been compared regarding therapeutic efficacy and adverse outcomes to warfarin in several pivotal studies and showed non-inferiority in terms of stroke prevention and superiority in terms of bleeding complications. However, comprehensive comparative studies are lacking for phenprocoumon, a Vitamin-K-Antagonist (VKA) prescribed frequently outside the US and the UK and accounting for 99% of all VKA prescriptions in Germany. Patients treated with phenprocoumon seem to meet more often international normalized ratio values in the therapeutic range, which may have implications concerning their efficacy and safety. This study aims at comparing the risk of stroke and bleeding in phenprocoumon and DOAC-treated patients with AF in an adequately powered observational study population.

Objectives: This study aims at comparing the risk of stroke and bleeding in phenprocoumon and DOAC-treated patients with AF in an adequately powered observational study population.

Methods: Retrospective analysis of stroke and bleeding incidence of 834.000 patients (1.27 million patient-years) treated with DOAC or VKA for stroke prevention in German ambulatory care between 2010 and 2017.

Results: Patients treated with DOAC had an overall higher risk for stroke (HR: 1.32; 95%CI: 1.29-1.35) and a lower risk for bleeding (0.89; 0.88-0.90) compared to VKA. When analyzed separately the risk for stroke was higher for dabigatran (1.93; 1.82-2.03), apixaban (1.52; 1.46-1.58) and rivaroxaban (1.13; 1.10-1.17) but not for edoxaban (0.88; 0.74-1.05). The risk for bleeding was lower for dabigatran (0.85; 0.83-0.88), apixaban (0.71; 0.70-0.73) and edoxaban (0.29; 0.17-0.51) but not for rivaroxaban (1.03; 1.01-1.04).

Conclusions: This study provides a comprehensive view of the stroke and bleeding risks associated with VKA and DOAC use in Germany. Phenprocoumon may be preferable to DOAC treatment for the prevention of strokes in AF in a real world population cared for in ambulatory care.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3790 | Survival outcome in patients with metastatic castration-resistant prostate cancer according to first-line treatment

Nicolas H. Thurin[1], Magali Rouyer[1], Jérémy Jové[1], Marine Gross-Goupil[2], Thibaud Haaser[2], Xavier Rebillard[3], Michel Soulié[4], Gérard de Pouvourville[5], Marie Pierrès[6], Camille Capone[6], Stéphanie Lamarque[1], Emmanuelle Bignon[1], Cécile Droz-Perroteau[1], Nicholas Moore[1,2] and Patrick Blin[1]

[1]*Bordeaux PharmacoEpi, INSERM CIC 1401, Université de Bordeaux, Bordeaux, France;* [2]*CHU de Bordeaux, Bordeaux, France;* [3]*Clinique Beau Soleil, Montpellier, France;* [4]*CHU de Toulouse, Toulouse, France;* [5]*ESSEC, Cergy-Pontoise, France;* [6]*Janssen, Issy les Moulineaux, France*

Background: Therapeutic strategy in metastatic castration-resistant prostate cancer (mCRPC) has evolved significantly with the introduction of abiraterone acetate in association with prednisone/prednisolone in first-line treatment in December 2012.

Objectives: To compare the effectiveness of abiraterone acetate and docetaxel as first-line treatments for mCRPC, in real-life setting.

Methods: Patients with mCRPC were identified in the main scheme of the National Healthcare System database (SNDS), which covers about 86% of the French population, and capturing all reimbursed healthcare expenditures and hospital discharge summaries. Those initiating docetaxel or abiraterone acetate in 1st line in 2014 were included and 1:1 matched on the previous prostate cancer stage before mCRPC status, the delay from the date of initial diagnosis and a high-dimensional propensity score. The 36-month overall survival and the 36-month discontinuation-free survival (i.e. survival time until treatment switch or death) were compared using Cox proportional hazards risk model.

Results: In 2014, out of the 12 951 patients with prevalent mCRPC, 1 214 initiated docetaxel in 1st line and 2 444 initiated abiraterone. A total of 716 patients per group were matched with good comparability (C-statistic = 0.6). The median duration of docetaxel - defined as the time between the first and the last infusion - was 7.3 months with a median of 6 infusions. The median duration of abiraterone acetate - corresponding to the period covered by the dispensed drug - was 9.1 months. Near 70% of the docetaxel and 62% of the abiraterone acetate patients received a 2nd line of treatment. The 36-month overall survival probability were 27.9% (95% CI 25.0 - 31.2) for docetaxel and 34.6% (95% CI 31.5 - 38.1) for abiraterone acetate. The corresponding median survivals were respectively of 18.5 months (95% CI 17.1 - 20.7) and 25.5 months (95% CI 23.0 - 27.3). The 36-month discontinuation-free survival probability were 2.9% (95% CI 2.1 - 4.1) for docetaxel and 13.8% (95% CI 11.7 - 16.4) for abiraterone acetate. The corresponding median survivals were respectively of 7.4 months (95% CI 7.0 - 8.0) and 10.8 months (95% CI 10.1 - 11.7).

Conclusions: First-line treatment with abiraterone acetate in mCRPC patients results in a better 36-month overall survival and discontinuation-free survival compared to docetaxel in real-life setting.

3794 | Implementation of cluster randomisation of prescribing policy for studying comparative effectiveness: Experience from the pilot of the evidence study

Robert Flynn, Angela Flynn, Amy Rogers, Lewis McConnachie, Thomas MacDonald, Isla Mackenzie and Alexander Doney

University of Dundee, Dundee, United Kingdom

Background: The randomised policy design has potential to assess comparative effectiveness where data from head-to-head trials is lacking. In 2011, the UK NICE hypertension guideline included a recommendation that thiazide-like diuretics (indapamide - IND) be used in preference to thiazide diuretics (bendroflumethiazide - BND) for hypertension. There is sparse evidence backing this recommendation and BND remains widely used the UK. The EVIDENCE study randomises GP practices to use either IND or BND as their first line diuretic for hypertension. Medication is switched where necessary.

Objectives: To describe the procedure and assess the effectiveness of the drug switch at practices participating in EVIDENCE.

Methods: For each practice a list was created of patients on prescriptions for either IND or BND. Patients were excluded if they were <18 years, had received both drugs in the past or received them for reason other than hypertension. Clinicians from each practice reviewed the list to remove any not appropriate for switching and the practice formulary was then randomised to either IND or BND. Patients were sent a letter explaining that their practice was taking part in the study and stating if their diuretic would change. Drug changes were implemented by a clinical pharmacist within the practice. The effectiveness of the drug switch was assessed by measuring the amount of IND prescribed as a proportion of total IND and BND prescribing within each participating practice on a monthly basis using open-access practice-level prescribing data. Time series analysis was used to assess the impact of the drug switch for 36 monthly time point prior to and 10 months after the implementation date. Research Ethics Committee approval was obtained prior to starting the study.

Results: Of 29 pilot practices in 5 health board regions of Scotland, 14 were randomised to IND and 15 to BND. Of 5,985 patients sent letters 40.7% had their medication changed. Amongst practices randomised to BND, the proportion of IND prescribing prior to the switch was 20.0% (95% 16.3 to 24.3) and this dropped to 9.6% (7.6 to 12.0) then falling at -0.15% (-0.12 to -0.19) per month. For practices randomised to IND the proportion of prescriptions for IND was 16.4% (13.3 to 20.0) and increased to 81.7% (77.6 to 85.1) then decreasing slowly at -0.14% (-0.15 to -0.12) per month.

Conclusions: The implementation of the drug switch was effective and sustained in all GP practices participating in the study. Future work will focus on patient level analysis of data linking prescribing to end points and the roll out of a fully powered study.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3797 | Effectiveness and safety of direct oral anticoagulants in patients with cancer associated venous thromboembolism: A population based cohort study

Antonios Douros[1,2,3], Christopher Filliter[4], Laurent Azoulay[2,5] and Vicky Tagalakis[1]

[1]*Department of Medicine, McGill University, Montreal, QC, Canada;* [2]*Department of Epidemiology, McGill University, Montreal, QC, Canada;* [3]*Charité – Universitätsmedizin Berlin, Berlin, Germany;* [4]*Lady Davis Institute, Montreal, QC, Canada;* [5]*Department of Oncology, McGill University, Montreal, QC, Canada*

Background: Patients with cancer associated venous thromboembolism (VTE) are at high risk of recurrent VTE and bleeding. Recent randomized controlled trials suggested that direct oral anticoagulants (DOACs) may be more effective, but with an increased risk of major bleeding compared to standard of care low-molecular-weight heparin (LMWH). To date, real-world evidence on the effects of DOACs in patients with cancer associated VTE is scarce.

Objectives: To assess the effectiveness and safety of DOACs compared to LMWH in patients with cancer associated VTE.

Methods: We conducted a population based cohort study using linked administrative health care databases from Québec. We included patients with incident VTE from 2012 to 2015 and a cancer diagnosis in the year before the VTE. Date of cohort entry was defined as the date of the first dispensed prescription for an anticoagulant in the 30 days after the VTE. Using an active comparator new-user design with an as-treated exposure definition, we compared the use of DOACs with the use of LMWH. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of recurrent VTE (defined as outpatient or inpatient diagnosis of VTE complemented by a diagnostic procedure) and major bleeding (defined as hospitalization with bleeding or death due to bleeding). In secondary analyses we stratified by age (≥70 years versus <70 years) and sex.

Results: Our cohort comprised 4,911 patients with cancer associated VTE initiating treatment with anticoagulants. Of those, 562 patients initiated DOACs and 3090 initiated LMWH (the remaining 1259 initiated vitamin K antagonists). Compared with the use of LMWH, the use of DOACs was associated with a decreased risk of recurrent VTE (HR, 0.52; 95% CI, 0.37 to 0.72) and a similar risk of major bleeding (HR, 0.74; 95% CI, 0.49 to 1.11). Age did not modify the association for recurrent VTE (≥70 years: HR, 0.55; 95% CI, 0.36 to 0.83 versus <70 years: HR, 0.45; 95% CI, 0.26 to 0.78) or major bleeding (≥70 years: HR, 0.65; 95% CI, 0.39 to 1.07 versus <70 years: HR, 0.92; 95% CI, 0.44 to 1.89). Sex also did not modify the association for recurrent VTE (male: HR, 0.49; 95% CI, 0.31 to 0.79 versus female: HR, 0.56; 95% CI, 0.36 to 0.90) or major bleeding (male: HR, 0.70; 95% CI, 0.38 to 1.28 versus female: HR, 0.78; 95% CI, to 0.45 to 1.37).

Conclusions: DOACs were associated with a decreased risk of recurrent VTE and a similar risk of major bleeding compared to standard of care LMWH in patients with cancer associated VTE in routine clinical practice.

3798 | Risk of cardiovascular outcomes following addition of SGLT2 inhibitors versus sulfonylureas to baseline GLP-1RA therapy

Chintan Dave, Seoyoung Kim, Allison Goldfine, Robert Glynn, Angela Tong and Elisabetta Patorno

Brigham and Womens Hospital, Boston, MA

Background: Several glucagon-like peptide agonists (GLP-1RA) and sodium-glucose co-transporter 2 inhibitors (SGLT2i) have demonstrated cardiovascular benefit in type 2 diabetes in large randomized controlled trials. However, few trial participants were on both agents and it remains unknown whether the addition of SGLT2i to GLP-1RA therapy has further cardiovascular benefits, compared to the addition of agents without demonstrated reduction of cardiovascular events.

Objectives: To assess whether SGLT2i reduced cardiovascular events in patients with baseline GLP-1RA therapy.

Methods: Patients adding either SGLT2i or sulfonylureas to baseline GLP-1RA were identified within 3 US claims datasets (2013-2018) and were 1:1 propensity score matched (PSM) adjusting for >95 baseline covariates. The primary outcomes were 1) composite cardiovascular endpoint (CCE; comprised of myocardial infarction, stroke, and all-cause mortality) and 2) heart failure hospitalization. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated in each dataset and pooled via fixed-effects meta-analysis.

Results: Among 12,584 propensity-score matched pairs (mean [SD] age 58.3 [10.9] year; male (48.2%)) across the 3 datasets, there were 102 CCE events [incidence rate per 1,000 person-years (IR) = 9.4] among SGLT2i initiators compared to 124 events [IR = 12.5] among sulfonylurea initiators corresponding to an adjusted pooled HR of 0.76 (95% CI: 0.59, 0.99); this decrease in CCE was driven by numerical decreases in the risk of MI (HR 0.71, 95% CI: 0.51, 1.001) and all-cause mortality (HR 0.60, 95% CI: 0.32, 1.14) but not stroke (HR 1.05, 95% CI: 0.62, 1.79). For the outcome of heart failure hospitalization, there were 141 events [IR = 13.0] among SGLT2i initiators versus 206 [IR = 20.8] events among sulfonylurea initiators corresponding to an adjusted pooled HR of 0.65 (95% CI: 0.52, 0.80).

Conclusions: In this large real-world cohort of diabetic patients on GLP-1RA, the addition of SGLT2i to GLP-1RA therapy conferred greater cardiovascular benefit compared to adding sulfonylureas. The magnitude of the cardiovascular risk reduction was comparable to the benefit seen in cardiovascular outcome trials of SGLT2i versus placebo where baseline GLP-1RA use was minimal.

3810 | Transporting treatment effects from clinical trials to clinical practice using a hybrid study approach: The case of adjuvant FOLFOX versus 5FU for colon cancer treatment

Jennifer L. Lund, Michael A. Webster-Clark, Alexander P. Keil, Daniel Westreich, Til Sturmer and Hanna K Sanoff

University of North Carolina at Chapel Hill, Chapel Hill, NC

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Treatment effects may differ between clinical trials and clinical practice, in part due to heterogeneous treatment effects combined with under-representation of certain patient subgroups in trials.
Objectives: We used a hybrid study approach combining clinical trial and real-world data to compare the effectiveness of adjuvant FOLFOX versus 5FU in reducing all-cause mortality among stage II-III colon cancer patients in community oncology practice.
Methods: We used the phase III Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) combined with electronic health record data for patients who met trial eligibility criteria within US Oncology, a nationwide community oncology practice network, from 1/1/2008-5/31/2019. In the combined data, we used logistic regression to estimate the probability of trial enrollment as a function of age, sex, cancer substage, body mass index (BMI), and performance status. We estimated inverse odds of sampling weights and weighted MOSAIC participants to reflect four US Oncology populations of interest: 1) patients meeting trial eligibility criteria, 2) stage III patients (the approved indication), 3) stage III patients initiating FOLFOX, and 4) untreated patients (those least likely to benefit). Within the weighted trial populations, we estimated mortality hazard ratios (HRs) and bootstrapped 95% confidence intervals (CIs) comparing FOLFOX with 5FU.
Results: There were 2246 MOSAIC participants and 9335 US Oncology patients. In general, MOSAIC participants were younger, had more stage II cancer, lower BMI, and worse performance status compared with US Oncology patients. By six years, approximately 22% of MOSAIC participants died. The crude mortality HR estimate in MOSAIC comparing FOLFOX versus 5FU was 0.84 (0.71, 1.00). After weighting trial participants to reflect the US Oncology populations, HRs were attenuated to: 1.05 (080, 1.33) for all eligible US Oncology patients, 0.97 (0.73, 1.31) in the stage III subgroup, 0.93 (0.71, 1.25) in the stage III FOLFOX-treated subgroup, and 1.31 (0.84, 1.95) in the untreated subgroup.
Conclusions: Compared with trial results, we found that effectiveness of FOLFOX versus 5FU was attenuated in community oncology practice. The elevated HR estimates in the untreated population support oncologists' and patients' decisions to forgo adjuvant chemotherapy in those least likely to benefit.

3814 | Use of sodium-glucose co-transporter-2 inhibitors, changes in body mass index and risk of fracture: The clinical practice research datalink gold

Frank de Vries[1,2], Annemariek Driessen[1], Andrea Burden[1,3], Martijn Brouwers[1], Peter Vestergaard[4], Joop van den Bergh[1,5], Richard Eastell[6] and Judith van Dalem[1]
[1]*Maastricht University Medical Centre, Maastricht, Netherlands;* [2]*Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands;* [4]*ETH, Zurich, Switzerland;* [4]*Aalborg University Hospital and Aalborg University, Aalborg, Denmark;* [5]*VieCuri Medical Centre, Venlo, Netherlands;* [6]*Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom*

Background: Type 2 diabetes mellitus is a metabolic disorder which has adverse effects on bone metabolism. Sodium-glucose co-transporter 2 inhibitors (SGLT2-Is) have been associated with reduced bone mineral density, increase in fracture risk and weight loss. Studies presented conflicting evidence regarding the association of SGLT2-Is on major osteoporotic fracture risk.
Objectives: The aim of this study was to investigate the association between SGLT2-Is, changes in Body Mass Index (BMI) and the risk of major osteoporotic fractures
Methods: Data from the Clinical Practice Research Datalink (CPRD) GOLD database (2013 - 2018) was used to conduct a retrospective population-based cohort study. The study population (n = 34,960) consisted of patients aged 18+ who had a first ever prescription of sulphonylureas (SU), dipeptidyl peptidase 4 inhibitors (DPP4-Is) or SGLT2-Is. Time-varying Cox proportional hazards models estimated the hazard ratio (HR) of major osteoporotic fracture risk of current SLGT-2I users versus current SU users. Analyses were stratified according to changes in BMI in current users of SGLT2-Is. Time-varying statistical adjustments were made for age, sex, life-style, comorbidities and drug use.
Results: Current use of SGLT2-Is was not associated with increased major osteoporotic fracture risk adjusted [adj.] HR: 0.89 (95% Confidence Interval [CI]; 0.61 - 1.31) when compared with SU users. Among current SGLT2-I users, loss of BMI ≥ than 1 kg/m^2 vs loss of BMI < than 0.5 kg/m^2 was not associated with major osteoporotic fracture, adj HR 0.81; 95% CI 0.63 - 1.04), whereas BMI gain ≥ than 1 kg/m^2 was associated with a 30% reduced risk of fracture, adj. HR 0.70; 95% CI (0.51 - 0.97).
Conclusions: Current use of SGLT2-Is was not associated with osteoporotic fracture risk when compared to current use of SUs. Among current SGLT2-I users, loss of BMI was not associated with risk of major osteoporotic fracture.

3828 | Impact of time in therapeutic range (TTR) on clinical outcomes in patients initiating treatment with warfarin

Kebede Beyene, Patricia Näslund, Amy Hai Yan Chan and Jeff Harrison
School of Pharmacy, The University of Auckland, Auckland, New Zealand

Background: The quality of warfarin therapy is markedly influenced by its time in therapeutic range(TTR), which is the duration of time in which the patient's International Normalized Ratio(INR) values are within a therapeutic range (INR: 2.0-3.0). Data on the quality of anticoagulation control and its effects on clinical outcomes in New Zealand(NZ) are lacking.
Objectives: To evaluate the quality of anticoagulation control and the association between TTR and clinical outcomes and all-cause mortality amongst incident warfarin users.
Methods: Using national healthcare databases, we performed a retrospective cohort study involving residents of Auckland (aged ≥18 year)

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

who newly started warfarin between January 2006 and December 2011. Only patients with more than 5 INR tests were included. TTR was calculated using the Rosendaal method. Patient were divided into 2 cohorts: those with good(TTR >60%) and poor(TTR ≤60%) anticoagulation control. Outcome measures were thromboembolic and bleeding events, and all-cause death. Patients were followed from warfarin initiation to the first occurrence of the target outcome, treatment discontinuation, death or end of follow-up(5 years). Time-varying Cox regression was used to evaluate whether TTR is independently associated with outcome measures, adjusting for sex, age, ethnicity, and deprivation index.

Results: A total of 4280 patients were included in the analysis. Mean age was 65±12 years, and 60.3% of the patients were male. The mean follow-up time was 2.76±1.7 years. Mean TTR was 55.3±17%, and 58.1% of patients had poor anticoagulation control(TTR ≤60%). A total of 435 thromboembolic and 758 bleeding events, and 657 deaths occurred during follow-up. Any thromboembolic(2.5 vs. 4.7) and bleeding events(4.5 vs 8.1), and all-cause death(3.4 vs. 7.5) incidence rates per 100-person years were lower in patients with good anticoagulation control compared with patients with poor control. Patients with good anticoagulation control had significantly lower risk for any thromboembolic events(HR: 0.546; 95% CI: 0.443-0.673), myocardial infraction(HR: 0.489; 95% CI: 0.355-0.673), any bleeding events(HR: 0.598; 95% CI: 0.509-0.703), major bleeding(HR: 0.636; 95% CI: 0.408-0.991), and all-cause mortality(HR: 0.433; 95% CI: 0.362-0.517) compared to patients with poor anticoagulation control.

Conclusions: The overall quality of anticoagulation control among Auckland residents was poor. Patients with poor anticoagulation control (TTR ≤60%) were at higher risk of adverse outcomes. These findings suggest a room for improvement in anticoagulation monitoring.

3892 | Effectiveness of dimethylfumarate on multiple sclerosis, a French cohort within SNDS nationwide claims database

Pauline Bosco-Levy[1,2], Patrick Blin[1], Séverine Lignot-Maleyran[1], Régis Lassalle[1], Abdelilah Abouelfath[1], Pauline Diez-Andreu[1], Marc Debouverie[3], Bruno Brochet[4], Francis Guillemin[5] and Nicholas Moore[1,6]

[1]Bordeaux PharmacoEpi, Univ. Bordeaux-INSERM CIC1401, Bordeaux, France; [2]Bordeaux Population Health Research Centre, INSERM UMR 1219, Bordeaux, France; [3]Department of Neurology, Nancy University-Hospital, EA 4360 APEMAC, Vandoeuvre-Lès Nancy, France; [4]CRC SEP, Service de Neurologie, CHU de Bordeaux, Bordeaux, France; [5]CHRU de Nancy, INSERM CIC 1433 Epidémiologie Clinique, Nancy, Université de Lorraine, EA 4360 APEMAC, Vandoeuvre-Lès Nancy, France; [6]CHU de Bordeaux, Bordeaux, France

Background: In the context of dimethylfumarate (Tecfidera®) registration renewal in 2020 in France, a cohort study was conducted using SNDS nationwide claims database.

Objectives: To assess the effectiveness of dimethylfumarate in the multiple sclerosis (MS) compared to other oral drugs (teriflunomide and fingolimod) and injectable immunomodulatory drugs (IID), in real life setting.

Methods: This cohort study included all patients identified in the SNDS with a first reimbursed dispensing of a MS drug (naive patients) from the 2015/07/01 to the 2017/12/31, with at least 4.5-year database history and followed until 31th December 2017. MS relapses were identified in the index drug exposure period using a validated algorithm (positive and negative predictive value: 95.2% and 100 %, respectively). We conducted multiple treatment-by-treatment comparisons of the mean annual number of relapses after 1:1 patients matching using a high-dimensional propensity scores (hdPS). A negative binomial regression model was used to estimate the relative risk (RR ± [95% CI]).

Results: During 1,5 years, 5812 naive patients were included: 1930 initiating teriflunomide (33.2%), 1800 an IID (31.0%), 1775 dimethylfumarate (30.6%) and 307 fingolimod (5.3%). The mean annual number of relapses was 0.14 in the 940 dimethylfumarate patients *versus* 0.17 in the 940 teriflunomide matched patients (RR = 0.79 [0.63 - 1.00], p=0.0457) and 0,14 in 1019 dimethylfumarate patients *versus* 0,18 in 1019 IID matched patients (RR =0,71 [0,56-0,90], p=0.0051). Too few fingolimod patients were identified to perform a treatment-by-treatment comparison.

Conclusions: This study showed a significantly lower risk of relapses with dimethylfumarate than teriflunomide and IID in real conditions of use among patients sharing the same characteristics.

3893 | Problematic alcohol use influences response to systemic therapies for psoriasis: Findings from a prospective multicentre cohort study

Ireny Y.K. Iskandar[1], Mark Lunt[2], Rachael J. Thorneloe[3], Lis Cordingley[4], Christopher E.M. Griffiths[5] and Darren M. Ashcroft[1]

[1]Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, University of Manchester, Manchester, United Kingdom; [2]Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom; [3]Department of Psychology, Sheffield Hallam University, Sheffield, United Kingdom; [4]Division of Musculoskeletal and Dermatological Sciences, University of Manchester, Manchester, United Kingdom; [5]NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom

Background: Psoriasis is a chronic inflammatory skin condition associated with considerable psychosocial difficulties; these may contribute to alcohol misuse. Conventional systemic and biologic therapies are used in the management of moderate to severe psoriasis; however, treatment effectiveness is lower in real-world clinical practice than in clinical trials. Factors that might influence response to treatment are varied, and generally, are poorly understood. The impact of alcohol misuse on response to treatment in psoriasis have not been investigated.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To investigate whether alcohol misuse influence response to treatment of moderate to severe psoriasis.

Methods: Prospective cohort study of patients with psoriasis aged at least 18 years old, attending 35 dermatology clinics across England and enrolled in the pharmacovigilance register the British Association of Dermatologists Biologics and Immunomodulators Register, and the iMAP (Investigating Medication Adherence in Psoriasis) study which collected biomedical and psychological data. Response to treatment was assessed using change in Psoriasis Area and Severity Index (PASI). The CAGE (cut-annoyed-guilty-eye) questionnaire was used to screen for alcohol misuse. A multivariable factional polynomial linear regression model, adjusting for other factors that could influence treatment response (demographic, clinical, and medication non-adherence), was implemented to analyse the data using STATAv15.0.

Results: The cohort included 266 patients (biologic treatment, n = 134; conventional systemic treatment, n = 132). In total, 16.6% of the study cohort were classified as non-adherent, with a higher proportion of patients using conventional systemic therapies classified as such (27.6%) compared to those using biologic therapies (5.9%). For the entire cohort, the median (interquartile range) PASI improved from 13 [10-18.3] at baseline to 3 [1-7.5] during follow-up. Obesity (regression co-efficient: 1.84; 95% CIs: 0.48-3.20), a higher CAGE score (1.40; 0.04-2.77), and receiving a conventional systemic rather than a biologic therapy (4.39; 2.84-5.95) were significantly associated with poor response to treatment; whereas a higher baseline PASI (-0.83; -0.92,-0.74) was associated with better response to treatment.

Conclusions: A poorer response to treatment associated with alcohol misuse calls for interventions to prevent, detect and manage alcohol consumption and misuse among people with psoriasis. These would minimise adverse health consequences and improve treatment response.

3956 | Comparative treatment effectiveness of oral fingolimod and injectable disease modifying agents in multiple sclerosis

Jagadeswara Rao Earla[1], George Joseph Hutton[2], J. Douglas Thornton[1], Hua Chen[1], Michael L. Johnson[1] and Rajender R. Aparasu[1]
[1]*University of Houston College of Pharmacy, Houston, TX;* [2]*Baylor College of Medicine, Houston, TX*

Background: Fingolimod was the first approved oral Disease Modifying Agent (DMA) to reduce relapses among individuals with Multiple Sclerosis (MS). Previous observational studies assessed the treatment effectiveness of DMAs only through relapse-based outcome measures and did not consider treatment switch as a measure of treatment effectiveness.

Objectives: To compare the treatment effectiveness of oral fingolimod and injectable DMAs using the composite treatment outcome measure - relapse/treatment switch - among patients with MS.

Methods: This retrospective longitudinal study included adults (≥18 years) with MS diagnosis (ICD-9-CM: 340) and a DMA prescription from the IBM MarketScan Commercial Claims and Encounters Database from 2010-2012. Patients were classified as oral fingolimod or injectable users based on their first DMA prescription (index DMA prescription). The relapse was defined as an inpatient hospitalization or an outpatient visit with a corticosteroid prescription within 30 days. The treatment switch was defined as switching of the index DMA to another DMA. The composite treatment outcome measure (relapse/treatment switch) was assessed during the one year followup period after the treatment initiation. Cox Proportional Hazards (PH) regression model adjusted for stabilized Inverse Probability Treatment Weights (IPTW) was used to evaluate composite treatment outcome measure -time to first relapse/treatment switch - between oral fingolimod and injectable DMA users. Patients who died or lost from follow-up due to the lack of insurance coverage were censored.

Results: The incident study cohort consisted of 1,997 MS patients who were initiated with oral (15.57%) or injectable (84.43%) DMAs during 2010-2011. The proportion of patients who had a composite outcome (relapse/treatment switch) in oral fingolimod and injectable DMA users was found to be 16.72% and 27.16%, respectively. The Cox PH regression model with stabilized IPTW revealed that fingolimod users were at lesser risk (Adjusted Hazards Ratio [AHR]-0.66, 95% CI: 0.50-0.86) of experiencing the composite outcome (relapse/treatment switch) than injectable DMA users.

Conclusions: Oral fingolimod was associated with a better composite treatment outcome compared to injectable DMAs. More comparative effectiveness research is needed based on the composite outcome measure to evaluate the newer oral DMAs introduced in the last decade.

3980 | Cohort selection in registry-based studies of direct oral anticoagulant users with atrial fibrillation: An inevitable trade-off between selection bias and misclassification

Maja Hellfritzsch[1,2], Erik L. Grove[2,3], Lotte Rasmussen[1], Simone B. Haastrup[2] and Anton Pottegård[1]
[1]*University of Southern Denmark, Odense, Denmark;* [2]*Aarhus University Hospital, Aarhus, Denmark;* [3]*Aarhus University, Aarhus, Denmark*

Background: Danish health registries are extensively used to study the safety and effectiveness of direct oral anticoagulants (DOAC) in atrial fibrillation (AF). Capturing the AF treatment indication is, however, challenging. Requirement of a registered hospital diagnosis of AF for cohort inclusion may introduce selection bias due to non-inclusion of many DOAC users with 'non-registered' AF. In contrast, not requiring this may introduce misclassification due to inclusion of DOAC users without AF.

Objectives: To assess the potential for selection bias and misclassification in studies on DOAC users with AF based on Danish registries.

Methods: We identified DOAC initiators between August 2011 and December 2018 (n=187,195). Using hospital diagnoses registered up until initiation, users were classified by assumed treatment indication in categories: AF (n=76,125), non-AF (*e.g.*, venous thromboembolism) (n=42,710), and no indication (n=68,360). The potential for selection bias was assessed by comparing one-year risks (cumulative incidence

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

proportions) of arterial thromboembolism, bleeding, and all-cause mortality between categories 'AF' and 'no indication'. To assess the potential for misclassification, we estimated the proportion of the 'no indication'-category that was diagnosed with AF or a non-AF indication in the year after initiation.

Results: The one-year risk of arterial thromboembolism was 4% and 5% in DOAC users with 'AF' and 'no indication', respectively (Hazards Ratio (HR) 1.27, 95% Confidence Interval (CI) 1.20-1.33). Mortality rates were also lower in the AF category (9%) than in the "no indication" category (11%) (HR 1.21, 95% CI 1.17-1.25). The one-year bleeding rates did not differ between groups (HR 0.95, 95% CI 0.91-0.99). In the 'no indication'-category, 32% and 4% received a diagnosis of AF and a non-AF treatment indication, respectively, in the year following DOAC initiation.

Conclusions: In 1/3 of Danish DOAC users, the indication for treatment cannot be identified when using hospital-based registries upon initiation. This study confirms that non-inclusion of these users likely introduces selection bias in effectiveness studies, whereas inclusion may lead to misclassification. To obtain the most balanced trade-off between these biases in cohort studies on DOAC users with AF, we suggest a main analysis including both the 'AF' and 'no indication'-category supplemented by a subgroup analysis including the 'AF'-category only.

4041 | Cardiovascular effectiveness of empagliflozin compared to DPP4 inhibitors and to GLP1 receptor agonists: Interim analysis from the empagliflozin comparative effectiveness and safety (EMPRISE) study

Elisabetta Patorno[1], Ajinkya Pawar[1], Jessica Franklin[1], Mehdi Najafzadeh[1], Deborah Wexler[2], Anouk Déruaz-Luyet[3], Kimberly Brodovicz[4], Lily Bessette[1] and Sebastian Schneeweiss[1]

[1]Brigham and Women's Hospital, Boston, MA; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA; [3]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [4]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT

Background: The EMPA-REG OUTCOME trial showed a reduction of 35% for heart failure hospitalization (HHF) and similar incidence of myocardial infarction and stroke in patients with type 2 diabetes (T2D) at high cardiovascular (CV) risk treated with empagliflozin (EMPA) vs. placebo, on top of standard of care. EMPRISE studies the comparative effectiveness, safety and healthcare utilization of EMPA in routine care of T2D patients across a broad spectrum of CV risk using data from Medicare and 2 U.S. commercial claims datasets from 08/2014 through 09/2019.

Objectives: To assess the association between EMPA and the risk of atherosclerotic cardiovascular (ASCV) events and HHF compared to DPP4 inhibitors (DPP4i) and to GLP1 receptor agonists (GLP-1RA) in an interim analysis from EMPRISE based on data from 08/2014 through 09/2017.

Methods: Within the 3 datasets (Medicare fee-for-service, Optum, and MarketScan), we identified 39,169 pairs of 1:1 propensity score (PS)-matched patients ≥18 years with T2D initiating EMPA or a DPP4i and 55,860 pairs initiating EMPA or a GLP-1RA. We assessed HHF, defined as either a discharge diagnosis of heart failure in the primary position (HHF-Specific) or in any position (HHF-Broad), and a combined ASCV outcome (comprised of myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization). In each cohort, we estimated pooled hazard ratios (HR) and 95% confidence intervals (CI) adjusting for >140 baseline covariates, including several proxies of diabetes progression.

Results: After PS-matching, covariates were balanced with standardized differences <0.1, including lab test results available in a subset of the cohort and thus not included in the PS model. Over a mean follow-up of approximately six months, EMPA was associated with a decreased risk of HHF [HHF-Specific: 0.42 (0.31-0.58); HHF-Broad: 0.59 (0.51-0.69)] and a similar risk of the ASCV outcome [HR (95% CI) = 0.88 (0.74-1.03)] compared with DPP4i. Results for EMPA vs GLP-1RA were similar: HHF-Specific [0.63 (0.49-0.80)], HHF-Broad [0.83 (0.74-0.93)] and ASCV outcome [0.99 (0.87-1.13)]. Results for the individual components of the ASCV outcome were consistent.

Conclusions: An interim analysis from EMPRISE showed that compared with DPP4i or GLP-1RA, EMPA was associated with a decreased risk of HHF in routine clinical care and a similar risk of ASCV events. These results are consistent with trial data and reinforce the notion of the major role that HHF risk may play in deciding when to prescribe EMPA.

4063 | Statins and risk of diverticular disease: nested case-control study in Denmark

Nils Skajaa[1], Frederikke Schønfeldt Troelsen[1], Ola Ekholm[2], Lars Pedersen[1], Rune Erichsen[1] and Henrik Toft Sørensen[1]

[1]Aarhus University, Aarhus N, Denmark; [2]National Institute of Public Health, Copenhagen, Denmark

Background: Statins may affect the occurrence of diseases not clearly related to cholesterol levels through direct and indirect pathways. Whether statins affect the development of diverticular disease, a highly prevalent condition, remains poorly understood with previous studies obtaining divergent results.

Objectives: To examine the association between statin use and diverticular disease.

Methods: We conducted a nested case-control study in Denmark during 2010-2018. The source population consisted of respondents (>18 years) of the 2010 or the 2013 Danish National Health Survey. We linked this population to nationwide health and administrative registries and identified 8,809 cases of hospital-diagnosed diverticular disease and risk-set sampled population controls without diverticular disease, matched 1:10 on age, sex, and year of survey. Using complete prescription (since 2005) and hospital records (since 1977) among

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

cases and controls, we applied conditional logistic regression to compute crude and adjusted odds ratios (ORs) associating statin use with diverticular disease. In adjusted analyses, we controlled for indications for statin initiation, including medication use other than statins, and lifestyle-related factors associated with diverticular disease, including diet, smoking, alcohol consumption, and physical activity.

Results: The adjusted OR for diverticular disease associated with ever use (≥1 statin prescription filling) was 1.18 (95% CI: 1.11-1.27) compared with no-use. This association was robust for both lipophilic and hydrophilic statins and across strata of age and sex. The adjusted OR was somewhat higher for cases of diverticulitis requiring surgery (1.36 [95% CI: 1.06-1.76]) than for those not requiring surgery (1.16 [95% CI: 1.07-1.25]). In analyses taking into account both the duration and intensity of statin use, associations resembled that of the main analyses. For example, among short-term users (<5 years), the OR was 1.15 (95% CI: 1.00 - 1.33) for low intensity users and 1.15 (95% CI: 1.02-1.29) for high intensity users. Similarly, among long-term users (≥5 years), the respective ORs were 1.25 (95% CI: 1.12-1.39) and 1.10 (95% CI: 0.97-1.24).

Conclusions: Statin use was associated with an increased risk of diverticular disease, particularly cases of diverticulitis requiring surgery. The increased risk persisted among the long-term and most intense users, but may be explained by residual confounding.

4065 | Statins and risk of amyotrophic lateral sclerosis: Danish population-based cohort study

Nils Skajaa[1], Istvan Bakos[1], Erzsébeth Horváth-Puhó[1], Victor W. Henderson[1,2], Timothy Lash[1,3] and Henrik Toft Sørensen[1]

[1]Aarhus University, Aarhus N, Denmark; [2]Stanford University, Stanford, CA; [3]Rollins School of Public Health, Emory University, Atlanta, GA

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease. The evidence of an association between statins, common cholesterol-lowering drugs with pleotropic properties, and ALS is scattered and inconclusive.

Objectives: To examine the effect of statin initiation on the risk of ALS.

Methods: We performed a population-based cohort study involving 767,694 statin initiators aged ≥ 18 years and 1,535,388 sex-, age-, and calendar year-matched (1:2) general population comparators identified 1 January 2005 to 31 December 2016 from Danish, nationwide registries. We computed cumulative risks and hazard ratios (HRs) of a first-time ALS diagnosis controlling for medically diagnosed comorbidities, including comedications, in one analysis and propensity-score in another.

Results: The 12-year cumulative risk of ALS among statin initiators was 0.11% (95% confidence interval [CI]: 0.10-0.12), yielding a comorbidity-adjusted HR of 1.26 (95% CI: 1.11-1.42). The risk was higher among women (HR: 1.38 [95% CI: 1.16-1.64]) than men (HR: 1.15 [95% CI: 0.97-1.37]) and during the first year since statin initiation (HR: 1.84 [95% CI: 1.39-2.42]). However, associations decreased to unity during 5-12 years since initiation (HR: 0.99 [95% CI: 0.79-1.23]). Associations were similar for lipophilic and hydrophilic statins, when a stricter definition of ALS was used, and when HRs were adjusted for the propensity-score.

Conclusions: We found evidence of an association between statin initiation and ALS. The association was strongest in the first year since statin initiation, suggesting a possible acute neurotoxic effect. However, the lack of a long-term effect may indicate bias which warrants further investigation.

4071 | The risk of overdose associated with concomitant use of antipsychotic agents and prescription opioids

Alejandro Szmulewicz[1], Brian Bateman[2], Raisa Levin[3] and Krista Huybrechts[1]

[1]Harvard School of Public Health, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: As chronic pain and mental conditions commonly co-occur, prescription opioids and antipsychotics (AP) are frequently used concomitantly. Concerns exist that concomitant use of these agents may increase the risk of unintended overdose.

Objectives: To determine the rate of overdose among patients using opioids and AP agents as compared to those using opioids alone, and to establish if sedating AP yield a higher risk than non-sedating AP.

Methods: We conducted a cohort study using IBM Health MarketScan research databases 2004-2017. Patient episodes with concomitant exposure to any AP agent and prescription opioids ('exposed') were 1:1 matched to patient episodes with exposure to prescription opioids alone ('reference') based on: type of opioid, morphine equivalents, calendar year, and hospitalization within the last 30 days of the qualifying prescription. Patients with cancer or palliative care were excluded. For the secondary analyses, episodes of opioids plus AP use were divided into 'sedating' (e.g., quetiapine) and 'non-sedating' (e.g., aripiprazole). The same matching factors plus chlorpromazine equivalents were applied. The primary outcome was opioid and/or psychotropic-related overdose within 30 days of index date (i.e., date of the AP prescription for the exposed and matched date for the reference), using an intention-to-treat approach. Hazard Ratios (HR) and 95% CI were estimated from Cox proportional hazard regression models with fine stratification on the propensity score (including 65 variables) to control for confounding.

Results: The cohort comprised 85,973 exposed and an equal number of matched reference episodes. Mean age was 49 years and 40% were male. Patients with concomitant AP use had higher concomitant psychotropics, number of clinical diagnoses, psychiatric visits and comorbidities at baseline. There were 143 overdoses among the exposed (20.6 per 1,000 person-years) versus 15 among the referent (2.2 per 1,000 person-years) within 30 days, for an unadjusted HR of 9.26 (95% CI: 5.44-15.76). With fine stratification on the PS, the HR attenuated to 1.31 (1.02-1.69). In secondary analyses, we found no

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

difference in the risk of overdose comparing sedating to non-sedating AP (HR: 1.00, 95% CI: 0.61-1.63).

Conclusions: Among patients receiving prescription opioids, concomitant AP use was associated with an increased risk of overdose. No differences between AP agents was found based on their sedating potential. Caution is required when prescribing these agents to patients on opioid therapy and interventions to improve rational prescribing are needed.

4091 | Outcomes in patients receiving nintedanib or pirfenidone for idiopathic pulmonary fibrosis

Vincent Cottin[1], Paolo Spagnolo[2], Philippe Bonniaud[3], Maeva Nolin[4], Faustine Dalon[4], Jenny Chia[5], Klaus Kirchgässler[6], Tripthi Kamath[5], Eric Van Ganse[4] and Manon Belhassen[4]

[1]National Reference Coordinating Center for Rare Pulmonary Diseases, Louis Pradel Hospital, Hospices Civils de Lyon, Université de Lyon, Université Claude Bernard Lyon 1, UMR754, IVPC, Member of ERN-LUNG, Lyon, France; [2]Respiratory Disease Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy; [3]Service de Pneumologie et Soins Intensifs Respiratoires, Centre de Référence Constitutif des Maladies Pulmonaires Rares de l'Adulte, Centre Hospitalo-Universitaire de Bourgogne, Faculté de Médecine et Pharmacie, Université de Bourgogne-Franche Comté, Dijon, France; [4]PELyon, Lyon, France; [5]Genentech, Inc., South San Francisco, CA; [6]F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, irreversible, and ultimately fatal disease of unknown aetiology. Currently, pirfenidone and nintedanib are the only two approved drugs for IPF.

Objectives: The aim of this study was to assess all-cause mortality and acute respiratory-related hospitalizations in IPF patients either untreated or receiving pirfenidone or nintedanib.

Methods: We conducted a cohort study using French National Health System claims data on individuals aged ≥50 years diagnosed with IPF between January 2015 and December 2016. Cumulative incidence rates were estimated for untreated and patients newly treated with pirfenidone or nintedanib. All-cause mortality, acute respiratory-related hospitalizations, and treatment discontinuations were compared among newly pirfenidone- and nintedanib-treated patients, using a Cox proportional hazards model adjusted for confounders.

Results: Among the 7,194 identified IPF patients (63% of males, mean age of 74.9 years old), 521 (7,2%) were not newly treated patients and were therefore not included in the study; 5,360 (74.5%) remained untreated, while 804 (11.2%) initiated pirfenidone and 509 (7.1%) initiated nintedanib during the study period. The cumulative all-cause mortality at three years was 50.23% (95% CI=[48.34%-52.09%]) in untreated patients, 25.5% (95% CI=[19.6%-31.7%]) in pirfenidone-treated patients, and 31.1% (95% CI=[21.2%-41.6%] in nintedanib-treated patients. After adjustment for age at index date, gender, year of index date, time in months between IPF diagnosis and index date, and proxies of severity identified during the 12 months before index date, nintedanib was associated with higher risks of all-cause death and acute respiratory-related hospitalization than pirfenidone over the exposure period (HR=1.80, 95% CI=[1.25-2.60], and HR=1.32, 95% CI=[1.01-1.73], respectively). However, nintedanib was also associated with a lower risk of treatment discontinuation at 12 months than pirfenidone (HR=0.72, 95% CI=[0.60-0.86]).

Conclusions: Compared to nintedanib, pirfenidone was associated with lower risks of death and acute respiratory-related hospitalizations but with a higher risk of treatment discontinuation at 12 months. Although data interpretation is limited by the observational design of the study, these findings suggest possible differences in effectiveness between available drugs for IPF.

Funding: F. Hoffmann-La Roche, Ltd/Genentech, Inc.

4100 | Comparative effectiveness of ovulation induction medications: Evidence from a large healthcare database in the United States

Jennifer J. Yland[1,2], Yu-Han Chiu[1], Sean McGrath[1] and Sonia Hernández-Díaz[1]

[1]Harvard T.H. Chan School of Public Health, Boston, MA; [2]Boston University School of Public Health, Boston, MA

Background: Clomiphene citrate (CC) and letrozole are used to induce ovulation in women with infertility. Several randomized trials have observed improved ovulation and pregnancy rates among women treated with letrozole compared with CC. However, little is known about the comparative neonatal outcomes associated with these medications.

Objectives: To evaluate pregnancy outcomes among women treated with CC compared to letrozole.

Methods: This study was conducted within the IBM MarketScan Commercial Claims and Encounters Database for 2011-2015. We identified dispensations of CC and letrozole among women aged 18-50 and excluded women with contraindications, breast cancer, or use of assisted reproductive technology. We followed women from first cycle, through up to one year of treatment, to end of pregnancy, treatment failure, or end of enrollment. We identified pregnancies with an estimated last menstrual period within 60 days of the last dispensation of CC or letrozole and evaluated pregnancy outcomes. We then identified pregnancies linked to a liveborn infant and evaluated preterm birth (PTB), small for gestational age (SGA), major congenital malformations overall, hypospadias, and cryptorchidism. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) and adjusted for potential confounders. We also stratified analyses by intrauterine insemination (IUI) and polycystic ovarian syndrome (PCOS).

Results: 35,288 and 15,661 women initiated ovarian stimulation cycles with CC and letrozole, respectively. We identified clinical pregnancies among 38% and 34% of women who received CC and letrozole, respectively over cumulative treatment cycles, among which

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

a livebirth was attained in 88% for each group. After infant-linkage, we analyzed data from 7,899 livebirths conceived with CC and 3,800 with letrozole. IUI was used among 21% and 24% of pregnancies in the CC and the letrozole groups, respectively. The proportion of pregnancies with multifetal gestation was about 10% in both groups. There were few differences in neonatal outcomes between infants conceived by the two treatment groups. The ORs (95% CIs) for PTB, SGA, and malformations overall were 1.10 (0.98, 1.23), 0.86 (0.72, 1.02), and 1.09 (0.88, 1.35), respectively, comparing newborns conceived with letrozole with those conceived with CC. Estimates were unstable for specific malformations. Results were similar within non-IUI and IUI pregnancies and within women with and without PCOS.

Conclusions: Conditioning on livebirth, neonatal outcomes were generally similar in pregnancies conceived with CC versus letrozole.

4112 | Risk of cardiovascular events and serious hypoglycemia comparing patients with type 2 diabetes initiating a GLP1RA or basal insulin: A propensity score matched cohort study

Jing Luo[1], Deborah Wexler[2], Dae Kim[3], Seoyoung Kim[4] and Elisabetta Patorno[4]

[1]University of Pittsburgh, Pittsburgh, PA; [2]Massachusetts General Hospital, Boston, PA; [3]Hebrew Rehabilitation Center, Boston, MA; [4]Brigham and Women's Hospital, Boston, MA

Background: Head-to-head open label trials comparing selected GLP-1RA(s) versus basal insulin(s) have not evaluated cardiovascular outcomes.

Objectives: To determine the risk of serious cardiovascular events and serious hypoglycemia comparing patients with type 2 diabetes newly initiating a GLP-1RA or basal insulin.

Methods: Using 2 large U.S. commercial claims databases (Optum and Truven MarketScan) from 01/2012 to 12/2017, we assessed the risk of a composite cardiovascular outcome (MI, stroke) and serious hypoglycemia defined by validated claims-based algorithms comparing 26,308 patients with type 2 diabetes with prior or concurrent metformin therapy newly initiating an injectable GLP-1RA or basal insulin. We estimated pooled incidence rates, meta-analyzed hazard ratios and 95% CI adjusting for >140 baseline clinical characteristics, including HbA1c.

Results: Baseline clinical characteristics were well-balanced in the two groups after 1:1 propensity score matching. In an as-treated analysis, the median follow-up was 148 days. The mean age was 57.9 (SD 4.4-4.9) with 48% female. Sixteen percent of patients had pre-existing ischemic heart disease at baseline. The mean(SD) baseline HbA1c was 8.64 (0.83). All patients had received prior or concurrent metformin therapy. Compared to basal insulin, initiating a GLP-1RA was associated with a lower risk of MI or stroke [HR 0.68; 95% CI 0.51-0.90] and lower risk of serious hypoglycemia [HR 0.38; 95% CI 0.25-0.57].

Conclusions: These results support recent clinical treatment guidelines that recommend starting a GLP-1RA before basal insulin for patients with type 2 diabetes with inadequate glycemic control despite metformin.

4129 | SGLT2 inhibitors and the risk of major adverse cardiovascular events: A multi-database study using a prevalent new-user design

Kristian B. Filion[1], Lisa M. Lix[2], Oriana H.Y. Yu[3], Sophie Dell'Aniello[3], Antonios Douros[1], Baiju R. Shah[4], Audray St-Jean[3], Anat Fisher[5], Eric Tremblay[6], Shawn C. Bugden[7], Silvia Alessi-Severini[2], Paul E. Ronksley[8], Nianping Hu[9], Colin R. Dormuth[5], Pierre Ernst[1], Samy Suissa[1] and the CNODES Investigators[10]

[1]McGill University, Montreal, QC, Canada; [2]University of Manitoba, Winnipeg, MB, Canada; [3]Lady Davis Institute, Montreal, QC, Canada; [4]University of Toronto, Toronto, ON, Canada; [5]University of British Columbia, Vancouver, BC, Canada; [6]Institut National d'Excellence en Santé et en Services Sociaux, Quebec City, QC, Canada; [7]Memorial University of Newfoundland, St John's, NL, Canada; [8]University of Calgary, Calgary, AB, Canada; [9]The Health Quality Council, Saskatoon, SK, Canada; [10]Canadian Network for Observational Drug Effect Studies (CNODES) Investigators, Montreal, QC, Canada

Background: Most randomized controlled trials suggest that sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of major adverse cardiovascular events (MACE) among patients with type 2 diabetes. However, their effectiveness in a real-world setting remains uncertain.

Objectives: We compared SGLT2 inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors on the incidence of MACE (a composite endpoint of myocardial infarction, ischemic stroke, and cardiovascular death), the individual components of MACE, heart failure, and all-cause mortality among patients with type 2 diabetes.

Methods: As part of the Canadian Network for Observational Drug Effect Studies (CNODES), we conducted a multi-database retrospective cohort study using healthcare databases from seven Canadian provinces and the United Kingdom over the period 2013-2018. Using a prevalent new-user design, we matched each new user of a SGLT2 inhibitor to a DPP-4 inhibitor user on time-conditional propensity scores. Our primary endpoint was MACE. We used Cox proportional hazards models to estimate site-specific adjusted hazards ratios (HRs) and 95% confidence intervals (CIs), comparing exposure to SGLT2 inhibitors with DPP-4 inhibitors using an as-treated approach. Site-specific results were pooled using random-effects meta-analysis.

Results: A total of 209,867 new users of SGLT2 inhibitors was matched to 209,867 users of DPP-4 inhibitors. During a mean follow-up of 0.9 years (standard deviation: 0.76), MACE occurred in 2,146 SGLT2 inhibitor users (incidence rate: 11.4 per 1,000 person-years) and 3,001 DPP-4 inhibitor users (incidence rate: 16.5 per 1,000 person-years). Compared with DPP-4 inhibitors, SGLT2 inhibitors were associated with decreased risks of MACE (HR: 0.76, 95% CI: 0.69-0.84), myocardial infarction (HR: 0.82, 95% CI: 0.70-0.96), cardiovascular death (HR: 0.60, 95% CI: 0.54-0.67), heart failure (HR:

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

0.43, 95% CI: 0.37-0.51), and all-cause mortality (HR: 0.60, 95% CI: 0.54-0.67). SGLT2 inhibitors had more modest benefits for ischemic stroke (HR: 0.85, 95% CI: 0.72-1.01). We observed similar benefits with respect to MACE with canagliflozin (HR: 0.79, 95% CI: 0.66-0.94), dapagliflozin (HR: 0.73, 95% CI: 0.63-0.85), and empagliflozin (HR: 0.77, 95% CI: 0.68-0.87). Similar results were observed for MACE across patient subgroups defined by age, sex, prior use of insulin, and history of cardiovascular disease.

Conclusions: In this large observational study, SGLT2 inhibitors were associated with a decreased risk of serious cardiovascular events compared with DPP-4 inhibitors.

4156 | The impact of opioids on adverse events among older breast cancer survivors

Aaron N. Winn[1], Devon Check[2], Nicole M. Fergestrom[1], Joan M. Neuner[1] and Andrew W. Roberts[3]
[1]*Medical College of Wisconsin, Milwaukee, WI;* [2]*Duke University, Durham, NC;* [3]*University of Kansas Medical Center, Kansas City, KS*

Background: Older adults and cancer survivors are underrepresented in prior research. As prevention of unnecessary opioid use gains importance in clinical practice, it is needed to fully capture the risks of opioid related adverse events among patients with cancer pain.

Objectives: The objective of this study was to determine the association between opioid use after cancer diagnosis and comprehensive opioid-related adverse events among older adult breast cancer survivors.

Methods: We conducted a retrospective cohort study using Surveillance, Epidemiology, and End Results tumor registry data linked with Medicare claims for women who received a new diagnosis of stage 0-III breast cancer at the age of 66 to 90 between 2008-2015. The study observation period was the year following a patient's end of active cancer treatment. The primary independent variable was a repeated daily measure of opioid exposure based on Part D prescription claims. The primary outcomes were daily indicators of all-cause hospitalization, substance use event and a composite of other opioid-related adverse events (infections, gastrointestinal events, falls/fractures, cardiovascular events). We estimated the association of current opioid use and the immediate risk of an outcome the following day using modified Poisson generalized estimating equation models. We adjusted for patient demographics, cancer characteristics and cancer treatments received. We conducted sensitivity analyses that examined a dose response relationship by measuring opioid exposure as greater than or less than 50 morphine milligram equivalents (MME).

Results: We found that opioid exposure more than doubled the immediate risk of all-cause hospitalization (aRR= 2.77; 95%CI=2.57, 2.99; p<0.001) and having a composite adverse event (aRR= 2.50; 95% CI=2.18, 2.87; p<0.001) and dramatically increases the immediate risk of a substance use event (aRR= 14.26; 95%CI=7.11, 28.59; p<0.001). In sensitivity analyses, we find consistent increased risk with increased dosages of opioids. For example, opioid exposure≥50 MME almost quadruples the risk of being hospitalized (aRR= 3.94; 95% CI=3.45, 4.51; p<0.001) whereas opioid exposure<50 MME doubles the risk of being hospitalized (aRR= 2.49; 95%CI=2.28, 2.71; p<0.001) compared to no opioid exposure.

Conclusions: Older adult breast cancer survivors with continued prescription opioid use in the year after completing cancer treatment experienced an immediate increased risk of all-cause hospitalization, substance use events, and opioid-related adverse effects. Clinicians should consider the comprehensive risks of opioids in managing cancer pain.

4184 | Interventions to improve medication adherence in patients with inflammatory bowel disease: A systematic review

Shrey Gohil, Zahra Majd, Jared C. Sheneman and Susan Abughosh
University of Houston College of Pharmacy, Houston, TX

Background: Medication nonadherence in patients with inflammatory bowel disease (IBD) is associated with disease aggravation, unsatisfactory clinical outcomes, high healthcare consumption, and increased costs.

Objectives: The aim of this study is to summarize existing literature examining interventions to enhance medication adherence and their impact on patients with IBD.

Methods: This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. PubMed and Embase were searched for studies from June 2014 to June 2019 using the following terms: "inflammatory bowel disease" or "IBD" or "ulcerative colitis" or "Crohn's disease," "adherence" or "compliance" or "persistence," "intervention," and "medication" or "treatment". Only the studies published in English were included. Randomized controlled trials, observational studies, and mixed methods design studies were included. Studies were excluded if they were reviews, case reports, case series, conference abstracts, or study protocols. At least two investigators independently determined the eligibility of studies, extracted data and summarized the results.

Results: Our systematic literature search identified four hundred eighty-eight published articles. Sixteen studies with a total of 6311 patients were included in this review based on inclusion and exclusion criteria. Out of sixteen different interventions, eight were classified as educational, five as multicomponent, two as behavioral and one as cognitive-behavioral. Adherence was measured using patient self-report, administrative/pharmacy claims data, and electronic monitoring devices/pill dispensing systems. Eleven out of sixteen interventions showed a statistically significant improvement in medication adherence including five educational, four multicomponent, one behavioral and one cognitive-behavioral intervention.

Conclusions: Literature assessing different intervention strategies to improve medication adherence among patients with IBD is sparse. Majorly, educational and multicomponent interventions are evaluated. Multicomponent interventions demonstrated the greatest impact on IBD patients in promoting medication adherence. Future research should focus on a multidisciplinary approach to design multicomponent interventions that synergize impact and maximize success.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4193 | Effect duration of intramuscular benzathine penicillin for preventing recurrence of cellulitis

Nai-Yu Chen[1], Kuan-Sheng Wu[2], Chien-Chou Su[1] and Edward Chia-Cheng Lai[1]

[1]*Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan;* [2]*Section of Infectious Diseases, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*

Background: Intramuscular benzathine penicillin (IM penicillin) every 3 to 4 week is often used to prevent recurrence of cellulitis. However, limited information on its effect duration was available, lingering the question that the optimal frequency of IM penicillin remained unclear.

Objectives: To evaluate the effect duration of IM penicillin for prevention of cellulitis recurrence.

Methods: We analyzed the data of 2 million individuals randomly sampled from Taiwan's National Health Insurance Database from 2004-2013. We included patients newly diagnosed with cellulitis receiving IM penicillin for prevention of recurrent cellulitis. We excluded patients receiving any kind of antibiotics within 14 days of wash-out period before IM penicillin. Included patients were followed up for 27 days from IM penicillin. We censored patients at the time of cellulitis recurrence or receive of the next IM penicillin. We calculated the incidence rate of recurrent cellulitis for the time intervals of day 0-6, 7-13, 14-20 and 21-27 respectively. We used piecewise Cox regression to evaluate the risk of recurrent cellulitis for each time interval, compared to the first time interval (ie, day 0-6).

Results: We included a total of 314 patients received IM penicillin. The mean age was 67.26 (SD 17.02) years old and 38.85% of them were female. The overall incidence rate of recurrent cellulitis within 27 days was 17.14 per 100 person-day. The incidence rate of recurrent cellulitis were 2.87, 6.56, 3.51, and 3.64 per 100 person-day for the intervals of day 0-6, 7-13, 14-20 and 21-27, respectively. Compared to the day 0-6, we found the hazard ratio of recurrent cellulitis were 2.29 (95% CIs, 1.47-3.39) for day 7-13,1.22 (95% CIs, 0.76-1.94) and 1.27 (95% CIs, 0.77-2.05) for day 21-27.

Conclusions: The findings indicated the risk of recurrent cellulitis was higher in day 7-13, suggesting the effect duration of IM penicillin may limit to only one week. The study warrants re-consideration on optimal frequency of using IM penicillin for preventing recurrent cellulitis.

4196 | Clinical outcome and medical cost of brand-name and generic antihypertensive drugs: A population-based study in Yinzhou, China

Tao Huang[1], Haishaerjiang Wushouer[2,3,4], Mingchun Yang[1], Luwen Shi[1,4] and Xiaodong Guan[1,4]

[1]*Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, China;* [2]*Center for Strategic Studies, Chinese Academy of Engineering, Beijing, China;* [3]*School of Medicine, Tsinghua University, Beijing, China;* [4]*International Research Center for Medicinal Administration, Peking University, Beijing, China*

Background: The substitution of generic drugs can effectively alleviate the rapid growth of drug cost, however, the clinical effectiveness and medical cost of Chinese brand and generic drugs were never studied.

Objectives: To compare the effectiveness of antihypertensive drugs and hypertension related medical cost between brand-name and generic initiators in Yinzhou, Zhejiang, China.

Methods: We conducted a population-based retrospective cohort study using healthcare database from The Chinese Electronic health Records Research in Yinzhou (CHERRY), from 1st July 2011 to 31st December 2018. Hypertension patients initiating with brand-name products were compared with patients initiating with generics, for irbesartan, valsartan, losartan, metoprolol, amlodipine, nifedipine and felodipine. We used 1:1 propensity score matching to pair the two groups based on sociodemographic, clinical, and health service utilization variables. Cox proportional regression was adopted to compare the rate of hospitalization with myocardial infarction or ischemic stroke between matched brand-name and generic initiators. Multivariable linear regression was used to compare the daily hypertension related medical cost within the follow-up between the two groups.

Results: Among 7 drugs, 17102 matched pairs of patients were included in the study. A majority (6 out of 7) of the clinical endpoint estimates showed similar outcomes between brand-name products and generics (irbesartan HR[95%CI]: 0.69[0.30-1.57], valsartan HR[95%CI]: 0.90[0.55-1.47], losartan HR[95%CI]: 0.89[0.59-1.35], metoprolol HR [95%CI]: 0.87[0.60-1.26], nifedipine HR[95%CI]: 0.91[0.56-1.47] and felodipine HR[95%CI]: 0.73[0.36-1.48], respectively). While for amlodipine, lower risk of hospitalization with myocardial infarction or ischemic stroke was observed in brand-name products (HR[95%CI]: 0.43[0.23-0.78]). For all 7 drugs, increasing daily medical cost of brand-name initiators versus generic initiators was observed (irbesartan β[95% CI]: 13.4[2.8-24.0], valsartan β[95%CI]: 7.5[5.0-10.1], losartan β[95% CI]: 15.8[11.0-20.6], metoprolol β[95%CI]: 29.3[11.1-47.6], amlodipine β[95%CI]: 24.0[7.1-41.0], nifedipine β[95%CI]: 29.4[17.6-41.3] and felodipine β[95%CI]: 5.54[3.43-7.67], respectively).

Conclusions: We observed comparable clinical outcomes and less medical cost associated with the use of antihypertensive generics versus brand-name products, which could help increase patient and provider confidence in the ability of generic medicines to manage hypertension diseases.

4197 | Real-world effectiveness of oral disease-modifying therapies for multiple sclerosis

Thanh Phuong Pham Nguyen, Dylan Thibault and Allison Willis

University of Pennsylvania, Philadelphia, PA

Background: Oral disease-modifying therapies (DMTs), namely dimethyl fumarate (DMF), fingolimod and teriflunomide, have become standard

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

treatments for multiple sclerosis (MS). Clinical trials demonstrated a reduction in annual relapse rate, but real-world data is lacking.

Objectives: To evaluate the real-world effectiveness of oral DMTs.

Methods: We used a multi-insurance database, Optum™ Clinformatics™, to conduct a retrospective cohort study of adult non-pregnant users of U.S.-approved oral DMTs for MS from 09/2010 until 9/2015. The study outcome was hospitalization with MS documented as the primary reason for hospitalization, an approximation of the clinical trial endpoint of hospitalization for MS relapse. Study subjects were required to have a minimum of two years of claims data after the first oral DMT prescription fill. Hospitalization for MS was estimated by the number of relapses per 1,000 patient-year1 using Poisson regression models. Time to first relapse was also examined using Cox proportional hazard models, which included individual level covariables for age, sex, race/ethnicity (white vs. minority), education level (high school or less vs. college or beyond), household income, previous treatment with injectable DMT, switching of oral DMT during observation period, and time since MS diagnosis.

Results: We identified 3,297 persons meeting all inclusion criteria. The unadjusted incidence rate ratios (IRRs) of MS hospitalizations were low for all DMTs, with a rate of 36 per 1,000 patient-years for DMF, 43 per 1,000 patient-years for teriflunomide, and 45 per 1,000 patient-years for fingolimod. Cox models found an increased risk of relapse associated with switching DMT (aHR 2.17, 95%CI 1.68-2.79), and minority race/ethnicity (aHR 1.39, 95%CI 1.28-1.51). As compared to the lowest income category, mid- and highest-level incomes had a lower risk of MS hospitalization, (aHRs 0.64, 95%CI 0.43-0.97 and 0.46, 95%CI 0.33-0.61, respectively), but the unknown/missing income category had the highest risk of MS hospitalization (aHR 1.24, 95%CI 1.03-1.52). There were no statistically significant differences in the risk of relapse associated with sex or education category, nor for fingolimod or DMF compared to teriflunomide.

Conclusions: Oral DMT performance in the real world is similar to clinical trials. Additionally, the three oral DMTs studied are comparably effective for the outcome of MS hospitalization. These data allow oral DMT therapy decision making to focus on other important factors such as safety potential, prior treatment response, disease progression, patient preference, therapy access and cost.

4212 | Comparing the effect of combining exercise with rosuvastatin versus atorvastatin on lipid profile and functional capacity: A retrospective cohort study

Sherif Eltonsy[1], Monique Dufour Doiron[2], Patrice Simard[3], Caroline Jose[2], Martin Senecal[4], Danielle Bouchard[4], Remi LeBlanc[5] and Mathieu Belanger[2]

[1]University of Manitoba, Winnipeg, MB, Canada; [2]Universite de Moncton, Moncton, MB, Canada; [3]Universite de Montreal, Montreal, MB, Canada; [4]University of New Brunswick, Fredericton, MB, Canada; [5]Universite de Sherbrooke, Winnipeg, QC, Canada

Background: Rosuvastatin and atorvastatin are the most commonly used types of statins, especially among older adults. Statins and exercise are recommended for managing hypercholesterolemia. However, statin types may vary in their interaction with exercise. Statin types vary in their lipophilicity and pharmacological properties, which affect their tissue penetration, including skeletal muscle tissues

Objectives: we present a real-world comparison of rosuvastatin versus atorvastatin combination with exercise to assess interactions between type of statin used and exercise on lipid profile and functional capacity

Methods: A retrospective cohort study using data from participants in a 12 week cardiovascular rehabilitation program between 2014-2016. Statins use was determined through prescriptions and average exercise minutes/week were computed from exercise logs. The cohort included 282 patients from 106 atorvastatin and 176 rosuvastatin users. The primary outcomes were changes in total cholesterol, low- and high-density lipoproteins (LDL & HDL), triglycerides and functional capacity (6-minute walk test [6MWT]). Directed acyclic graphs were used to identify potential confounders and specify variables to be included in the models to minimize bias. Three classes of potential confounders were included in the analysis, sociodemographic and clinical variables, medications used at admission, and exercise related variables.

Results: The average exercise minutes/week was 109.4±66.1 among atorvastatin and 106.7±49.1 among rosuvastatin users. Interaction models suggested a higher number of exercise minutes/week was more favorable among atorvastatin users on total cholesterol and LDL (0.004, 95% CI: 0.001, 0.008 and 0.004, 95% CI: 0.001, 0.007, respectively), but did not reach significance for HDL and triglycerides. Rosuvastatin use was associated with greater increases in 6MWT, however we observed no between-group differences in interaction estimates by type of statin used.

Conclusions: Rosuvastatin use could blunt the beneficial effect of exercise on LDL and total cholesterol compared to atorvastatin. No significant differences were observed in triglycerides, HDL and functional capacity levels. Additional studies are warranted with randomized treatments and larger samples. Healthcare providers should continue prescribing statins alongside recommending exercise modalities, with a careful follow-up for rosuvastatin users.

4214 | Efficacy and safety of antithrombotic therapy in atrial fibrillation patients undergoing percutaneous coronary intervention with stent or concomitant acute coronary syndrome

Han-Hsin Chueh, Shih-Tsung Huang and Fei-Yuan Hsiao

National Taiwan University, Taipei City, Taiwan

Background: For atrial fibrillation (AF) patients undergoing percutaneous coronary intervention (PCI) with stent or concomitant acute coronary syndrome (ACS), dual antiplatelet and anticoagulant might be warranted to prevent cardiovascular events and stroke. However, the optimal strategy of antithrombotic medication in "real-world" practice are not well studied in Asian population.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To compare major adverse cardiovascular event (MACE) and bleeding risk among different antithrombotic regimens.

Methods: We conducted a retrospective cohort study by using National Health Insurance Research Database (NHIRD) in Taiwan. Non-valvular AF patients who newly underwent PCI with stents or hospitalized due to ACS in 2007 to 2016 were included. Patients who received PCI, coronary artery bypass graft (CABG) or hospitalized for ACS one year before inclusion were excluded. The cohort was followed until MACE or bleeding events occurred, one year after discharge, or switched to different antithrombotic regimen. All prescriptions of antithrombotic therapy received by our study cohort were captured monthly and categorized into five groups: single antiplatelet (SAPT), single anticoagulant (SAC), dual antiplatelet (DAPT), SAPT +SAC (double) and DAPT+SAC (triple). Multivariable Cox proportional hazard model was used to compare 3-point MACE consisting of myocardial infarction, ischemic stroke and death from cardiovascular causes, all-cause mortality and major bleeding risk of aforementioned antithrombotic regimens.

Results: We identified 11,492 patients (mean age 71.7, SD=10.9; male 68.5%). Among them, the median CHA_2DS_2-VASc score is 3 (IQR 2-4), and 80.4% has a score ≥2 (≥3 if female). At discharge, most (60.75%) of the patients received DAPT as initial antithrombotic regimen, followed by SAPT (23.72%), triple (6.33%), double (6.01%) and SAC (3.19%). As compared with DAPT, there is no significant difference in 3-point MACE among other four antithrombotic regimens (SAPT: adjusted HR 1.02 [95% CI 0.85-1.32]; SAC: 0.55 [0.29-1.02]; double: 0.71 [0.47-1.07]; triple: 0.87 [0.56-1.37]. On the other hand, SAPT significantly reduced the risk of major bleeding (0.47 [0.30-0.73]), while triple therapy was associated with a nearly two-fold risk of bleeding (1.96 [1.21-3.16]).

Conclusions: Our study found that there were comparable risks of 3-point MACE among the five antithrombotic regimens (SAPT, SAC, DAPT, double and triple) identified. However, triple therapy was associated with a higher risk of major bleeding.

4230 | Comparison of effectiveness and safety between glecaprevir/pibrentasvir and sofosbuvir/velpatasvir in patients with chronic hepatitis C - A multi-institutional cohort study in Taiwan

Mu-Hsuan Hou[1], Shih-Chieh Shao[1,2], Hui-Yu Chen[3], Yuk-Ying Chan[4] and Edward Chia-Cheng Lai[2]

[1]Keelung Chang Gung Memorial Hospital, Keelung, Taiwan; [2]National Cheng Kung University, Tainan, Taiwan; [3]Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; [4]Chang Gung Medical Foundation, Taoyuan, Taiwan

Background: Pangenotypic direct-acting antiviral agents (DAA), glecaprevir/pibrentasvir (GLE/PIB) and sofosbuvir/velpatasvir (SOF/VEL), have been proven in clinical trials to be effective for chronic hepatitis C (CHC) infection. However, evidence comparing the effectiveness and safety of GLE/PIB vs. SOF/VEL is lacking.

Objectives: To compare the real-world effectiveness and safety between GLE/PIB and SOF/VEL in CHC patients.

Methods: We conducted a retrospective cohort study using the Chang Gung Research Database, which includes about 13% of CHC patients receiving DAA treatment in Taiwan. We included CHC patients without compensated liver cirrhosis newly initiating GLE/PIB or SOF/VEL between June 1, 2019 and September 31, 2019, and excluded patients without virology analyses before or after DAA treatment (n=20). We compared the rate of undetectable serum HCV RNA at the end of treatment (EOTR) as the effectiveness rate between GLE/PIB and SOF/VEL new users. The safety outcome included the elevation of liver enzymes during the GLE/PIB or SOF/VEL treatment, defined by alanine aminotransferase (ALT) reaching ≥3X upper limit of normal (ULN) or total bilirubin ≥2X ULN. We followed patients from the initiations of GLE/PIB or SOF/VEL to December 31, 2019.

Results: We identified a total of 528 CHC patients newly initiating GLE/PIB (n=247; 51.0% female; 68.4% genotype 2; 11.7% cirrhosis) and SOF/VEL (n=281; 49.0% female; 50.8% genotype 2; 21.3% cirrhosis). The mean age was 59.6 (SD 13.1) and 63.4 (SD 13.8) years old for GLE/PIB and SOF/VEL new users, respectively. The baseline mean serum HCV RNA level before treatment was 3.8 million IU/mL (SD 7.5) for GLE/PIB and 3.1 million IU/mL (SD 7.5) for SOF/VEL users. GLE/PIB and SOF/VEL had similar EOTR rates (99.5% vs. 99.6%). Patients receiving GLE/PIB had similar incidence rates of elevated ALT ≥3X ULN (1.2% vs. 1.4%), but higher rates of elevated total bilirubin ≥2X ULN (4.5% vs. 0.4%) than those receiving SOF/VEL.

Conclusions: The real-world effectiveness of GLE/PIB and SOF/VEL was comparable, based on evaluation of EOTR rate, but GLE/PIB may be associated with higher rates of elevated total bilirubin levels, compared to SOF/VEL. Our findings provide an important ground for future head-to-head studies evaluating the clinical effects among different pangenotypic DAA.

4234 | Real-world effectiveness of mood stabilizer use in persons with schizophrenia

Arto Puranen[1,2], Marjaana Koponen[2,3], Lähteenvuo Markku[1], Antti Tanskanen[1,4], Jari Tiihonen[1,4,5] and Heidi Taipale[1,2,4]

[1]Niuvanniemi Hospital, Kuopio, Finland; [2]University of Eastern Finland, Kuopio, Finland; [3]Monash Univeristy, Parkville, Australia; [4]Karolinska Institutet, Stockholm, Sweden; [5]Center for Psychiatry Research, Stockholm City Council, Stockholm, Sweden

Background: Information regarding the real-world effectiveness of mood stabilizer (MS) use in persons with schizophrenia is important, since these medications are often used as adjunctive medication in this population.

Objectives: The objective of this study was to investigate the real-world effectiveness of mood stabilizer use in persons with schizophrenia.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: This retrospective cohort study used combined data from nationwide Finnish registers. The study cohort included all persons treated in inpatient care due to schizophrenia during 1972-2014 in Finland (N=61,889). Drug purchase data were obtained from the national Prescription register, and then modelled with PRE2DUP method. The follow-up period covered the years 1996-2017. Mood stabilizers in this study included carbamazepine, valproic acid, lamotrigine and lithium. Main outcome was psychiatric rehospitalization, defined as a hospitalization with psychosis (ICD-10: F20-29) as the main diagnosis. Within-individual design was used to compare the risk of outcome between time periods of MS use and non-use within the same person. Stratified COX regression analyses were utilized in calculating hazard ratios (HR) with 95% confidence intervals (CIs).

Results: Mean age of the study population was 46.2 years (SD 16.0) and 50.3% were males. During the follow-up (maximum of 22 years, mean 14.0 [SD 7.3]) 28.1% (N=17,370) of the study cohort used mood stabilizers, valproic acid being the most often used MS (16.9%, N=10,483). Risk of psychiatric re-hospitalization was lower during MS use than non-use (incidence rate 3.04 events per 10 person-years, aHR 0.88, 95% CI 0.86-0.90). Use of lithium (HR 0.84, 95% CI 0.81-0.88), valproic acid (HR 0.87, 95% CI 0.85-0.90), and lamotrigine (HR 0.90, 95% CI 0.85-0.95) were associated with lower risk of psychiatric rehospitalization compared with non-use, whereas carbamazepine use was not (HR 0.97, 95% CI 0.92-1.03).

Conclusions: Mood stabilizers are relatively often used as adjunctive treatments in schizophrenia and their use was associated with a decreased risk of psychiatric rehospitalization, which is a marker of relapse in schizophrenia.

4238 | Midodrine for prevention of intradialytic hypotension in high risk patients at a tertiary referral hospital: A retrospective study

Saja Alhabardi[1], Maryam Aldhaefi[2], Mohammed Alessa[3], Maha Alammari[3], Yousef Alrajhi[3] and Rami Bustami[2]

[1]Saudi Food and Drug Authority, Riyadh, Saudi Arabia; [2]College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [3]King Abdulaziz Medical City, Pharmaceutical Care Services, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

Background: Intradialytic hypotension (IDH) is the most common complication that is well recognized during hemodialysis. Midodrine, an oral α-1 adrenergic agonist, is the widely utilized approach to prevent IDH. However, more clinical studies are needed to validate its efficacy in prevention of IDH in high risk hemodialysis patients.

Objectives: The primary outcome measures included the identification of treatment failure, frequency of recurrent IDH, and identify the appropriate dose and frequency of midodrine.

Methods: A retrospective cohort study was approved by IRB in January 2018. The data was retrieved from the BESTCare® hospital information system. This included all medical records for adult patients with end-stage renal disease on hemodialysis, who were placed on midodrine for over a year. The variables that related to midodrine dose, frequency, and IDH risk factors were recorded for each hemodialysis session. IDH was defined as a decline in SBP by ≥20 mmHg or a decline in MAP by ≥10 mmHg. Recurrent IDH was labeled if the patient had at least three episodes of IDH.

Results: From a total of 68 screened patients' charts, 45 patients were included in the final analysis. Among them, 40.4% had an IDH that required additional interventions to restore the SBP and MAP. IDH was significant in 23 (68%) patients who had hypoalbuminemia. Moreover, recurrent IDH occurred in 16 hemodialysis patients (35.6%). The efficacy was similar among all doses of midodrine that were administered (P> 0.05). However, treatment failure and recurrent IDH were significant in the hemodialysis patients were received Midodrine only three days per week (57%, P= 0.02; 36%, P= 0.04) respectively.

Conclusions: Midodrine appears to be effective in maintaining SBP, DBP, and MAP during the hemodialysis session in patients with high IDH risk. A Long-term follow-up with presence of comparative group would be useful to evaluate the magnitude of efficacy of Midodrine in hemodialysis patients with high risk IDH.

4289 | Lithium use in patients with bipolar disorder in inpatient care and readmission: A prospective cohort study in the central Denmark region in 2015-2018

Kazi Ishtiak-Ahmed, Louise Meyer, Christiane Gasse and Søren Dinesen Østergaard

Aarhus University Hospital Psychiatry, Aarhus N, Denmark

Background: Despite lithium (Li) being considered the first line of treatment for bipolar disorder (BD), the use of Li declined in patients with BP in Denmark in 1995-2012. However, the use of Li in Danish psychiatric hospitals is still unknown.

Objectives: As part of quality assurance assessment in the Central Denmark Region (CDR), we investigated the trend of Li use among patients with BD during their 1st psychiatric admission spell (FAS). We further investigated the association between Li use and the risk of subsequent readmission (RA). Moreover, as patients' characteristics could affect the RA, we explored trajectories of Li administration across all admission spells to identify vulnerable subgroups.

Methods: We used hospital electronic healthcare records of all psychiatric hospitals/departments in CDR. We carried out a cohort study of all patients aged ≥18 with a 1st inpatient care contact (index date) due to manic episodes (ICD-10: F30) or bipolar affective disorder (F31) in 2015-18 (N=782, 56% female, mean age 46.4 years). We followed patients from the date of discharge until the 1st RA or the end of 2018, whichever came first. We identified administrations of Li (ATC code N05AN01) during the FAS in all patients with BD. We used Cox regression analysis adjusting for age, sex, hospital site, calendar year, BD sub-types at 1st contact, number of prior contacts and diagnoses within 365 days before the index date. Group-based trajectory modeling was used to explore hidden clusters in the trajectories of Li administration.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: A total of 136 (17.4%) patients were treated with Li in the FAS. Patients with and without Li treatment did not differ on baseline characteristics. The percentage of patients with Li therapy at FAS was 20.5%, 15.7%, 15.7%, and 15.8% in 2015-18, respectively. The proportion of 1st RA was slightly lower in patients with Li administrations than in patients without (39.7% vs. 41.0%). The time to 1st RA was longer in patients with Li administration than in patients without (mean: 305 vs. 222 days). The crude and adjusted hazard rate of RA was 0.89, 95% CI: 0.66-1.19 and 0.90 (0.66-1.21), respectively. Because of the low use of Li, the trajectory analyses did not yield any meaningful hidden clusters.

Conclusions: This is the first study looking at the current trend of Li use in patients with BD in inpatient care in Denmark and in relation to RA. The use of Li remained relatively stable (but low) in inpatients patients with BD in recent years, even though time to readmission was much delayed in patients using Li.

4333 | Use of thiazolidinediones and glucagon-like peptide-1 receptor agonists and the risk of non-alcoholic fatty liver disease

Johanna H.M. Driessen[1], Judith van Dalem[1], Andrea M. Burden[2], Coen D.A. Stehouwer[1], Olaf H. Klungel[3], Frank de Vries[1] and Martijn C.G.J. Brouwers[1]

[1]*Maastricht University Medical Centre, Maastricht, Netherlands;*
[2]*Institute of Pharmaceutical Sciences, ETH Zurich, Zurich, Switzerland;*
[3]*Utrecht Institute of Pharmaceutical Sciences, Utrecht, Netherlands*

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Western countries. Thiazolidinediones (TZDs) and glucagon-like peptide 1 (GLP-1) receptor agonists, both drugs used in the treatment of type 2 diabetes, have demonstrated to have beneficial effects on liver histology and are therefore potential pharmacological treatment options for patients with NAFLD.

Objectives: To assess the risk of NAFLD associated with current use of TZDs compared with current use of sulphonylureas, and between GLP-1 receptor agonists compared with current use of insulin, respectively

Methods: A population-based cohort study using data from the UK Clinical Practice Research Datalink (CPRD) GOLD was conducted. All patients with at least one oral glucose lowering agent prescription (2007-2018) and aged ≥18 years were included. The date of the first glucose lowering agent prescription determined the index date. Patients were followed from the index date until the date of death, end of study, disenrollment or NAFLD, whichever came first. Follow-up time was divided into fixed intervals of 90 days. Based on the time since the most recent oral glucose lowering drug prescription an interval was classified as current (≤ 90 days) use or past (>90 days) use.

Time-dependent Cox regression models were used to compare the risk of NAFLD between current use of TZDs and current use of sulphonylureas and to compare the risk between current use of GLP1 receptor agonists and current use of insulin. Analyses were adjusted for life-style factors, comorbidities and concomitant drug use. Two sensitivity analyses were performed. First, a propensity score matched analysis was applied to estimate the risk of NAFLD comparing use of TZDs with use of sulphonylureas. Second, the risk of NAFLD was estimated using Cox regression models comparing current GLP1 receptor agonist use to current sulphonylurea use.

Results: In total 207,367 patients (mean age 61 years, 45% women, mean follow-up 5.1 years) were included. Current use of TZDs was associated with an almost 70% reduced risk of NAFLD as compared to current sulphonylurea use (adj. HR: 0.32, 95% CI 0.20-0.52). While no difference in risk of NAFLD was observed comparing current GLP-1 receptor agonist use with current insulin use (adj. HR: 1.19, 95% CI 0.88-1.59). Results remained consistent in sensitivity analyses.

Conclusions: Results of our study endorse the use of TZDs for selected patients with NAFLD and type 2 diabetes. However, our study does not support previous findings regarding the beneficial effect of GLP-1 receptor agonists on NAFLD.

4337 | Impact of multiple cardiovascular medications on mortality after an incidence of ischaemic stroke or transient ischaemic attack: A 10-year cohort study

Tiantian Ma, Ian C.K. Wong, Cate Whittlesea, Zixuan Wang, Kenneth K.C. Man, Wallis Lau, Ruth Brauer and Li Wei
UCL School of Pharmacy, London, United Kingdom

Background: Combination therapy is common in patients with ischaemic stroke or transient ischaemic attack (TIA), but the evidence is limited on its long-term effects on mortality.

Objectives: To assess the effect of multiple cardiovascular drugs on long-term survival in patients following the first diagnosis of ischaemic stroke or TIA.

Methods: A cohort study was conducted using The Health Improvement Network database from 2007 to 2016. The study included 45,072 patients aged 45 and above years with their first record of stroke or TIA. Cardiovascular drugs were categorised into groups according to the number of individual cardiovascular medicines and the number of classes of cardiovascular drugs during the first 90 days. We estimated the risk of all-cause mortality using a marginal structural model to calculate hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: During a mean follow-up of 3.7 years, there were 7,794 deaths. There were 714 patients where no drugs were prescribed, 4,434 patients with one drug, 9,646 with two drugs, 11,014 with three drugs, 9,271 with four drugs, 5,789 with five drugs and 4,204 patients with ≥ 6 drugs prescribed. The mean age was 71.8 (SD:11.6) years old. Compared with patients who were prescribed one drug only, the risk ratios of mortality (95% CIs) were 1.78 (1.61-1.97) for no drug, 0.76 (0.69-0.83) for two drugs, 0.63 (0.58-0.69) for three drugs, 0.58 (0.53-0.64) for four drugs, 0.59 (0.53-0.66) for five drugs and 0.62 (0.55-0.70) for ≥ 6 drugs. Similar results were found among the combination of different drug classes.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: The results suggest multiple drug treatment, especially combinations of four or five cardiovascular drugs can improve long-term survival after stroke of TIA.

4340 | Rationale, design and feasibility of conducting a real-world study of outcomes in patients with a history of MI receiving extended DAPT with ticagrelor 60 mg

Eva Lesén[1], Chris Hewitt[1], Evangelos Giannitsis[2], Jonatan Hedberg[1], Tomas Jernberg[3], Dimitra Lambrelli[4], Daniel Lindholm[1], Aldo P. Maggioni[5], Jennie Medin[1], Anna Schultze[4], Albert Ariza Solé[6], Robert F. Storey[7], Karolina Andersson Sundell[1], Jurrien ten Berg[8], Narinder Bhalla[1] and Marc Bonaca[9,10]

[1]AstraZeneca, Gothenburg, Sweden; [2]University of Heidelberg, Heidelberg, Germany; [3]Karolinska Institute, Solna, Sweden; [4]Evidera, London, United Kingdom; [5]ANMCO Research Center, Florence, Italy; [6]Hospital Universitari de Bellvitge, Barcelona, Spain; [7]University of Sheffield, Sheffield, United Kingdom; [8]St Antonius Hospital, Nieuwegein, Netherlands; [9]University of Colorado Anschutz, Aurora, CO; [10]CPC Clinical Research and CPC Community Health, Aurora, CO

Background: Comparative effectiveness research (CER) using real-world data is increasingly recognized to complement RCTs as a valuable support for health care decision making. However, concerns about bias and confounding in CER have been raised. A stepwise approach of understanding data and its feasibility for CER can help to avoid biased analyses.

Objectives: To assess the feasibility of 1) describing bleeding and cardiovascular (CV) outcomes in clinical practice and 2) conducting comparative analyses of dual antiplatelet therapy (DAPT) with ticagrelor 60 mg vs. low-dose aspirin alone in patients with a history of MI.

Methods: Our assessment followed the guidelines for CER according to Good ReseArch for Comparative Effectiveness (GRACE) principles. An estimated 15,000 patient-years on treatment with ticagrelor 60 mg are needed to detect an HR of 0.85 in the rate of CV death, MI or stroke vs. aspirin alone with 85% power. Seven relevant databases in Europe and US were evaluated with respect to their characteristics, population coverage and availability of data on key variables, to assess if sufficient statistical power could be achieved for well-balanced comparative analyses of bleeding and CV outcomes.

Results: The characteristics of the targeted databases will be presented along with the assumptions for the power calculations, estimated patient numbers and how requirements for CER are fulfilled. Differences between the 7 databases were identified. Some lacked complete information on all variables assumed to be needed to adequately adjust for treatment allocation bias and baseline confounding in CER, leading to potential residual confounding. Key methodological challenges for CER were identified, such as determining aspirin use, which is not captured in all databases, and defining a relevant index date for patients with continuous aspirin monotherapy. Due to these limitations, it was determined that CER could not be robustly performed and instead, a multi-national observational study is being conducted to describe rates of bleeding and CV outcomes in patients with ticagrelor 60 mg. Estimates derived from each database will be combined via meta-analysis.

Conclusions: An extensive feasibility assessment is an important step prior to conducting CER. Describing real-world bleeding and CV outcomes in patients with ticagrelor 60 mg can further support decision-making on long-term antithrombotic treatments.

4342 | Differences between randomized clinical trial participants and real-world empagliflozin users and the changes in their glycated hemoglobin levels

Nicolai E. Munk[1], Jakob S. Knudsen[1], Anton Pottegård[2], Daniel R. Witte[3,4,5] and Reimar W. Thomsen[1]

[1]Aarhus University Hospital, Aarhus, Denmark; [2]University of Southern Denmark, Odense, Denmark; [3]Aarhus University, Aarhus, Denmark; [4]Steno Diabetes Center Aarhus, Aarhus, Denmark; [5]Danish Diabetes Academy, Odense, Denmark

Background: Use of the sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin has increased substantially since 2015. Little is known about characteristics of real-world patients who use empagliflozin or about empagliflozin's effectiveness in reducing glycated hemoglobin (HbA1c) levels in routine clinical care.

Objectives: To characterize real-world initiators of empagliflozin, to examine the proportion of initiators who would have been eligible for participation in phase 3 randomized clinical trials (RCTs) of empagliflozin, and to assess changes in HbA1c levels after empagliflozin initiation.

Methods: This cross-sectional study used linked population-based medical databases containing complete information on redeemed prescriptions, laboratory tests, and diagnoses for all residents in Northern Denmark. A total of 7034 residents of Denmark who filled a first-time empagliflozin prescription from January 2014 to December 2018 were included. Main outcomes were proportion of real-world users ineligible for RCT inclusion and absolute reduction in HbA1c level 6 months after empagliflozin initiation.

Results: Of 7034 first-time empagliflozin initiators (median [interquartile range] age, 61.50 [53.30-69.38] years; 4475 [63.6%] men), 3878 (55.1%) would have been ineligible for phase 3 RCT participation; frequent reasons were concurrent use of specific glucose-lowering drugs (1955 initiators [27.8%]), baseline HbA1c level outside the eligibility range (1772 [25.2%]), or presence of comorbidities (1067 initiators [15.3%]). Initiation of empagliflozin was associated with a mean HbA1c reduction of −0.91% (95%CI, −0.94% to −0.87%) after 6 months, similar to phase 3 RCT results. Real-world empagliflozin initiators who would have been eligible for RCT participation experienced slightly lower mean HbA1c reductions (−0.78%; 95%CI, −0.82% to −0.74%) compared with patients who would have been ineligible (−1.01%; 95%CI, −1.07% to −0.95%). Ineligible initiators had higher median (interquartile range) baseline HbA1c values than eligible initiators (8.5% [7.4% to 10.1%] vs 8.2% [7.6% to 9.8%]).

Conclusions: In this cross-sectional study, more than half of empagliflozin initiators exhibited clinical characteristics that would

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

have led to ineligibility for the RCTs leading to the drug's approval. While the findings suggest that the efficacy of empagliflozin in reducing HbA1c levels translates into real-world effectiveness, further studies should examine clinical outcome effectiveness and drug safety in routine clinical care.

4457 | Comparative safety of JAK inhibitors in patients with rheumatoid arthritis: A network meta-analysis of clinical trials

Carlos Alves[1,2], Diogo Mendes[2], Ana Penedones[1,2] and Francisco Batel Marques[1,2]

[1]School of Pharmacy, University of Coimbra, Coimbra, Portugal; [2]AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal

Background: Janus kinases (JAKs) inhibitors act in an intracellular signalling pathway activated by pro-inflammatory cytokines involved in the pathogenesis of rheumatoid arthritis. Although JAK inhibitors are effective in reducing the symptoms of rheumatoid arthritis, they have been associated with premature discontinuation of the treatment due to adverse events.

Objectives: This study is aimed at assessing the safety of JAK inhibitors in patients with rheumatoid arthritis.

Methods: A literature search was conducted in order to identify randomized controlled trials (RCTs) evaluating the efficacy and safety of JAK inhibitors in patients with rheumatoid arthritis. The outcomes assessed were serious adverse events and adverse events leading to treatment discontinuation. Network meta-analyses were performed using STATA 13.0.. For each outcome, treatments were ranked according to the probability of being the safest (best) alternative using the surface under the cumulative ranking curve (SUCRA).

Results: Thirty-one RCTs met the inclusion criteria. No differences were observed between the treatments regarding the risk of serious adverse events. The ranking probability based on the SUCRA suggests that adalimumab is probably the safest treatment (SUCRA=0.811), followed by methotrexate (SUCRA=0.666) and baricitinib (SUCRA=0.657) [SUCRAs for remaining drugs; placebo=0.569; peficitinib=0.544; tofacitinib=0.542; filgotinib=0.310; upadacinitib=0.279; etanercept= 0.123]. Upadacitinib increases the risk of adverse events leading to discontinuation compared to placebo (1.43; 95%CI 1.16 - 1.75), to baricitinib (1.54; 95%CI 1.04 - 2.30) and to tofacitinib (1.36; 95%CI 1.05 to 1.74). The ranking probability based on the SUCRA suggests that baricitinib is probably the safest treatment (SUCRA=0.831), followed by placebo (SUCRA=0.791) and tofacitinib (SUCRA=0.656) [SUCRAs for remaining drugs; peficitinib=0.559; filgotinib=0.463; etanercept=0.411; adalimumab = 0.391; methotrexate=0.305; upadacitinib=0.092].

Conclusions: In patients with rheumatoid arthritis, JAK inhibitors were not associated with a significant risk of serious adverse events. However, upadacitinib slightly increases the risk of adverse events leading to treatment discontinuation when compared to baricitinib and tofacitinib.

4461 | Comparative risk of infections among JAK inhibitors used in rheumatoid arthritis: A network meta-analysis of clinical trials

Carlos Alves[1,2], Diogo Mendes[2], Ana Penedones[1,2] and Francisco Batel Marques[1,2]

[1]School of Pharmacy, University of Coimbra, Coimbra, Portugal; [2]AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal

Background: The Janus kinases (JAKs) are cytoplasmic tyrosine kinases associated with membrane cytokine receptors that mediate signalling of multiple cytokines and growth factors, contributing to the pathogenesis of multiple autoimmune disorders. JAK inhibitors are a new class of targeted therapies that improve the symptoms of rheumatoid arthritis, but have been with an increased risk of infections.

Objectives: This study is aimed at assessing the risk of tuberculosis and the risk of herpes zoster infection associated with JAK inhibitors in patients with rheumatoid arthritis.

Methods: A literature search was conducted in order to identify randomized controlled trials (RCTs) evaluating the efficacy and safety of JAK inhibitors in patients with rheumatoid arthritis. The outcomes assessed were the risk of tuberculosis and the risk of herpes zoster infection. Network meta-analyses were performed using STATA 13.0.. For each outcome, treatments were ranked according to the probability of being the safest (best) alternative using the surface under the cumulative ranking curve (SUCRA).

Results: Thirty-one RCTs met the inclusion criteria. Filgotinib has a reduced risk of herpes zoster when compared to adalimumab (0.24; 95%CI 0.06 - 0.89), etanercept (0.19; 95%CI 0.05 - 0.75), peficitinib (0.15; 95%CI 0.03 - 0.80) and tofacitinib (0.25, 95%CI 0.08 - 0.81). The ranking probability based on the SUCRA suggests that filgotinib is probably the safest treatment (SUCRA=0.945), followed by placebo (SUCRA=0.715) and baricitinib (SUCRA=0.619) [SUCRAs for remaining drugs; upadacitinib=0.481; tofacitinib=0.437; methotrexate=0.424; adalimumab=0.400; etanercept=0.296; peficitinib=0.184]. No differences were observed between the treatments regarding the risk of tuberculosis. The ranking probability based on the SUCRA suggests that baricitinib is probably the safest treatment (SUCRA=0.811), followed by methotrexate (SUCRA=0.571) and upadacitinib (SUCRA=0.446) [SUCRAs for remaining drugs; placebo=0.441; tofacitinib=0.437; filgotinib=0.437; adalimumab=0.356].

Conclusions: The results suggest that filgotinib may have the lower the risk of herpes zoster infection among the drug evaluated. Evidence also suggests that the risk of tuberculosis among JAK inhibitors may be comparable.

4498 | Ascertainment of schizophrenia relapse and impact on the comparative effectiveness of oral versus injectable antipsychotics in the real-world setting: A systematic review

Tiffany Cristarella[1,2], Mareva Faure[2], Genaro Castillon[2], Jean-François Nepveu[1,2] and Yola Moride[1,2,3]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada; [2]YOLARX Consultants, Montreal, QC, Canada; [3]Center for Pharmacoepidemiology and Treatment Science, Rutgers, The State University of New Jersey, New Brunswick, NJ

Background: Relapse of schizophrenia symptoms is frequent, with non-adherence to oral antipsychotics (OAPs) being a major contributor. Long-acting injectables (LAIs) are considered an important treatment option in improving adherence and thus, preventing relapse. Comparative effectiveness data on OAPs and LAIs in the real-world (RW) setting remain conflicting. It is hypothesized that absence of a universally accepted definition for schizophrenia relapse is a source of heterogeneity, which hampers comparability between studies.

Objectives: To identify criteria used to define schizophrenia relapse in comparative effectiveness studies of OAPs and LAIs, and to evaluate the impact of such definitions on comparative effectiveness estimates.

Methods: A systematic review of comparative effectiveness studies in the RW setting was conducted using MEDLINE and Embase between 2013 and 2019. Searches of the grey literature were conducted to identify additional sources. Studies that compared effectiveness of OAPs and LAIs in schizophrenia patients and, that reported relapse-related outcomes were independently screened by two assessors, with conflicts resolved by a third.

Results: Of the 543 sources identified, 52 individual studies and 17 reviews were found. Four main schizophrenia relapse definitions were identified: i) schizophrenia-related hospitalization (specific to symptoms of schizophrenia), ii) psychiatric hospitalization (overall psychotic, mental/behavioural disorders), iii) hospitalization associated with recurrence of significant psychotic symptoms, dangerous/violent behaviour, deteriorated functioning, or inadequate response to outpatient treatment, and, iv) schizophrenia-related emergency room (ER) visit. However, in the majority of studies (60%), there was no operational definition of relapse. Inconsistent results depending on the definition of relapse were found, where LAIs were superior to OAPs in reducing the risk of schizophrenia-related hospitalization, while no difference was observed in reducing the risk of schizophrenia-related ER visits.

Conclusions: This systematic review confirms that there is no universal definition of schizophrenia relapse in RW studies, which leads to heterogeneity in comparative effectiveness estimates. The quantitative impact of relapse definitions on comparative effectiveness estimates will be presented, using a meta-regression analysis.

4506 | Use of glycolysis enhancing medications is associated with a decreased risk of developing Parkinson's disease

Jacob E. Simmering[1], Nandakumar Narayanan[1], Lei Liu[2], Michael J. Welsh[1] and Anton Pottegård[3]

[1]Carver College of Medicine University of Iowa, Iowa City, IA; [2]Capital Medical University, Beijing, China; [3]University of Southern Denmark, Odense, Denmark

Background: Impaired energy metabolism has been implicated in the pathogenesis of Parkinson's disease (PD). Prior work has suggested the commonly used α1-adrenergic receptor antagonists terazosin (Tz), alfuzosin (Az), and doxazosin (Dz) bind to phosphoglycerate kinase 1, a key enzyme in metabolism, and increase levels of ATP. Animal models of PD suggest that use of Tz/Dz/Az increases ATP levels in the brain and dopamine neurons, thus slowing or preventing development PD.

Objectives: To assess the association between use of Tz/Dz/Az and risk of PD.

Methods: We conducted two independent cohort studies using the Truven Marketscan Database in the US and Danish nationwide health registries. We identified new users of Tz/Dz/Az as well as new users of tamsulosin. Tamsulosin is a medication with a similar indication and use but is structurally unrelated to Tz/Dz/Az and does not promote metabolism, making it an attractive active comparator. We propensity score matched PD-free new users of Tz/Dz/Az and tamsulosin accounting for age, comorbidities, healthcare utilization, and, in the case of Truven, enrollment duration. Followup started 365 days after medication start and continued until the individual developed PD or was censored. Development of PD was defined as starting medications for PD or having a diagnosis of PD. Risk of PD was assessed using Cox proportional hazards regression. A Cox model with time-varying hazard ratios based on the cumulative dose in daily defined doses (DDD) was estimated to determine if a dose response pattern was present.

Results: Overall, the hazard of developing PD for Danish users of Tz/Dz/Az was 11% lower (95% CI: 2% to 19%) compared to users of tamsulosin while the reduction was 25% (95% CI: 18% to 31%) in the US database. A dose response pattern was observed in both databases: short use (1 to 499 DDD) had a HR of 0.94 (95% CI: 0.83 to 1.06) in the Danish database and 0.87 (95% CI: 0.77 to 0.97) in Truven while the longest term use (over 2,000 DDD) had a HR of 0.79 (95% CI: 0.65 to 0.95) and 0.46 (95% CI: 0.34 to 0.60) in the respective databases.

Conclusions: Users of Tz/Dz/Az have lower hazard of developing PD than users of an active comparator, tamsulosin. This result is observed in two different data sources from two different countries and exhibits a dose response relationship with longer duration of therapy having a greater protective effect.

4517 | Hypothetical intervention of sodium-glucose cotransporter-2 inhibitors on renal outcome in type 2 diabetes

Masato Takeuchi and Koji Kawakami

Kyoto University, Kyoto, Japan

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are the latest class of diabetic medications. Although we recently demonstrated that SGLT2i exert superior renoprotective effects to other classes of diabetic medications in the real-world context, there were two limitations in our analysis; the observation period was short (median: 17 months) and we did not fully account for the time-varying nature of drug regimen.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To estimate the effect of SGLT2i exposure on renal outcome using a parametric g-formula.

Methods: We used the RWD database, an electronic database of healthcare records in Japan, comprising data from approximately 20 million patients from approximately 160 medical institutions. Prevalent users of diabetic medications in April, 2014 were eligible for the study, but patients with type 1 diabetes, <19 years of age, or with end-stage renal disease at baseline (defined by estimated glomerular filtration rate [eGFR]< 30 mL/1.73 m2/min) were excluded. The primary endpoint was the composite of renal deterioration (>40% decline in eGFR) and the development of eGFR<30 mL/1.73 m2/min. We estimated the risk of the occurrence of the composite renal endpoint for the hypothetical SGLT2i exposure scenario of "always treat". The computation used the g-formula framework, with R statistical environment. Age and sex were used as time-fixed covariates, and glycemic control and exposure histories to other diabetic medication were adjusted as time-varying covariates.

Results: Data from 9449 patients were analyzed, of whom 1031 patients were exposed at least once to SGLT2i. The median age of this cohort was 70 years, and male patients accounted for 61%. In the "natural course" scenario, 16.7 % of patients reached the primary endpoint at 56 months, almost identical to the observed data (16.7%); this ensures that the chance of our model misspecification was limited. In contrast, the composite endpoint was expected to occur in 7.5% in "always treat" scenario. The risk difference between two scenarios was 9.3%, with 95% confidence interval of 3.3-13.6%.

Conclusions: In comparison with the "natural course" scenario or the observed data, the hypothetical intervention of SGLT2i was associated with a risk reduction of the renal endpoint by 9.3% at ~5 years of drug therapy.

4522 | Comparative effectiveness of amoxicillin-clavulanate versus metronidazole and a fluoroquinolone on hospital admission risk among outpatient diverticulitis patients in the United States, 2000-2005

Charles E. Gaber, Anne F. Peery, Jessie K. Edwards, Jennifer L. Lund, Til Stürmer, Sharon Peacock-Hinton, Robert S. Sandler and Alan C. Kinlaw

University of North Carolina-Chapel Hill, Chapel Hill, NC

Background: Acute diverticulitis is most commonly treated in the outpatient setting with either amoxicillin-clavulanate or a combination of metronidazole and a fluoroquinolone. Despite being commonly prescribed for diverticulitis, the effect of these antibiotics on long-term outcomes remains uncertain.

Objectives: To determine hospital admission risk in diverticulitis patients treated with amoxicillin-clavulanate versus a combination of metronidazole and a fluoroquinolone.

Methods: We used administrative claims data from Medicare (2006-2015) and IBM Watson Health MarketScan (2000-2015) to conduct active-comparator, new-user cohort studies in patients with incident outpatient diverticulitis who initiated amoxicillin-clavulanate versus a combination of metronidazole and a fluoroquinolone. We estimated 1-year risk of hospital admission for diverticulitis with 95% confidence intervals (CI), using the Aalen-Johansen estimator to account for the competing risk of death (in the Medicare cohort). We implemented inverse probability of treatment weights to control for confounding by baseline variables.

Results: The Medicare cohort included 19,787 individuals with diverticulitis in the outpatient setting who filled prescriptions for either amoxicillin-clavulanate (n=2,645) or metronidazole and a fluoroquinolone (n=17,142). The one-year risk of admission amongst amoxicillin-clavulanate initiators was 2.7% (95% CI: 2.0, 3.4), compared to 3.3% (95% CI: 3.1, 3.6) in metronidazole + fluoroquinolone initiators (adjusted risk difference = -0.7%, 95%: -1.4, 0.1). The MarketScan cohort included 89,824 individuals with diverticulitis in the outpatient setting who filled prescriptions for either amoxicillin-clavulanate (n=9,073) or metronidazole and a fluoroquinolone (n=80,751). The one-year risk of inpatient admission amongst amoxicillin-clavulanate initiators was 3.3% (95% CI: 2.9, 3.7), compared to 3.9% (95% CI: 3.8, 4.0) in metronidazole + fluoroquinolone initiators (adjusted risk difference = -0.6%, 95%: -1.0, -0.2).

Conclusions: In this analysis of administrative claims from Medicare and commercial plans, we found that amoxicillin-clavulanate was associated with decreased risk of hospital admission compared to metronidazole and a fluoroquinolone. Further research will assess additional effectiveness endpoints, the regimens' comparative safety, and treatment effect heterogeneity by immunosuppression status.

4546 | Persistence to bone targeting agents in patients with bone metastases from solid tumors in Hong Kong, Korea, and Taiwan

Chin-Yao Shen[1], Philip Chun-Ming Au[2], Yeon-Hee Baek[3], Ching-Lung Cheung[2], Wei-Pang Chung[4], Seasea Nan Gao[5], Yea-Huei Kao Yang[1], Nora Kleinman[5], Ju Hwan Kim[3], Jeff Lange[6], Tzu-Chi Liao[1], Tzu-Chieh Lin[6], Ju-Young Shin[3], Chor-Wing Sing[2], Ian Chi Kei Wong[2] and Edward Chia-Cheng Lai[1,7]

[1]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong; [3]School of Pharmacy, SungKyunKwan University, Suwon, Republic of Korea; [4]Division of Hemato-Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [5]Amgen Asia Holdings Limited, Hong Kong, Hong Kong; [6]Amgen Inc., Thousand Oaks, CA; [7]Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan

Background: Bone targeting agents (BTAs) are used to prevent skeletal-related events in patients with bone metastases from solid tumors. Persistence is a construct expected to correlate with expectations of therapy benefits, risks, and tolerability.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To compare persistence to denosumab (D), zoledronic acid (Z), and pamidronate (P) among patients with bone metastasis from solid tumors.

Methods: This population-based retrospective cohort study included patients from electronic health records in Hong Kong (HK, 2013-2017) and national claims databases in Korea (KR, 2012-2016) and Taiwan (TW, 2013-2017). Inclusion criteria were adult patients with breast, lung, or prostate cancer; and initiation of BTA after metastases diagnosis. The primary outcome was persistence by BTA type, from treatment initiation to interruption (switching or discontinuation, defined as no treatment within 90 days). Patients were censored at death or study end. Risk of treatment interruption by BTA type was compared with Cox-proportional hazard models adjusted for age, sex and other clinical covariates.

Results: The study included 883 (D:458, Z:357, P:68) patients from HK, 4800 (Z:4068, P:732) from KR, and 5127 (D:3440, Z:1210, P:477) from TW. Denosumab was unavailable in KR during the study period. The proportion of lung, breast and prostate cancer were similar between HK (39%, 43%, 18%) and TW (36%, 42%, 22%) while KR differed (8%, 73%, 19%). For all tumor types in HK, persistence was longer in denosumab users (median, 219 days; Interquartile Range (IQR), 132-451 days) and zoledronic acid users (163 days; IQR, 90-236 days) relative to pamidronate users (90 days; IQR, 90-124 days). For all tumor types in TW, persistence was longer in denosumab users and zoledronic acid users relative to pamidronate users (D: 188 days; 111-342 days, Z: 173 days; 90-334 days, P: 111 days; 90-169 days). For all tumor types in KR, persistence was longer in zoledronic acid users relative to pamidronate users (Z: 240 days; 145-409 days and P: 124 days; 90-208 days). Relative to denosumab users, treatment interruption was more likely in both pamidronate users (adjusted hazard ratio (aHR) 3.1 [95% CI 1.8-5.1] in HK and 3.1 [95% CI 2.6-3.6] in TW) and zoledronic acid users (aHR 2.8 [95% CI 2.2-3.6] in HK and 2.3 [95% CI 2.1-2.6] in TW). Results were consistent for analyses stratified by tumor type.

Conclusions: Patients were persistent to denosumab longer than to other BTAs, although there was a wide range of persistence to BTAs. Clinical significance of this variation in persistence in real-world clinical practice warrants subsequent study.

4576 | Genetic alternations correlated with resistant to abiraterone and enzalutamide in metastatic prostate cancer

Yu-Hsuan Joni Shao[1], Tzu-Hung Hsiao[2] and Yen-Chuan Ou[3]
[1]Taipei Medical University, Taipei, Taiwan; [2]Taichung Veterans General Hospital, Taichuang, Taiwan; [3]Tung's Taichung MetroHarbor Hospital, Taichung, Taiwan

Background: Heterogeneity in the genomic landscape of metastatic castration resistant prostate cancer (mCRPC) has become apparent through several comprehensive profiling studies, but little is known about the impact of this heterogeneity on clinical outcome especially following new generation androgen receptor directed therapy (ARDT), abiraterone or enzalutamide.

Objectives: To examine the association of germline and somatic mutations with disease progression in mCRPC patients treated with new generation of ARDT.

Methods: A prospective cohort including patients with mCRPC were enrolled between 2016 and 2019 in three medical centers in Taiwan. A total of 84 patients received ARDT were selected. Blood was collected before therapies—enzalutamide (n = 36) or abiraterone (n = 48). We performed whole exome sequencing on 84 blood derived DNA samples from patients as well as next-generation sequencing to analyze cfDNA using QIAseq™ Targeted DNA Panels and Human Comprehensive Cancer Panel. Cancer stage, clinical characteristics and prostate specific antigen (PSA) were collected through electronic medical records before treatment and during follow-up. Primary end points were prostate-specific antigen response, and prostate cancer antigen progression-free survival (PFS).

Results: The median PFS time was 28.9 weeks (Interquartile range 48.4 weeks) in our population. Germline DNA repair genes mutations were not significantly associated with PFS following treatments. The adjusted hazard ratio (aHR) was 0.87 (95% confidence interval [CI] 0.52-1.45) in patients who did not carry any germline DNA repair genes mutations comparing with those with mutations after adjusting for baseline PSA and drug type. In contrast, comparing to patients carried somatic mutations, those without somatic mutations are associated with an improved progression free survival with an aHR of 0.44 (95% CI:0.21-0.94) after adjusting for baseline PSA.

Conclusions: This analysis integrating mCRPC genomics with histology and clinical outcomes identifies somatic genomic alteration as a potent predictor of poor outcome, and with great potential to understand therapeutic resistant of mCRPC.

4602 | Non-vitamin K antagonist oral anticoagulant and proton-pump inhibitor cotreatment and the association with upper gastrointestinal bleeds in patients with atrial fibrillation: A multi-database cohort study

Joris Komen[1], Anton Pottegård[2], Tomas Forslund[3], Aukje Mantel-Teeuwisse[1], Björn Wettermark[4], Maja Hellfritzsch[2], Jesper Hallas[2], Lisa Smits[5], Ron Herings[5], Paul Hjemdahl[3] and Olaf Klungel[1]
[1]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [2]Department of Public Health, University of Southern Denmark, Odense, Denmark; [3]Clinical Epidemiology/Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden; [4]Uppsala University, Uppsala, Sweden; [5]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands

Background: Non-vitamin K antagonist oral anticoagulants (NOAC) reduce the risk of stroke in patients with atrial fibrillation (AF), but increase the risk for upper gastrointestinal bleeding (UGIB). Proton pump inhibitors (PPIs) may reduce this risk, but guidelines are inconclusive whether to recommend PPI cotreatment in NOAC treated patients.

Objectives: To assess the association between PPI use and UGIB in AF patients treated with a NOAC.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: We used a common data model to select all AF patients initiated on a NOAC between April 2011 and July 2018 in the Swedish Stockholm Healthcare database, the Danish National registries, and the Dutch PHARMO database. Patients were followed until they stopped NOAC treatment, moved out of the region/database, died, or suffered an UGIB. The outcome of interest was an UGIB diagnosed in a secondary care inpatient setting. We used time-varying inverse probability weighted (IPW) Poisson regression to calculate incidence rate ratios (IRRs), contrasting PPI use to no PPI use periods, taking age, sex, 20 comorbidities, and 13 comedications into account. Comorbidities and comedications were risk factors for UGIB. We used fixed effects meta-analyses to pool the results. We analyzed non GI major bleeds and lower GI major bleeds as non-PPI related falsification endpoints.

Results: In 161 872 patients, with 283 619 years of follow-up and 50 402 years of PPI exposure, 781 patients suffered from a UGIB (IR: 27.5/10 000py). Patients receiving PPIs were older, had more comorbidities, and received more comedication in all three databases. Taking IPW into account, all databases showed similar trends toward protective effects of PPI treatment on UGIB, with IRRs of 0.75 in Stockholm (95% confidence interval (CI): 0.47 - 1.19), 0.79 in Denmark (CI: 0.59 - 1.05) and 0.73 in PHARMO (CI: 0.40 - 1.32). The meta-analysis showed a significant risk reduction during PPI treatment (IRR: 0.77; CI: 0.61 - 0.96). We found a null association between PPI use and non-GI major bleeds, but a significantly increased risk for lower GI bleeds during PPI cotreatment (non-GI IRR: 1.08; CI: 0.93 - 1.26, lower GI IRR: 1.40; CI: 1.25 - 1.57).

Conclusions: Concomitant use of a PPI in NOAC treated AF patients was associated with a reduced risk for UGIB. One falsification endpoint analysis showed potential residual confounding, which indicates that the true protective effect might be even larger. In the absence of randomized trial data, these results indicate that PPI cotherapy might be beneficial for UGIB prevention in these patients.

4641 | No added benefit of benzodiazepines to antidepressant monotherapy on mortality in patients with depression

Han Eol Jeong[1], Woo Jung Kim[2,3], In-Sun Oh[1], Ha-Lim Jeon[1] and Ju-Young Shin[1]

[1]Sungkyunkwan University (SKKU), Suwon, Republic of Korea; [2]Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea; [3]Gyeonggi Provincial Dementia Center, Suwon, Republic of Korea

Background: With antidepressants (AD) having minimal therapeutic effects during its initial weeks of treatment, benzodiazepines (BZD) are used concomitantly to alleviate depression symptoms. However, the safety associated with prolonged BZD use with ADs and mortality in patients with depression is yet to be evaluated.

Objectives: To evaluate the risk of mortality associated with concomitant AD plus BZD therapy (AD+BZD), or concomitant therapy of two AD classes (AD+AD), compared to AD monotherapy among patients with depression.

Methods: We conducted a cohort study using Korea's nationwide healthcare database from 2002 to 2017. We defined our cohort as those without a depression diagnosis, and prescriptions for ADs or BZDs in the two years prior to their incident date of depression diagnosis (cohort entry). Exposure was defined using an intention-to-treat approach and classified into three groups: AD, AD+AD, and AD+BZD, with follow-up starting on their incident AD prescription within six months of depression diagnosis. Our primary and secondary outcomes were mortality and hospitalizations, respectively, with patients censored on the earliest of outcome, 1-year of follow-up, or end of study. To balance baseline characteristics, we matched 1:1:1 using propensity score, estimated using multivariate logistic regression. A multivariable Cox proportional hazards model was used to estimate hazards ratios (HR) with 95% confidence intervals (CI), adjusting for various confounders.

Results: The matched cohort had 44,052 patients with 14,684 patients in each treatment group. Compared to patients receiving AD monotherapy, AD+BZD therapy was associated with an increased risk of mortality (HR 1.71, 95% CI 1.33-2.20), while AD+AD therapy had a null association (1.26, 0.97-1.63). Risk of hospitalization was moderately increased with AD+AD (1.11, 1.05-1.18) and AD+BZD (1.10, 1.03-1.17) therapy. Despite stratifying for sex, risk of mortality remained elevated for AD+BZD therapy, with a higher risk in males (1.98, 1.40-2.80) than females (1.44, 1.02-2.03). Risk was not increased with AD+AD therapy. For age-stratified analysis, only AD +BZD therapy increased the risk of mortality in those aged <65 years (2.83, 1.92-4.19), whereas both types of concomitant therapies did not increase the risk of mortality in those aged ≥65 years.

Conclusions: Our study found no overall added benefit of BZDs on AD monotherapy as its concomitant use was associated with an increased risk of mortality, especially in those aged <65 years. This signals clinicians to take precaution when co-prescribing BZDs with ADs in treating depression.

4648 | The impact of childhood pneumococcal conjugate vaccine immunisation on pneumonia admissions in Hong Kong: A population-based interrupted time series analysis from 2004-2017

Min Fan[1], Qiuyan Yu[1], Hong Qiu[2] and Xue Li[1,3,4]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, University of Hong Kong, Hong Kong, Hong Kong; [2]Institute of Environment, Energy and Sustainability, Chinese University of Hong Kong, Hong Kong, Hong Kong; [3]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Hong Kong; [4]Department of Social Work and Social Administration, Faculty of Social Sciences, University of Hong Kong, Hong Kong, Hong Kong

Background: Nine years after its introduction in the US, PCV was introduced to Hong Kong (HK) childhood immunisation program in September 2009; however, the burden of pneumonia remains high in the post-PCV period. It is important to investigate the herd immunity

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of childhood PCV immunisation on pneumonia hospitalization to inform further vaccination policies.

Objectives: To evaluate changes in all-cause pneumonia admissions following the introduction of childhood PCV immunisation in HK, using interrupted time series (ITS) analysis.

Methods: In this population-based study quasi-experimental study, we used Clinical Data Analysis and Reporting System (CDARS), which contains the electronic medical records of all public hospitals in HK, to evaluate the vaccine effect. We identified target patients with a principal diagnosis of all-cause pneumonia between 2004 and 2017 and applied segmented quasi-Poisson regression model to estimate the change of pneumonia admission after the childhood PCV introduction. Whereas there was an H1N1 pandemic during 2009-2011 in HK, we decided to take January 2012 as the intervention time point to minimize the potential bias associated with the influenza outbreak. Subgroup analysis was conducted by dividing age into seven groups.

Results: From 2004 to 2017, the monthly age-standardised incidence of pneumonia admission fluctuated between 2.83 and 7.47 per 10,000 persons. There was a marginal significant decrease in the trend of all-cause pneumonia admission after PCV13 introduction (incidence rate ratio: 0.997, 95% CI: 0.995, 0.999). We also observed a similar decreasing trend in older adults aged 75 years or above but not the younger age groups.

Conclusions: After the introduction of childhood PCV13 immunization, there is a significant reduction in pneumonia admission among the overall population in HK. The herd immunity of childhood PCV13 immunisation was determined in older adults. Future study should investigate the long-term effect of PCV immunization under the circumstance of possible serotype replacement upon the vaccine introduction.

4725 | Sex disparities in the effect of statins on lipid parameters: The PharmLines initiative

Nicholas Byron Hunt[1], Johanna Emmens[2], Sylvi Irawati[3], Jens H.J. Bos[3], Bob Wilffert[3], Eelko Hak[3] and Rudolf A. de Boer[2]

[1]Utrecht University, Groningen, Netherlands; [2]University Medical Center Groningen, Groningen, Netherlands; [3]University of Groningen, Groningen, Netherlands

Background: Statins prevent cardiovascular events by modifying lipid parameters, including total cholesterol (T-c), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG). Real-world evidence on a potential statin effect modification by sex is inconclusive, especially for the primary prevention of cardiovascular disease (CVD).

Objectives: To quantify the differences in the effect of statin therapy on lipid parameters between men and women.

Methods: The PharmLines Initiative linked the Lifelines Cohort Study and the IADB.nl prescription database. The linked database covers a representative population from the Netherlands. We selected participants aged >= 40 years at the index date, defined as the date of the first prescription of any statin monotherapy in the study period 2006-2017. Participants' lipid parameters were followed from baseline to the follow-up measurement. Multivariate regression modeling was used to compare the difference of the mean percentage change of lipid parameters (%MD) from baseline to follow-up between the sexes.

Results: Out of 5,366 statin users from approximately 50,000 participants available in the final linked database, 685 were statin initiators. At baseline, women had significantly higher levels of mean T-c, LDL-c, and HDL-c than men (all p-values < 0.01). At follow-up, women had a significantly higher mean percentage change of HDL-c compared to men (adjusted %MD 5.59, 95% CI 2.42-8.75, p < 0.01). There was no significant sex difference in other parameters, nor in the proportion of men and women who achieved LDL-c <=2.5 mmol/L.

Conclusions: Statins appear to have a greater effect on increasing HDL-c levels in women than men while showing similar effect on T-c, LDL-c, and TG levels in both sexes independent of adherence and statin dose or type. Other factors might play a role in opposing statin HDL-c elevating effects in men. Men should not be treated differently than women.

4758 | Real-world short- and long-term effects of antibiotic treatment of acute COPD exacerbations in outpatients: A cohort study under the Pharmlines initiative

Yuanyuan Wang[1], Victor Pera[1], H. Marike Boezen[2], Jan-Willem C. Alffenaar[3], Bob Wilffert[1], Rolf H.H. Groenwold[4] and Eelko Hak[1]

[1]Groningen Research Institute of Pharmacy, University of Groningen, Groningen, Netherlands; [2]University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [3]School of Pharmacy, University of Sydney, Sydney, Australia; [4]Leiden University Medical Center, Leiden, Netherlands

Background: Although antibiotic treatment is recommended for acute exacerbations of COPD (AECOPD) under specific circumstances, the treatment's value in an outpatient setting is unclear.

Objectives: To evaluate the real-world short- and long-term effects of antibiotic treatment on AECOPD outpatients.

Methods: This cohort study was conducted under the PharmLines Initiative that linked the Lifelines database with the prescription database IADB.nl during 2005-2017. We included participants with a first recorded diagnosis of COPD who underwent systemic glucocorticoids treatment for an AECOPD episode. The exposed and reference group was defined as patients who received and not received any antibiotic prescriptions during AECOPD treatment. The short-term outcome was AECOPD treatment failure within 14 -30 days after the index date. The long-term outcome was the time to next exacerbation within one year's follow-up. Binary logistic regression analysis combined with propensity scores (PS) were used to estimate the association between antibiotic use and treatment failure. The risk of another exacerbation was assessed using Kaplan-Meier survival and Cox regression analyses. Several subgroup and sensitivity analyses were also performed.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: We analyzed data for 1,105 AECOPD patients. Antibiotics were prescribed for 518 patients (46.9%) while 587 patients (53.1%) received no antibiotics. The overall antibiotic use was associated with a significant relative risk reduction of AECOPD treatment failure by 33%-37% compared with the risk for the reference group (adjusted odds ratio [aOR]: 0.67 [95% CI: 0.42-1.04] and 0.63 [95% CI: 0.40-0.99] by regression and PS analyses, respectively). Similar protective effects were observed for doxycycline, macrolides and co-amoxiclav, but not for amoxicillin, and only the effects of doxycycline were statistically significant (aOR 0.53 [95% CI: 0.28-0.99] by PS analysis). There was no difference between the exposure and reference groups regarding the risk of and time to next exacerbation, irrespective of the follow-up duration.

Conclusions: Our finding that antibiotics treatment supplementing systemic glucocorticoids reduces short-term AECOPD treatment failure in real-world settings concurs with those of clinical trials. Larger studies of high quality are needed to confirm the beneficial effects for specific antibiotics. Our results after controlling for confounding suggest that unmeasured confounding in observational studies may induce underestimated antibiotic beneficial effects on AECOPD.

4996 | Safety and effectiveness of medical cannabis in the real-world: Results of the Quebec cannabis registry

Yola Moride[1,2], Michelle Canac-Marquis[3], Rihab Gamaoun[4], Pierre Beaulieu[5], Andrée Néron[5], Marc O. Martel[3], Jordi Perez[3], Julie Desroches[5], Maja Kalaba[6], Marc Ware[6] and Antonio Vigano[3]

[1]Université de Montréal, Montreal, QC, Canada; [2]Rutgers, The State University of New Jersey, New Brunswick, NJ; [3]McGill University, Montreal, QC, Canada; [4]Research Institute of the McGill University Health Centre, Montreal, QC, Canada; [5]Université de Montréal, Montreal, QC, Canada; [6]Canopy Growth Corporation, Montreal, QC, Canada

Background: Although medical cannabis (MC) has been available in Canada since 1999, the non-recognition of cannabis-based medical products as a drug restricted its medical access. To overcome this situation, the Quebec College of Physicians authorized the use of MC in 2014 only within a research framework.

Objectives: The Quebec Cannabis Registry (QCR) aimed to describe the indications, dosages, safety and effectiveness of medical cannabis products used in the real-world setting.

Methods: All adult (≥18 years) Quebec residents who were authorized to use MC between May 2015 and October 2018 were enrolled. Data were collected at inclusion (demographics, indications, dosage, medical history, concomitant medications) and every three months for 24 months (characteristics of cannabis treatment, clinical outcomes, adverse events (AEs), pain severity and interference (Brief-Pain Inventory), well-being (Revised-Edmonton Symptom Scale-R), quality of life (EQ5D5L).

Results: A total of 2,991 eligible patients were enrolled. Gender distribution was similar and mean age was 50.9 years (SD 15.7 years). The top four indications were chronic pain (62.4%), mood disorders (12.1%), oncology (11.8%), neurological disorders (8.2%). Statistically significant improvements in all outcome domains (i.e., pain severity, pain interference, well-being, quality of life) were observed between baseline and the 3-month follow-up. Results also revealed significant improvements in pain intensity, pain interference, and quality of life between the 3 and 6 months. A total of 110 (3.7%) patients reported AEs: 26 case reports met the criteria of seriousness (Psychiatric disorders [30.8%], Respiratory, thoracic and mediastinal disorders [30.8%], Nervous system disorders [23.1%]), eight of which were likely or probably related to MC. There were two deaths, although unlikely related to MC.

Conclusions: Real-world evidence provided by the QCR in the form of a population-based study supports the safety and effectiveness of MC use for the improvement of pain severity, pain interference, well-being and the quality of life in a variety of medical conditions.

4999 | Effect of adherence to anticoagulation on the incidence of ischemic stroke in the patients with atrial fibrillation: A retrospective cohort study

Won Kyung Lee[1], Young-Jin Ko[2], Sun-Young Jung[3], Seongill Woo[1], Byung-Joo Park[2] and Joongyub Lee[1]

[1]Inha University Hospital, Incheoin, Republic of Korea; [2]Seoul National University, Seoul, Republic of Korea; [3]Chung-Ang University, Seoul, Republic of Korea

Background: Although NOAC had comparable or superior effectiveness compared to VKA in AF, outcomes in low compliance group was limited in the published literature.

Objectives: The purpose of this study is to evaluate the effectiveness and safety of anticoagulation among noncompliant patients using NOAC or VKA compared to those compliant to NOAC treatment.

Methods: This study was performed using the National Health Information Database from 2009 to 2018. A retrospective cohort was constructed with the patients newly diagnosed as non-valvular atrial fibrillation from 2010 to 2018. All participants were required to be between 18 to 100 years old, newly diagnosed AF from 2010.1-2018.6 without AF-related claim in the previous year, and CHA2DS2-VASc score of at least two. Patients with diagnosis codes indicating prosthetic heart valves or valvular heart disease, end stage renal disease, joint replacement surgery, ischemic stroke or major bleeding before enrollment were excluded. The primary exposure is compliance of NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) or VKA (warfarin) defined based on 80% Proportion of Days Covered (PDC) measured during 180 days after starting OAC. Study subjects were categorized into four treatment groups: VN (VKA non-compliant), VC (VKA compliant), NN (NOAC non-compliant), and NC (NOAC compliant). We followed up patients to the incidence of ischemic stroke, bleeding, switching of drug, death, 910 days after enrollment, or end of study period whichever came first. The differences in the baseline characteristics of a group from NC were calculated as standardized differences before and after the IPT weighting.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

The IPT weighted cumulative incidence rate of ischemic stroke was estimated considering bleeding, switching and death as competing events. Subdistributional hazard model was used to calculate the weighted hazard ratio. NNT and NNH for each outcome was presented as the reciprocal for difference of the IPT weighted cumulative incidence.

Results: We identified 84,227 eligible patients who was diagnosed as AF and started to take oral anticoagulants from 2010 to 2018. IPT weighted cumulative incidence of ischemic stroke in VN, NN, and NC was 0.07005, 0.07787, and 0.05579 respectively. Weighted hazard ratios for VN and NN was 1.31 (1.26-1.37) and 1.34 (1.29-1.40). NNH by non-compliance to anticoagulation for ischemic stroke in VN and NN was 44 and 39.

Conclusions: Non-compliant groups are prone to have a higher risk of stroke, regardless of OAC class.

5002 | Comparative safety of epoetin versus darbepoetin in prevention of major adverse cardiovascular events in patients undergoing hemodialysis

Raj Desai, Steven Smith, Rajesh Mohandas and Haesuk Park
University of Florida, Gainesville, FL

Background: Anemia is a common and prognostically-significant complication affecting patients requiring hemodialysis. Erythropoietin-stimulating agents (ESAs), including epoetin (EPO) and darbepoetin (DPO), are used widely and interchangeably for treatment of anemia in these patients. A meta-analysis of randomized trials found no difference in mortality between EPO and DPO but was limited by small sample size (2000 patients in 9 trials), short follow-up (< 1 year), and inadequate power.

Objectives: We sought to compare EPO (alpha or beta) and DPO on risk of major adverse cardiovascular events (MACE), including stroke, acute myocardial infarction (AMI) and all-cause mortality in patients initiating maintenance hemodialysis.

Methods: We conducted a retrospective cohort study using US Renal Data System data, which includes Medicare patients initiating hemodialysis, from 2012 to 2016. Patients were included if they were aged ≥ 18 years, and initiated EPO or DPO. Follow-up started from drug initiation until the first occurrence of: MACE, discontinuation of therapy (i.e., no fill for 30 days), switch to the comparator, initiation of pegylated epoetin, end of hemodialysis, end of Medicare enrollment, or end of study period (31st December 2016). We controlled for confounding using propensity score (PS) 1:3 matching. Cox proportional hazards regression model was used to compare the risk of MACEs between EPO and DPO.

Results: After PS matching, a total of 32,155 patients were included (24,116 EPO users and 8,039 DPO users). MACE incidence was 37.3 and 39.9 per 100 person-years in the EPO and the DPO groups, respectively. In the multivariable model, use of EPO was associated with a 32% lower risk of MACE (adjusted hazard ratio (aHR): 0.68; 95% CI: 0.66, 0.70). EPO users were also at lower risk of AMI (aHR: 0.87; 95% CI: 0.81,0.93), stroke (aHR: 0.85; 95% CI: 0.80, 0.90) and all-cause mortality (aHR: 0.63; 95% CI: 0.61,0.65) compared to DPO users.

Conclusions: Our findings suggest that risk of MACE is very high in Medicare patients with incident ESA use. Furthermore, EPO appears to be superior to DPO in preventing the development of MACE among such patients.

5024 | Newer generation diabetes medications and cardiovascular outcomes among older women with breast cancer and diabetes

Jifang Zhou, Nadia Nabulsi, Alemseged Asfaw, Inyoung Lee, Colin Hubbard and Gregory Calip
University of Illinois at Chicago, Chicago, IL

Background: Sodium-glucose co-transporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are newer generation diabetes drug classes with efficacy demonstrated in reducing HbA1c and conferring cardiovascular benefits, although evidence on these associations is limited among cancer patients with high treatment-related cardiovascular risk.

Objectives: To describe rates of major cardiovascular outcomes among older women with breast cancer and diabetes using SGLT-2 inhibitors, DPP-4 inhibitors and GLP-1 agonists.

Methods: *1. Design, Setting and Participants* We conducted a retrospective cohort study of women with incident stage I-III breast cancer and pre-existing diabetes at the time of diagnosis between 2008 and 2016 using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Women were required to be continuously enrolled in Medicare Parts A, B and D for at least one year prior to breast cancer diagnosis and followed until the first of disenrollment, death or end of follow up. *2. Exposures* Time-varying use of SGLT-2 inhibitors, DPP-4 inhibitors and GLP-1 agonists. *3. Main outcome measures* Major adverse clinical events (MACE) defined as the composite of death, myocardial infarction, coronary revascularization, stroke, and hospitalization due to heart failure. *4. Statistical analysis* Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for risk of MACE.

Results: A total of 13,993 women with breast cancer and diabetes with a mean (SD) age at diagnosis of 74.9 (6.6) years were included in our analyses, among whom newer generation diabetes medication exposure included ever users of SGLT-2 inhibitors (n=300), DPP-4 inhibitors (n=2,476) and GLP-1 agonists (n=444). Over a median duration of 3.1 years follow-up, 3,702 (26.5%) patients experienced MACE with rates of 65.9, 74.5 and 62.6 per 1,000 person-years among SGLT-2 inhibitor, DPP-4 inhibitor and GLP-1 agonist users respectively. In Cox proportional hazards models, the risk of MACE was reduced with use of GLP-1 agonists (HR 0.75; 95% CI, 0.58-0.96), but not SGLT-2 inhibitors (HR 1.22; 95% CI, 0.82-1.83) or DPP-4 inhibitors (HR 1.07; 95% CI, 0.95-1.19).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: We found reduced incidence of major cardiovascular adverse events among breast cancer survivors with diabetes that used GLP-1 agonists. Our study and future research may provide evidence on the safety and cardiovascular benefits of newer type 2 diabetes medications among breast cancer survivors.

5073 | Longitudinal LDL changes among proprotein convertase subtilisin kexin type 9 inhibitor (PCSK9i) users in the United States

Kathleen M. Andersen[1,2], Derek K. Ng[1], Michael J. Blaha[1,3], Jodi B. Segal[1,2,4] and G. Caleb Alexander[1,2,4]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [2]Center for Drug Safety & Effectiveness, Johns Hopkins University, Baltimore, MD; [3]The Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Baltimore, MD; [4]Division of General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, MD

Background: The PCSK9i are associated with ~60% reduction in low density lipoprotein (LDL) cholesterol in clinical trials, compared to maximal statin doses. However, their effect among real-world users is unclear.

Objectives: To characterize LDL changes in response to PCSK9i initiation.

Methods: Data are from individuals with at least 1 dispensation for alirocumab or evolocumab between July 2015 (FDA approval of first PCSK9i) and December 2017 in the IBM MarketScan® Commercial Claims and Encounters Database. Analyses were further restricted to PCSK9i users with LDL results available 3 months prior to initiation, as well as at least one measure in the 12 months after initiation. LDL values more than 3 months after last PCSK9i claim were excluded. Biologically implausible results (<5 or >1,000 mg/dL) were also excluded; to convert to mmol/L, multiply by 0.02586. In cases where multiple lab values within a given period were available, the later LDL value was chosen. We report mean LDL change with standard deviations (SD), percentage of persons <70 mg/dL by 6 months, and pre-post percent change while on PCSK9i therapy.

Results: We identified 378 eligible PCSK9i users, of whom 40% used lipid-lowering therapy in the 6 months prior to PCSK9i initiation (21% maximal statin, 18% non-maximal statin, 1% ezetimibe). The mean LDL 3 months prior to initiation was 140 mg/dL (SD 58). A rapid decrease in LDL after 3 months of PCSK9i treatment was noted (n=259, mean -53 mg/dL change from baseline, SD 51), with no additional decreases after 6 months (n=200, -59 mg/dL (SD 50) from baseline, difference from 3 months p-value=0.23) nor 12 months (n=226, -50 mg/dL (SD 53) from baseline, difference from 6 months p=0.07). By 6 months, 42% were <70mg/dL, a pragmatic goal from pivotal trials now adopted by guidelines. There was substantial variability across individual pre-post change (median -39%, interquartile range -5% to -60%).

Conclusions: While the average LDL reduction in PCSK9i clinical trials was ~60%, only one in four PCSK9i real-world users experienced such magnitude of decrease. The individuals we observed had 20-40 mg/dL higher pre-treatment LDL values than those enrolled in clinical trials for initial FDA approval in 2015, and were well above current indications for PCSK9i treatment in the US. This may reflect worse disease severity, or the fact that only one in five individuals were also using high dose statins as recommended. This work highlights important differences between clinical trial and real-world PCSK9i users, and supports the value of real-world investigations of PCSK9i utilization, safety and effectiveness.

5105 | Comparing cardiovascular benefits of sodium glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists in older adults with diabetes

Phyo Htoo[1], John Buse[1], Tiansheng Wang[1], Virginia Pate[1], Matthew Crowley[2] and Til Stürmer[1]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Duke University, Durham, NC

Background: Antihyperglycemic agents, sodium glucose co-transporter-2 inhibitors (SGLT-2i) and some glucagon-like peptide-1 receptor agonists (GLP-1ra) were found in clinical trials to reduce major cardiovascular disease (CVD) outcomes relative to placebo. But their comparative effects in real world populations with various underlying CVD risks are unknown.

Objectives: To estimate the effects of SGLT-2i vs. GLP-1ra on the risk of congestive heart failure (CHF) hospitalization, stroke, myocardial infarction (MI) and a composite of stroke, MI and all-cause mortality.

Methods: We identified SGLT-2i and GLP-1ra initiators among Medicare fee-for-service enrollees from 2013-16, after a 1-year washout during which there was no SGLT-2i or GLP-1ra prescription. Follow-up for outcomes began on the second prescription date until death or disenrollment (intent-to-treat, ITT) additionally censoring for drug changes in separate as-treated analyses. We used validated claims-based algorithms and diagnoses in inpatient care to define cardiovascular outcomes. Propensity score (PS) weighted Cox models were used to estimate hazard ratios (HR), controlling for demographics, major comorbidities, co-medications, frailty indicators, behavioral and socioeconomic risk factors. We used Fine and Gray Cox model to account for death as competing risk to examine each CVD separately. We conducted analyses with and without excluding major CVD at baseline.

Results: Among 21,596 SGLT-2i and 17,718 GLP-1ra initiators, we identified 824 and 1,149 CHF hospitalizations respectively. After a median 1-year follow-up, ITT HR for the effect of SGLT-2i vs. GLP-1ra on CHF was 0.83 (95% CI: 0.71, 0.96). As-treated HR was 0.70 (95% CI: 0.58, 0.85). After excluding prevalent CHF, HRs were slightly higher: 0.92 (0.69, 1.22) for ITT and 0.70 (0.48, 1.03) for as-treated. Risk of composite outcome was similar: ITT HR of 1.04 (0.93, 1.17) but after excluding prevalent CVD, the risk was slightly higher for SGLT-2i: ITT HR of 1.11 (0.92, 1.33). The MI risk was slightly higher for SGLT-2i: ITT HR of 1.13 (0.91, 1.42) and with no prevalent

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

outcomes, HR was 1.20 (0.86, 1.67). HR for stroke was 1.25 (0.96, 1.64) and with no prevalent events, it was 1.35 (0.92, 1.97). As-treated HRs were similar.

Conclusions: SGLT-2i were found to have lower risk of CHF hospitalization and similar risk of a combined MI, stroke and all-cause mortality outcome, vs. GLP-1ra initiators but a slightly higher risk of each of MI and stroke. This has implications in optimizing cardiovascular outcomes in older diabetes patients.

5109 | Dementia and effectiveness and safety of apixaban versus warfarin and other direct oral anticoagulants in older adults with atrial fibrillation

Kueiyu Joshua Lin[1,2], Sebastian Schneeweiss[1], Ajinkya Pawar[1] and Dae Hyun Kim[1,3]

[1]*Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA;* [2]*Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA;* [3]*Hebrew Rehabilitation Center, Harvard Medical School, Boston, MA*

Background: Apixaban has been considered a preferred choice for stroke prevention in older adults with non-valvular atrial fibrillation (AF). Dementia is prevalent in the elderly and associated with higher risks of complications while taking oral anticoagulants (OAC), but how dementia affects comparative effectiveness and safety of apixaban vs. other OACs is unknown.

Objectives: To determine the comparative safety and effectiveness of apixaban vs. other OACs in patients with dementia and non-valvular AF.

Methods: We used the US Medicare claims data to establish 4 new-initiator cohorts: patients aged ≥ 65 year with a dispensing of warfarin, dabigatran, rivaroxaban, and apixaban, respectively, without any OAC use in the preceding 180 days from 2013/1 to 2017/12 (cohort entry date= first dispensing date). The study cohorts were required to have a diagnosis of dementia and non-valvular AF in the preceding 180 days (baseline assessment period, BAP). Primary outcome was a composite endpoint of death, hospitalization for ischemic stroke or major bleeding and we studied each specific outcome secondarily. We used 1:1 propensity score-matching to adjust for 79 potential confounders assessed in BAP.

Results: Our study cohort included a total of 32,440 warfarin (mean age 81.5 years, female 60.8%), 23,134 rivaroxaban (mean age 81.3 years, female 63.7%), 3,643 dabigatran (mean age 80.8 years, female 57.3%), and 31,218 apixaban (mean age 82.0 years, female 61.6%) initiators with dementia and non-valvular AF. In the warfarin-apixaban cohort (17,187 matched pairs), the rate (per 100 person-years) of the composite endpoint in warfarin-initiators was higher than that of apixaban-initiators (52.8 vs 34.3; adjusted hazard ratio [aHR], 1.4; 95% confidence interval [CI] 1.3-1.5). In the rivaroxaban-apixaban cohort (18,268 pairs), the rate of the composite endpoint in rivaroxaban-initiators was higher than apixaban-initiators (43.9 vs. 31.1; aHR, 1.3; 95% CI, 1.2-1.4). In the dabigatran-apixaban cohort (3,166 pairs), the rate of the composite endpoint in dabigatran-initiators was higher than that of apixaban-initiators (34.1 vs 25.3; aHR, 1.3; 95% CI, 1.1-1.5). The superiority of apixaban was primarily due to higher risks of major bleeding associated with other OACs (aHR [95% CI] comparing warfarin, rivaroxaban, and dabigatran vs. apixaban was 1.7 [1.5, 1.9], 1.6 [1.4-1.8] and 1.3 [1.0-1.7], respectively).

Conclusions: In older adults with dementia and non-valvular AF, apixaban was associated with a favorable benefit-risk profile compared to other OACs for stroke prevention.

5121 | Safety and effectiveness of extended treatment with oral anticoagulants in patients with venous thromboembolism

Ajinkya Pawar, Katsiaryna Bykov, Chandrasekar Gopalakrishnan, Geetha Iyer, Helen Tesfaye, Kristyn Chin and Joshua J. Gagne

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: Guidelines for the treatment of venous thromboembolism (VTE) recommend that patients should be treated for at least 90 days with oral anticoagulants. For patients who require extended treatment, there is limited evidence on which agent provides the best balance of benefits and risks.

Objectives: To compare extended treatment for VTE with apixaban, rivaroxaban, and warfarin with respect to recurrent VTE, major bleeding, and death.

Methods: Using three databases (Optum Clinformatics, 2009-2018; Medicare fee-for-service and IBM MarketScan 2009-2017), we identified adults (≥18 years) who initiated oral anticoagulation following discharge from first VTE hospitalization and compared those who extended treatment with apixaban, rivaroxaban, or warfarin beyond an initial 90-day treatment episode. We adjusted for 74 confounders using propensity score (PS) matching weights. In the primary analysis, patients were followed from the end of the initial 90-day treatment episode until treatment cessation, outcome, death, disenrollment, or end of available data. Outcomes of recurrent VTE and major bleeding were based on hospitalized events using validated algorithms. Weighted Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). In secondary analyses, we compared extended treatment beyond 180, 270, and 360 days.

Results: We identified 64,487 eligible patients who received extended treatment beyond 90 days (8,769 apixaban, 12,281 rivaroxaban, 43,437 warfarin); 32,380 extended treatment beyond 180 days, 17,739 beyond 270 days, and 5,808 beyond 360 days. Covariates were well-balanced across groups after PS-weighting. We observed 493 recurrent VTE events, 827 major bleeding events, and 1,418 deaths during 17,571 person-years of follow-up in the primary analysis. HRs (95% CIs) comparing extended treatment with apixaban

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

vs. warfarin were 0.75 (0.62-0.91) for recurrent VTE, 0.92 (0.80-1.06) for major bleeding, and 0.79 (0.71-0.88) for death. Corresponding HRs for rivaroxaban vs. warfarin were 0.91 (0.79-1.06), 1.01 (0.89-1.14), and 0.91 (0.83-1.00). Comparative results were consistent when treatment was extended beyond 180, 270, and 360 days.

Conclusions: This study found that extended treatment with apixaban was associated with a lower rate of recurrent VTE and death compared with warfarin in routine clinical care without an increased rate of major bleeding. Smaller differences were observed when comparing rivaroxaban with warfarin for recurrent VTE and death.

5156 | Risk of major adverse cardiac and bleeding events with antiplatelet-apixaban compared to antiplatelet-rivaroxaban in patients with acute coronary syndrome

Ghadeer K. Dawwas[1], Eric Dietrich[2] and James D. Lewis[1]
[1]*University of Pennsylvania, Philadelphia, PA;* [2]*University of Florida, Gainesville, FL*

Background: The beneficial effect of apixaban, a novel direct-acting oral anticoagulant, has been established in patients with atrial fibrillation (AF). However, evidence regarding its effectiveness and safety in combination with antiplatelet in patients with acute coronary syndrome (ACS) remains limited.

Objectives: We aimed to assess the comparative effectiveness and safety of antiplatelet-apixaban compared to antiplatelet-rivaroxaban in patients with AF and ACS.

Methods: We conducted a retrospective cohort analysis using Optum Clinformatics from Jan 1, 2013 to Dec 31, 2018, among patients aged ≥18 years, with a history of AF, and who were hospitalized for ACS (principal discharge diagnosis (ICD-9: 410.xx and 411.xx; ICD-10: I21 and I22)). The AF diagnosis required the presence of one inpatient or two outpatient diagnoses within 1 year. Patients were required to have twelve months of continuous enrollment in medical and pharmacy benefits prior to the index-date, and have used a combination of antiplatelet-apixaban or antiplatelet-rivaroxaban within 30 days of their first ACS diagnosis. The primary effectiveness outcome was the incidence of major adverse cardiac events (MACE) and the primary safety outcome was the incidence of major bleeding events including intracranial hemorrhage, gastrointestinal bleeding and other major bleeding events. We used Cox-proportional hazard models after propensity score matching (PSM) (1:1) to obtain hazard ratio (HR) and 95% confidence interval (CI).

Results: We identified a total 2,586 patients with AF followed by ACS who used a combination of antiplatelet-apixaban or antiplatelet-rivaroxaban. In the PSM cohort, patients' characteristics, including age, sex, and the presence of comorbid conditions were well balanced between the two groups (all standardized differences <0.1). The incidence rate of MACE was 23 and 35 per 100 person-years in the antiplatelet-apixaban and antiplatelet-rivaroxaban groups, respectively. The incidence of major bleeding events per 100 person-years was 7 and 13 in the antiplatelet-apixaban and the antiplatelet-rivaroxaban, respectively. Compared to antiplatelet-rivaroxaban, the use of antiplatelet-apixaban was associated with a lower risk of CVD, HR, 0.73 [0.58- 0.93] and major bleeding events HR, 0.60 [0.37, 0.80].

Conclusions: In this population-based cohort of incident ACS patients, the use of antiplatelet-apixaban was associated with a lower risk of MACE and major bleeding events compared to antiplatelet-rivaroxaban.

5158 | Safety of off-label dose reduction of non-vitamin K oral anticoagulants in patients with atrial fibrillation treated in routine care

Carline van den Dries[1], Rianne van den Ham[2], Patrick Souverein[2], Romin Pjouheshnia[2], Geert-Jan Geersing[1] and Sander van Doorn[1]
[1]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands;* [2]*Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands*

Background: While non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly being prescribed, concerns have emerged about patients receiving a reduced NOAC dose without a clear indication. The clinical impact of such 'off-label' dose reduction is yet unknown.

Objectives: To investigate the safety of off-label NOAC dose reduction compared to on-label standard dosing in AF patients treated in routine care.

Methods: This population based cohort study used data from general practitioner practices contributing to the United Kingdom Clinical Practice Research Datalink. Adult, non-valvular AF patients with a first NOAC prescription between January 1st 2010 and July 1st 2018 were included if they received an on-label standard dose or an off-label reduced dose, based on the summary of product characteristics. The primary outcome was ischaemic stroke. Secondary outcomes were major and non-major bleeding. We performed Cox proportional hazards analyses with inverse probability of treatment weighting (IPTW) on the propensity score to adjust for measured confounding.

Results: 20,688 new NOAC users contributing to 23,665 person years of follow-up were included, of whom 18,194 (88%) patients used an on-label standard dose and 2,494 (12%) patients used an off-label reduced dose. Median age was 72 years (interquartile range (IQR) 66-78) for on-label standard dose users and 79 years (IQR 73-86) for off-label reduced dose users. 152 ischaemic strokes occurred in the on-label standard dose group, vs. 19 ischemic strokes in the off-label reduced dose group (incidence rates 0.70 vs. 0.94 per 100 person years, respectively). The crude hazard ratio (HR) for ischemic stroke was 1.27 (95% confidence interval (CI) 0.79-2.05) for the off-label reduced dose users versus the on-label standard dose users. IPTW using the propensity score resulted in a HR of 1.10 (95% CI 0.88-1.38).

Conclusions: In this study using data from routine practice, 12% of AF patients used an off-label reduced NOAC dose. This did not appear to

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

significantly increase the risk of ischaemic stroke in patients with AF, although numbers of events were small. Results on the secondary outcomes will be ready to present at the conference.

Drug Utilization Research -> Changing drug utilization (interventions and implementation research)

68 | Changes in prescribing of sodium-glucose co-transporter 2 inhibitors and dipeptidyl peptidase 4 inhibitors in Singapore

Louise G.H. Goh, Jiandong Sun and Kwong Ng
Agency for Care Effectiveness, Ministry of Health, Singapore, Singapore

Background: The Agency for Care Effectiveness issued subsidy guidance and an Appropriate Care Guide in mid-2017 to encourage use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) over dipeptidyl peptidase 4 inhibitors (DPP4i) as dual or triple therapy based on clinical and cost-effectiveness assessment. It was unclear if these efforts were associated with desired changes in prescribing for managing type 2 diabetes mellitus (T2DM).
Objectives: To assess changes in prescribing of SGLT2i and DPP4i in T2DM patients managed at public healthcare institutions in Singapore post-subsidy.
Methods: A retrospective cohort study was conducted using drug utilisation data and electronic health records. Two random samples (n = 10,000 T2DM patients each) stratified by care setting (i.e. 25% and 75% of patients managed at public hospitals and polyclinics or primary care clinics where most patients and milder cases are managed respectively) were selected from two periods, pre-subsidy (Sep-Dec 2016) and post-subsidy (Sep-Dec 2017). Changes in prescribing rates (PR = number of patients prescribed with studied drug among all T2DM patients in a given period) from pre- to post-subsidy were assessed using logistic regression, adjusted for covariates. Effect size was estimated using odds ratios (ORs) with 95% confidence intervals (CIs).
Results: The two samples were similar in age and gender distribution. Overall, PR of SGLT2i was significantly increased by four times from 1.5% to 6.1% after subsidy listing (OR 3.9, 95%CI 3.2-4.8). The increase was more pronounced when SGLT2i was used with metformin (OR 5.4, 95%CI 4.1-7.2) or insulin (OR 2.7, 95%CI 1.9-3.9) compared with other non-recommended therapies (OR 2.0, 95%CI 1.4-3.1). Metformin monotherapy use also increased significantly by 3.5 times (OR 3.5, 95%CI 3.2-3.9). Conversely, PR of DPP4i was significantly reduced by 50% from 22.4% to 18.3% (OR 0.5, 95%CI 0.5-0.6), particularly for DPP4i monotherapy (OR 0.2, 95%CI 0.2-0.3) or when used with insulin (OR 0.6, 95%CI 0.5-0.7). The increase in overall PR of SGLT2i was primarily driven by increased use in polyclinics (0.01% to 4.8%), despite a significant increase in hospitals (5.9% to 10.0%). The decrease in DPP4i PR occurred only at polyclinics (23.3% to 17.0%, OR 0.4, 95%CI 0.4-0.4) but not at public hospitals (19.7% to 22.0%, OR 1.0, 95%CI 0.9-1.2).
Conclusions: Changes in prescribing suggest early success in driving appropriate use of diabetic drugs, to increase SGLT2i use as second-line dual or triple therapy and reinforce metformin monotherapy use. Differential effect by care setting warrants investigation.

90 | Use of hydrochlorothiazide in Denmark following publication of skin cancer risk findings

Anton Pottegård[1], Bodil H. Bech[2], Sidsel A. Pedersen[1] and Bo Christensen[2]
[1]*University of Southern Denmark, Odense, Denmark;* [2]*Aarhus University, Aarhus, Denmark*

Background: The antihypertensive agent hydrochlorothiazide has recently been linked to an increased the risk of non-melanoma skin cancer, in particular squamous cell carcinoma (SCC). The three key papers were published in rapid succession on June 6th 2017, December 4th 2017, and May 29th 2018, respectively. Based on an evaluation by the Pharmacovigilance Risk Assessment Committee (PRAC) under, Summary of Product Characteristics (SmPC) were updated and 'dear health care professionel' (DHCP) letters were distributed to prescribers across Europe October 17th 2018.
Objectives: In this study, we sought to describe the impact of the dissemination of these findings on the use of hydrochlorothiazide and health care utilization among antihypertensive users in Denmark.
Methods: In this nationwide observational study, we performed descriptive analyses of a cohort comprising all Danish antihypertensive treatment users 2016-2018 (n=1,253,886) with special focus on hydrochlorothiazide users (n=296,597). Data was retrieved from the Danish nationwide health registries, including the Danish National Prescription Registry.
Results: The proportion of antihypertensive fills constituted by hydrochlorothiazide dropped from 12.7% to 9.3% during 2016-2018. This drop was more pronounced among younger patients and patients with a history of skin cancer. Simultaneously, the monthly rate of new hydrochlorothiazide users in Denmark dropped from 2350 to 742. The publication of an increased risk of non-melanoma skin cancer led to an estimated excess of up to 11510 physical and 228700 e-mail/phone consultations to general practitioners. No evidence for increased risk of adverse outcomes was found.
Conclusions: The publication of increased risk of skin cancer with hydrochlorothiazide use have led to a decline in the use of hydrochlorothiazide in Denmark, in particular among younger patients and patients with a skin cancer history.

2347 | Hospitalization for thromboembolic events does not improve adherence to oral anticoagulants in high-risk atrial fibrillation patients

Thanh Phuong Pham Nguyen, Yong Chen, Dylan Thibault, Charles E. Leonard, Sean Hennessy and Allison Willis
University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Adherence to oral anticoagulants (OACs) in atrial fibrillation (AF) patients is poor in practice. It is not known whether and how adherence changes after hospitalization for a thromboembolic event (i.e., ischemic stroke (IS) or thromboembolism (TE)), a sentinel health event that may represent an opportunity to enhance medication adherence.

Objectives: The purpose of this study is to examine the impact of hospitalization for an IS/TE on post-discharge adherence to OACs in high-risk AF patients.

Methods: We conducted a quasi-experimental pre-post observational study design using population-based U.S. commercial insurance healthcare claims from the 2009-2016 Optum™ Clinformatics™ Data Mart. Adult AF patients taking OACs with a random hospitalization for a nonbleeding-related reason occurring after the first observed OAC prescription fill, with no other admissions within the preceding and following six months, were identified. Adherence was estimated by the proportion of days covered (PDC) within six months before and after hospitalization. Difference-in-difference (DID) analysis via a generalized linear model was employed to compare pre- and post-hospitalization PDCs by reasons for hospitalization (i.e., IS/TE versus other nonbleeding-related reasons), adjusting for imbalanced baseline characteristics between groups.

Results: We identified 21,400 individuals with AF on OACs who were subsequently hospitalized for a nonbleeding-related reason. Of these, 1,147 (5.4%) were hospitalized for IS/TE, and 20,253 (94.6%) for other reasons. Baseline characteristics were similar between groups. After covariate adjustment, 6-month adherence declined by 1.1% less in individuals hospitalized for IS/TE, compared to other nonbleeding reasons, even though this difference was not statistically significant (p=0.17). Individuals with minority race/ethnicity had a larger reduction by 0.7% in PDC as compared to white patients after discharge (p=0.006).

Conclusions: This real-world study suggests that more effective collaborative strategies across care settings are needed to improve adherence to OACs, particularly after a thromboembolic event and during transition of care.

2364 | Changes in sales of over-the-counter and prescription medicines after rescheduling of codeine to a prescription-only medicine in Australia

Andrea L. Schaffer[1], Rose Cairns[2], Jared A. Brown[1], Natasa Gisev[3], Nicholas A. Buckley[4] and Sallie-Anne Pearson[1]

[1]Centre for Big Data Research in Health, University of New South Wales, Sydney, Australia; [2]School of Pharmacy, University of Sydney, Sydney, Australia; [3]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia; [4]School of Medical Sciences, University of Sydney, Sydney, Australia

Background: Due to concerns over increasing harms, over-the-counter (OTC) codeine-containing products were rescheduled to prescription-only in February 2018 in Australia. This led to a reduction in codeine sales, but it is unknown how the use of other analgesic products changed.

Objectives: We determined the impact of the rescheduling on sales of potential market substitutes for OTC codeine, including OTC and prescription analgesics, products to treat cold and flu symptoms, and cough suppressants.

Methods: We conducted interrupted time series analyses using pharmaceutical sales data to Australian community pharmacies (2015-2019). We quantified changes in monthly tablet sales/10,000 population of: codeine-containing products, OTC analgesics (paracetamol, NSAIDs, and their combinations), prescription analgesics (NSAIDs, tramadol, strong opioids, gabapentinoids, antimigraine medicines), and OTC cold/flu products and cough suppressants containing opioid derivatives (dextromethorphan, pholcodine, dihydrocodeine).

Results: In the year before rescheduling was announced, OTC codeine sales were 248,127 tablets/10,000 population and prescription codeine sales were 106,621 tablets/10,000 population. After rescheduling, we observed a small level shift increase in prescription codeine sales (+2247 tablets/10,000 population, 95%CI 1231-3264) that did not offset the decrease in OTC sales. We observed an increase in sales of all OTC non-codeine-containing analgesics combined (+37,856 tablets/10,000 population, 95%CI 26,143-49,569), with the greatest increases observed for single-ingredient paracetamol (+41,415 tablets/10,000 population, 95%CI 31,374-51,456), ibuprofen (+1392 tablets/10,000 population, 95%CI 916-1868), combination paracetamol/ibuprofen (+1618 tablets/10,000 population, 95%CI 1567-1669) and other paracetamol combinations (+233 tablets/10,000 population, 95%CI 112-353). We did not observe increases in any non-codeine-containing prescription analgesic sales or a meaningful increase in sales of OTC cold/flu products or cough suppressants containing opioid derivatives with the potential for extra-medical use.

Conclusions: The reduction in OTC codeine sales was offset by sales of OTC paracetamol, ibuprofen, and paracetamol combinations rather than prescription analgesics. These products carry no risk of dependence, but excessive or inappropriate use is associated with harms such as liver damage or gastrointestinal bleeding. Further monitoring of adverse events associated with these products is warranted.

2418 | Trends over time in the implementation of opioid risk minimization measures and in opioid-related harms in Canada: A mixed-methods study

Camille Goyer[1], Genaro Castillon[2] and Yola Moride[1,2,3]

[1]Université de Montréal, Montreal, QC, Canada; [2]YOLARX Consultants, Montreal, QC, Canada; [3]Rutgers, The State University of New Jersey, New Brunswick, NJ

Background: Canada is experiencing a major opioid epidemic. Multiple guidance's, policies and risk minimization measures (RMMs) have so far been implemented without an integrated approach, which makes the evaluation of their effectiveness challenging.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To develop a timeline of policies and interventions in Canada over the past five years and assess trends over time in pharmacovigilance metrics, including the reporting of opioid-related harms, including deaths and, social media coverage.

Methods: The study involved four components: 1) Scoping review of opioid RMMs between 1 January 2016 to 15 November 2019 in Canada; 2) Descriptive analysis of opioid-related harms reported to Canada Vigilance, the national post-market spontaneous reporting database; 3) Qualitative review of opioid-related deaths using narratives of Quebec coroner's reports; 4) Social media coverage on opioids and opioid-related harms (Facebook, Twitter and Reddit) using web-scrapping. Time period for the last three components covered 1 January 2009 to 31 August 2019. Trends over time in RMMs implementation was compared to trends over time in the reporting and social media coverage, without implying causality.

Results: There were 414 Canadian RMMs and policies identified over the study period with a 4-fold increase as of 2016. The most common types were harm reduction (32.0%) (e.g., supervised injection site) and opioid awareness/education (20.0%) (e.g., educational webinars). In Canada Vigilance, there were 6,727 opioid-related harms (4,970 patients) with oxycodone being the most common suspected opioid (30.3%). Most cases were reported by consumers (63.8%) and 98.2% were considered serious. The number of reported cases remained constant over the years 2009 and 2018 (range: 53 - 177/year) while it increased dramatically during the fourth quarter of 2018 (n=661). There were 1,320 opioid-related deaths in Quebec; based on the Coroners' reports, 69.8% were caused by opioids other than heroin, methadone and opium. Compared to 2015, the number of posts increased by 35.4% (Reddit), 329.0% (Facebook) and 381.5% (Twitter) in 2016. Trends plateaued for Reddit and Twitter as of 2017 and increased by 92.5% in 2019 for Facebook, compared to 2016.

Conclusions: A large number of RMMs have recently been implemented in Canada. Trends in the reporting of opioid-related harms increased dramatically as of 2018 and opioid-related deaths in Quebec continue to rise. Media coverage and public awareness have dramatically increased since 2016. Further research is needed to identify which RMM has the greatest impact.

2434 | Application of a frailty index threshold to identify older patients at risk of potentially inappropriate prescribing and adverse drug reactions: A prospective observational study

Shane Cullinan[1], Denis O'Mahony[2] and Stephen Byrne[3]
[1]*Royal College of Surgeons in Ireland, Dublin, Ireland;* [2]*Cork University Hospital/University College Cork, Cork, Ireland;* [3]*University College Cork, Cork, Ireland*

Background: Potentially inappropriate prescribing (PIP) and adverse drug reaction rates (ADR) remain high in the older population. Recent discourse in this area has shown that factors such as fear of deprescribing and lack of time mean that prescribers do not routinely assess the appropriateness of prescriptions for older patients. Previous research by our group identified a frailty index (FI) threshold of 0.16, above which patients were twice as likely to experience PIP and ADRs. The hypothesis was that if these patients at increased risk could be highlighted using a simple indicator such as this, it would urge prescribers to review the medications with an aim to deprescribing or amending the prescription accordingly.

Objectives: The aim of this study was to prospectively apply the frailty index threshold to a new cohort to validate the results obtained previously, and also determine if using such an indicator is more predictive of PIP and ADRs than just using the number of medications a patient takes.

Methods: A FI was constructed and applied to comprehensive geriatric assessments for 545 hospital in-patients. Each patient was then assigned a FI score. Patients above and below the threshold of 0.16 were identified and the relationship between their frailty status and instances of PIP and ADRs was quantified (chi-square test and odds ratios). This was compared to simply using the number of medications as an indicator for predicting PIP/ADRs.

Results: Patients above the FI threshold were significantly more likely to experience an ADR (OR=2.86, p=0.001), and while they were also more likely to experience PIP, this was not significant (OR=1.755, p=0.185). Patients taking 6 or more medications were more likely to experience an ADR, although not significantly (OR=1.27, p=0.189), but *were* significantly more likely to experience PIP (OR=2.45, p<0.0001).

Conclusions: PIP was found to be highly dependent on the number of medications a patient takes. ADRs were found to be more dependent on frailty status. Our previous work found that PIP was highly dependent on *both* frailty and number of medications whereas, similar to this study, ADR occurrence was just found to be related to frailty. Therefore the use of both a FI as well as 'number of medications' seems the best approach to identify patients at risk. These indicators could potentially be implemented in practice by simple 'tick boxes' on a patients chart alerting prescribers to their heightened risk of adverse events.

3715 | Changes in utilization of antihypertensive drugs following angiotensin receptor blocker product recalls in Germany

Salka Enners[1], Marita Kieble[1], Ulrike Rudolph[2], Felix Mahfoud[3], Michael Böhm[3], Ulrich Laufs[2] and Martin Schulz[1,4,5]
[1]*German Institute for Drug Use Evaluation, Berlin, Germany;* [2]*University Hospital Leipzig, Leipzig, Germany;* [3]*Saarland University Medical Center, Homburg, Germany;* [4]*Drug Commission of German Pharmacists (AMK), Berlin, Germany;* [5]*Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany*

Background: Angiotensin receptor blockers (ARBs) are one of the most common drug classes, used by approximately 8 million patients in Germany. Discovery of unacceptable amounts of potentially carcinogenic nitrosamines resulted in more than 30 recalls of generic ARBs, primarily valsartan, between July 4 and December 20, 2018, and in subsequent drug shortages.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: We explored the potential impact of the recalls on the dispensings of valsartan, all ARBs, and other antihypertensives (AHTs).
Methods: We performed a descriptive drug utilization study using the DAPI database of anonymized dispensing data from >80% of community pharmacies at the expense of the statutory health insurance (SHI) funds. Nearly 88% of Germany's population is insured by the SHI system. We included all oral mono and fixed-dose combination products of ARBs, ACE inhibitors (ACEi), calcium channel blockers, and beta-blockers. For the analysis of ARBs individually, we only included mono preparations and combinations with hydrochlorothiazide (HCTZ) because only those were affected by the recalls. We calculated utilization as defined daily doses per 1,000 inhabitants per day (DID). Time trends were analyzed on a quarterly level.
Results: The market shares for valsartan and valsartan/HCTZ drug products recalled in July and November 2018 were both 45% of all valsartan and valsartan/HCTZ-containing drugs. Valsartan dispensings decreased substantially and continuously after first recalls in July 2018 (2Q18: 41.1 DID, 2Q19: 14.0 DID). A simultaneous increase of other ARBs, primarily candesartan was observed. Other ARBs: 2Q18: 77.8 DID, 2Q19: 116.0 DID, of which candesartan was: *2Q18: 57.7 DID, 2Q19: 93.4 DID*. Effects on utilization of ACEi and AHTs overall were not observed. ACEi: 2Q18: 212.3 DID, 2Q19: 209.7 DID; AHTs: 2Q18: 520.9 DID, 2Q19: 529.5 DID. Similarly, there was no impact on the moderate, but continuous increase of the total volume of ARB dispensings (2Q18: 129.4 DID, 2Q19: 141.1 DID).
Conclusions: We noted a substantial decrease in utilization of valsartan but not losartan, irbesartan, olmesartan, or telmisartan after generic ARB product recalls. The total volume of ARB further increased and AHT utilization overall remained nearly unchanged suggesting shifts within the class of ARBs, mostly to candesartan.

3762 | Use of tramadol and other opioids following media attention and risk minimization measures from regulators: A Danish nationwide drug utilization study

Anne Mette S. Sørensen[1], Lotte Rasmussen[2], Martin T. Ernst[2], Stine H. Mogensen[3], Mona V. Laursen[3], Espen Jimenez Solem[1] and Anton Pottegård[2]
[1]*Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark;* [2]*University of Southern Denmark, Odense, Denmark;* [3]*Danish Medicines Agency, Copenhagen, Denmark*

Background: Use of tramadol, including its potential for abuse, has been heavily discussed in recent years. In Denmark, use of tramadol received considerable attention from lay media in June and December 2017. Further, several regulatory actions were taken in September 2017 and January 2017 to restrict the use of tramadol and other opioids.
Objectives: To describe the use of tramadol and other opioids in Denmark following lay media attention in June and December 2017 and regulatory actions in September 2017 and January 2018.
Methods: Using the Danish nationwide health registries, we described the use of tramadol and other opioids in the adult Danish population during 2014 to mid-2019.
Results: From early 2017 until mid-2019, total tramadol use decreased markedly (37%) while total use of morphine and oxycodone use decreased slightly. The quarterly prevalence of tramadol use decreased from 32/1,000 individuals in 2014 to 19/1,000 mid-2019, dropping mainly at the time of media attention. Concomitantly, the prevalence increased for oxycodone (from 5.1 to 7.7) and morphine (from 8.5 to 9.5), mainly due to more short-term and sporadic users, and decreased for codeine (from 14 to 9.4). From 2014 to mid-2017, the incidence of tramadol use was stable (around 2.2/1,000 person-months) but dropped in June 2017 to 1.7/1,000, coinciding with the media attention, and continued to decrease thereafter (to 1.1/1,000 in mid-2019). Tramadol was primarily initiated by GPs (64% in 2018) and hospital prescribers (27%), while treatment was mainly maintained by GPs (93%).
Conclusions: We identified a decline in the use of tramadol coinciding in time with the media attention in 2017 which continued during the regulatory actions taken in 2017-2018. During the same period, the use of other opioids also decreased slightly and generally, there was no evidence of unintended effects on the utilization of opioids related to the media attention and regulatory actions.

3825 | Utilization of sacubitril/valsartan in real-world settings

Efe Eworuke[1], Talia Menzin[2], Joy Kolonoski[2] and Ting-Ying Huang[2]
[1]*US Food and Drug Administration, Silver Spring, MD;* [2]*Harvard Pilgrim Health Care Institute, Boston, MA*

Background: Sacubitril/Valsartan (SV) is first-in-class angiotensin-neprilysin-receptor-inhibitor (ARNI) and angiotensin-receptor-blocker (ARB) approved for the treatment of patients with Heart Failure with Reduced Ejection Fraction (HFrEF). In 2016, the American College of Cardiology (ACC) recommended replacing of angiotensin-converting-enzyme inhibitors (ACEI) or ARB by an ARNI for chronic symptomatic HFrEF to further reduce morbidity or mortality. Real-world utilization of SV is unknown.
Objectives: To evaluate SV use among patients with heart failure (HF) and describe patient characteristics.
Methods: We conducted a retrospective cohort study including HF patients 18 years and older between January 2015 and July 2019 in the Sentinel Distributed Database. We identified new users of ACEI, ARB and the following SV cohorts: new SV users with ACEI (ACEI-SV new users) or ARB (ARB-SV new users) use in the 183 days prior (baseline); SV users who switched from new use ACEI (new-ACEI-SV switchers) or ARBs (new-ARB-SV switchers); and new users of SV without ACEI or ARB in the baseline (new SV users). We followed patients from the SV dispensing (index) date to the earliest of switching to ACEI or ARB, end of treatment episode, disenrollment, death or end of available data, whichever came first. For each cohort,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

we obtained the number of users each month, time to switch, and patient characteristics before and on the index date.

Results: We identified 703,848 and 318,588 new ACEI and ARB users, compared to 58,141 and 41,351 ACEI- and ARB-SV new users; 6,622 and 3,361 new-ACEI- and new-ARB-SV switchers; and 30,557 and 30,547 new SV users without same-day ACEI and ARB dispensing respectively. Over time, the use of SV increased in all cohorts, with the ACEI-SV new user cohort consistently being the largest. Baseline characteristics were comparable across all SV cohorts. The proportion of SV users who switched to ACEI or ARB was generally low but switching to ARB was more frequent (5.7%). The shortest time to switch (median [Q1-Q3]: 42 [20-99] days) was observed among new SV users who switched to ACEI. The longest time to switch (75 [39-169]) was observed among new-ACEI-SV switchers who switched back to ACEI.

Conclusions: The use of SV for HF remains low with no impact from the recent recommendation by ACC. Barriers to utilization of SV need to be further assessed.

4031 | Utilization and evaluation of chemotherapeutic agents in management of carcinoma breast

U.R. Rakshith[1] and M.S. Vishveswara[2]

[1]JSS College of Pharmacy, JSS AHER, Mysuru, India; [2]Bharath Hospital and Institute of Oncology, Mysuru, India

Background: Breast cancer are the cancer which arising from breast tissue. The incidence of cancer in India is 70-90 cases per 100,000 populations and cancer prevalence is established to be around 2,500,000 (2.5 million) with over 800,000 in India breast cancer has been associated with greater urbanization and changing lifestyles. A drug utilization evaluation study can help us in understanding the prescribing patterns of a drug and possibly the factors influencing the prescribing. Implementation of DUE helps to improve the quality and cost-effectiveness of the drug use thereby improving the patient care.

Objectives: The study was undertaken with aim to assess the prescribing pattern in treatment of breast cancer, to determine the rational use of drug according to the type and grade of breast cancer.

Methods: The prospective observational study was carried out for a period of 6 months in Bharath hospital and institute of oncology Mysuru. The study included all the participants who are receiving adjuvant and neoadjuvant chemotherapy in wards as well as in day care center for carcinoma of breast. All the data were collected from patient case records, laboratory data, Patient or patient's caretaker(s) interview, Treatment chart, by Interviewing healthcare professionals. assessment of utilization of chemotherapeutic agents were carried in hospital. Descriptive statistics were applied to establish the findings.

Results: A total of 100 patients who were receiving anti-cancer agents as either adjuvant or neoadjuvant therapy for breast cancer. Breast cancer were found to be more common among age groups of 50-59 (n=55%), followed by 36-49 years(n=27%), ≤ 35 years (n=13%), ≥70 years (n=5%). Out of 100 study participants 49 women were in premenopausal, 51 individuals were postmenopausal. Majority of participants (34%) were prescribed with AC regimen followed by FAC (17%), FEC (11%). The single drug treatment (2%) was given only for the palliative purpose. 91.17% of individuals who received AC regimen were found be appropriate and 8.82% individuals were found to be in appropriate. In AC Paclitaxel regimen 100% appropriateness was able to find out according to the patient condition. 94.44% FAC regimen was found to be appropriate and 5.55% were found to be inappropriate.

Conclusions: The selection of chemotherapeutic agents was found in compliant with NCCN guidelines. Uses of antiemetic drugs need further improvement in terms of frequency and choice of drug in many cases. Education and training program to nursing staff would certainly help to improvise the delivery of chemotherapy.

4084 | A mixed methods analysis of the use of the systematic tool to reduce inappropriate prescribing in Swiss primary care practices

Katharina T. Jungo[1], Fabian Schalbetter[1], Michael J. Deml[2,3] and Sven Streit[1]

[1]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland; [2]Swiss Tropical and Public Health Institute, Basel, Switzerland; [3]University of Basel, Basel, Switzerland

Background: With an increasing number of older multimorbid adults (ages >65) with potentially inappropriate polypharmacy, evidence-based clinical decision support systems (CDSS), such as the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant, are promising tools for assisting medication reviews. Little is known about how general practitioners (GPs) perceive the use of CDSS.

Objectives: To explore the use of the STRIP assistant by GPs during a randomized controlled trial.

Methods: We utilized an explanatory mixed methods design, meaning that we first collected quantitative data, which we sought to subsequently better understand through qualitative methods. First, quantitative data about the acceptance and implementation of 'Screening Tool of Older Person's Prescriptions' (STOPP) and 'Screening Tool to Alert doctors to Right Treatment' (START) recommendations, generated by the STRIP assistant, were collected from GPs (N=19) about their patients (n=149). The mean number of recommendations generated, the proportions of different recommendation types, and the proportions of recommendations accepted and implemented by GPs were calculated. Then, semi-structured qualitative interviews (n=9) were conducted with GPs, with the interview guide having been informed by preliminary quantitative data. A framework method analysis will be conducted upon qualitative data collection completion. The combined analyses of both quantitative and qualitative data will allow for better data triangulation.

Results: The mean number of STOPP, START, dosage recommendations and drug-drug interaction alerts generated by the STRIP assistant per study participant was 1.4, 2.3, 0.2, and 1.8 respectively. 40%

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

were START recommendations, 25% were STOPP recommendations, 3% were to adapt the dosage, and the rest highlighted drug-drug interactions. GPs reported to discuss 16% of all recommendations generated with patients in a shared decision-making process. 42% of the latter were reported to be implemented. Preliminary qualitative results demonstrate that there are technical problems related to the STRIP assistant's usability, GPs had high expectations about the tool's functionalities, and they had difficulties implementing recommendations together with patients.

Conclusions: Findings indicate that the use of the STRIP assistant by GPs is affected by several limiting factors. GPs only discussed and implemented a small number of recommendations with patients. The qualitative findings help explain the low acceptance and implementation rate of recommendations.

4126 | When less is better: Increase in paracetamol use and poisonings in Switzerland following the introduction of 1,000mg oral tablets

Adrian Martinez-De la Torre[1], Stefan Weiler[1,2], Dominic Stefan Bräm[1], Hugo Kupferschmidt[2] and Andrea M. Burden[1]
[1]*ETH Zurich, Zurich, Switzerland;* [2]*National Poisons Information Centre, Tox Info Suisse, Zurich, Switzerland*

Background: Paracetamol (acetaminophen) is one of the most used pain medications worldwide. While safe within the therapeutic range (<4,000mg daily), intake exceeding daily dose thresholds can lead to hepatotoxicity. In October 2003, 1,000mg oral tablet paracetamol was approved for use in Switzerland. Prior to this, only the 500mg oral tablets were available.

Objectives: To evaluate the impact of the introduction of 1,000mg paracetamol tablets to the Swiss market on utilization and potential poisonings.

Methods: National community pharmacy sales data of oral paracetamol tablets were obtained between 2000 and 2018. Using data from the National Swiss Poisons Centre (Tox Info Suisse), all calls related to poisonings with oral paracetamol tablets between 2000 and 2018 were identified. The total pills sold were tabulated and plotted by calendar year and quarter, and stratified by formulation (500mg vs 1,000mg). The poisonings data were stratified by circumstance of poisoning (accidental vs intentional). An interrupted time series (ITS) analysis examined the impact of introducing 1,000mg, with quarter four (Q4) of 2003 identified as the intervention date. Patient characteristics at the time of reported poisoning were summarised, stratified by pre- and post-intervention periods. Ibuprofen related poisonings were used as a comparator.

Results: There was a rapid uptake in the sales of 1,000mg paracetamol from the introduction in Q4 of 2003, while sales of 500mg steadily decreased. National sales of paracetamol tablets plateaued in 2012, after which an average of 920,000 tablets of 500mg and 6.9 million 1,000mg tablets were sold monthly. From the Tox Info Suisse, we identified 15,790 paracetamol related calls between 2000 and 2018. The ITS analysis identified a significant increase in the number of reported poisonings for paracetamol tablets after the introduction of the 1,000mg dosage form, particularly for accidental circumstances. The proportion of accidental poisonings increased significantly from 20% to 31%. Similarly, the mean dose increased from 6,900mg to 9,000mg. While ibuprofen poisonings increased during the observation period, the significant change point was Q3 2012.

Conclusions: The introduction of 1,000mg paracetamol tablets to the Swiss market in 2003 resulted in an immediate increase in the sales and reports on poisonings with paracetamol in Switzerland. As there is lacking evidence of the clinical effectiveness of paracetamol (500mg or 1,000mg) on pain management, the availability of 1,000mg should be re-evaluated to minimise the risk of accidental poisonings.

4258 | The impacts of publishing evidence on the utilization of oseltamivir and peramivir at an emergency department in South Taiwan

Chen-En Liu[1] and Teng-Chou Chen[2]
[1]*Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan;* [2]*Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom*

Background: About 10% of the emergency department (ED) visits in Taiwan were related to respiratory diseases including influenza in 2018. In addition to taking oral oseltamivir for 5 days, a systematic review (SR) published in July 2017 suggested that the time to alleviation of influenza symptoms or fever was shorter in patients receiving single-dose intravenous peramivir for influenza. However, the influence of the SR on the utilization of these two medicines was still unclear.

Objectives: This study aimed to explore the impacts of the published SR on the utilization of oseltamivir and peramivir at an ED.

Methods: This retrospective cross-sectional study used aggregate-level dispensing data extracted from the hospital information system in a medical center in southern Taiwan from January 2017 to December 2019. Patients who were prescribed oseltamivir and peramivir for influenza at ED were included and the prescriptions of these two medicines were extracted. Monthly utilization of oseltamivir and peramivir was quantified by the number of total defined daily doses (DDDs). An interrupted time-series analysis was performed to evaluate the impacts of the SR on the monthly utilization of oseltamivir and peramivir in July 2017. As influenza has seasonal pattern, an additional time point (December 2017) was tested in the sensitivity analysis to identify potential delay of the effects from July 2017.

Results: Before July 2017, the monthly utilization of oseltamivir increased by 70.8 DDDs (p=0.026) per month. After publishing the SR, the level (β_2: -214.0, p=0.047) and the trend (β_3: -70.9, p=0.027) of monthly utilization of oseltamivir decreased significantly. However,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

there was no significant change in the level and the trend of monthly utilization of peramivir after July 2017, and the baseline trend of monthly utilization of peramivir keep increasing (β_1: 2.3, p<0.001) from the introducing of peramivir in the medical center in January 2017. The utilization of both oseltamivir and peramivir were not change significantly in December 2017, and this implied that there is no delay effect.

Conclusions: The utilization of oseltamivir decreased after publishing the SR, and peramivir remained its increasing trend from its introducing in January 2017. Further studies need to apply individual patient data to evaluate the appropriateness of prescribing peramivir by identifying patients' characteristics and treatment outcomes.

4309 | Effectiveness of a targeted and tailored pharmacist-led intervention to improve adherence to antihypertensive drugs among patients with type 2 diabetes in Indonesia: A cluster randomized controlled trial

Sofa Dewi Alfian[1,2], Petra Denig[3,4], Rizky Abdulah[5], Hadyana Sukandar[6], Job F.M. van Boven[3,4] and Eelko Hak[1,4]

[1]University of Groningen, Groningen, Netherlands; [2]Universitas Padjadjaran, Jatinangor, Indonesia; [3]University of Groningen, University Medical Centre Groningen, Groningen, Netherlands; [4]Medication Adherence Expertise Centre Of the Northern Netherlands (MAECON), Groningen, Netherlands; [5]Universitas Padjadjaran, Jatinangor, Indonesia; [6]Universitas Padjadjaran, Bandung, Indonesia

Background: Current intervention programs to improve drug adherence are either too complex or expensive for implementation and scale-up in low-middle income countries.

Objectives: To assess the effects of implementing a low-cost, targeted and tailored pharmacist intervention among patients with type 2 diabetes who are non-adherent to antihypertensive drugs in a real-world primary care Indonesian setting.

Methods: A cluster randomized controlled trial with 3-month follow-up was conducted in 10 community health centers (CHCs) in Indonesia among type 2 diabetes patients aged 18 years and older who reported non-adherence to antihypertensive drugs according to the Medication Adherence Report Scale (MARS). Patients in CHCs randomized to the intervention group received a tailored intervention based on their personal adherence barriers at baseline and at 1-month follow-up. Interventions might include reminders, habit-based strategies, family support, counseling to educate and motivate patients, and strategies to address other drug-related problems. Patients in CHCs randomized to the control group received usual care based on the Indonesian guideline. Primary outcome was the between-group difference in medication adherence change from baseline to 3-month follow-up. Secondary outcomes included changes in patients' blood pressure and their medication beliefs.

Results: In total, 201 patients were screened for eligibility to participate. Of them, 113 patients (56 in control group and 57 in intervention group) met the inclusion criteria. Compared with usual care, the intervention significantly improved patient's self-reported adherence (mean difference 2.78 [95%CI: 1.65; 3.91, p-value = <0.001]) at 3-month follow-up. No significant differences in blood pressure level and concern beliefs were found within and between intervention and control groups. Perceived necessity for using antihypertensive drugs increased significantly over time among patients in the intervention group (p-value = 0.024).

Conclusions: A targeted and tailored pharmacist-led intervention resulted in a statistically significant increase in medication adherence and perceived necessity but no significant differences were found in blood pressure level between groups. Future study is needed on identifying which groups derive the most clinical benefit from adherence improvement.

4383 | Protocol for a cluster randomized tailored educational intervention to reduce potentially inappropriate medication among older adults at community healthcare institutions in Beijing

Mengyuan Fu[1,2], Xiaodong Guan[1,2,3] and Luwen Shi[1,3]

[1]School of Pharmaceutical Sciences, Peking University, Beijing, China; [2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [3]International Research Center for Medicinal Administration, Peking University, Beijing, China

Background: Potentially inappropriate medications (PIMs) are prominent prescribing issues in elderly patients worldwide. Evidence suggests that adequate interventions of PIMs can affect behaviors of healthcare providers, and improve appropriate drug use. However, no study has involved interventions to reduce the PIMs among elderly patients in China.

Objectives: To evaluate the effectiveness of tailored educational intervention, carried out towards general practitioners (GPs) in Chinese primary healthcare institutions, aiming at reducing the occurrence of PIMs in elderly patients.

Methods: 20 primary healthcare stations (CHSs) in Dongcheng district in Beijing will be recruited to a cluster randomized controlled trial. CHSs will be randomized to intervention or control arm with allocation ratio of 1:1. A multifaceted intervention has been tailored towards GPs in intervention arm, where key components are 2-day general training of PIMs guidelines, distributing printed drug handbook including risk and alternative therapeutic options for each drug, and sending individual feedback reports of baseline practice to each participating GP. The control arm will continue their current procedures during the study period. Prescription data for eligible elderly patients (age≥60) from both arm, 3-month prior and after the initiation of the trial, will be derived from Dongcheng Health Service System. *Criteria of PIM for Older Adults in China* will be used as both an educational tool and a quality measure. The primary outcome is the change in proportions of elderly patients exposed to at least one PIM following the intervention. The trial has received ethic approval from Peking University Institution Review Board.

Results: /

Conclusions: /

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4513 | Effect of bariatric surgery on opioid uses for osteoarthritis in the United States, 2010-2017

Enoch J. Abbey[1], Richard Nudotor[1], Joseph Canner[2], Jennifer Mammen[2] and Kimberley Steele[1]

[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [2]*Johns Hopkins Hospital, Baltimore, MD*

Background: Obesity is a well-known risk factor for osteoarthritis (OA) which in turn may be treated with prescription opioids. We quantified changes in such use among individuals with OA undergoing bariatric surgery.

Objectives: We aimed to determine the effect of bariatric surgery on opioid prescription use among patients with osteoarthritis.

Methods: We performed a retrospective cohort study of individuals captured within the IBM MarketScan commercial claims database, from 2010 to 2017. To do so, we first derived a cohort of individuals undergoing bariatric surgery and a diagnosis of OA using ICD-9, ICD-10 & CPT codes at baseline. Individuals had at least a 6-month history of opioid-use prior to surgery. Remission of opioid use was defined as no refill of opioids 90 days after a patients' medication was expected to run out post-operatively and relapse as medication refill after at least 90 days of remission. Cox proportional hazards regression to estimate crude and adjusted hazard rations were used.

Results: Of 718 patients with a diagnosis of OA undergoing bariatric surgery between 2010 and 2017, 523(72.8%) experienced remission of opioid-use after surgery. A total of 262 (50%) later experienced relapse and were placed back on opioids, likely for osteoarthritis. Roux-en-Y Gastric Bypass was associated with a lower risk of remission (HR= 0.80 [95% CI; 0.66, 0.96]) and a higher rate of relapse (HR= 1.22 [95% CI; 0.94, 1.6]) compared to Sleeve Gastrectomy. A greater exposure to opioids at the time of surgery and a higher BMI were associated with a lower rate of remission and a higher rate of relapse of opioid use after bariatric surgery.

Conclusions: Bariatric surgery appears to reduce opioid use in patients with osteoarthritis by reducing chronic opioid use and therefore the risk of addictions. A higher exposure of opioids at time of surgery and a higher preoperative BMI are important predictors of remission of opioid use after weight loss surgery, and may correspond to existing dependence and limited improvement in OA respectively.

4568 | Antihypertensive treatment patterns in the United Kingdom

Tianze Jiao[1], Kristian B. Filion[1,2], Antonios Douros[1,2] and Robert W. Platt[1]

[1]*Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada;* [2]*Department of Medicine, McGill University, Montreal, QC, Canada*

Background: Several drug classes are marketed for treating hypertension, and international treatment guidelines are inconsistent in recommendations. As a result, there is a need to better understand how antihypertensive drugs are used in clinical practice.

Objectives: To describe antihypertensive treatment patterns in the UK, which include treatment pathway and length of utilization on each combination, among newly treated hypertensive patients by emulating a target trial.

Methods: The data source for our study was the Clinical Practice Research Datalink, a population-based clinical database that contains electronic clinical records for > 16 million patients seen at > 700 general practitioner practices in the UK. We created a base-cohort of patients with hypertension, defined by a new diagnostic code or elevated blood pressure readings. We included patients initiating an antihypertensive drug between January 1998 and June 2018, with cohort entry defined by the date of this prescription. We applied the same inclusion criteria as the SPRINT trial, a blood pressure management trial, but included patients regardless of their estimated cardiovascular (CVD) risk or diabetes status. Visualization techniques and descriptive statistics were applied to present the treatment pattern, demographic and clinical characteristics.

Results: Our cohort included 660,545 patients. The mean age was 59.7 (standard deviation [SD]: 13.5) years, and 49.0% were men. Patients at low, medium, and high CVD risk were 29.8%, 30.6% and 39.6% of the population. On average, patients received 1.04 (SD: 0.24) antihypertensive drugs at baseline. Overall, 29.0.%, 22.1%, and 21.0% of patients received angiotensin-converting enzyme inhibitors (ACEI), thiazide diuretics (TD), and calcium channel blocker (CCB) as monotherapy at baseline, with subsequent treatment changes occurring after a median of 299, 112, and 182 days. Compared to 2001, patients were more likely to receive an ACEI (16.5% vs. 38.0%) or a CCB (9.4% vs. 36.2%) in 2011. Women were more likely to receive a TD (27.0% vs. 17.0%) as first line therapy than men. Black patients were twice as likely to receive CCB as the first line therapy as Caucasians. Compared to patients at low CVD risk, high-risk patients were less likely to receive an ACEI (33.5% vs. 24.4%) but more likely to receive a CCB (14.4% vs. 25.3%). Over time, fewer different treatment combinations were prescribed, with beta-blockers rarely prescribed with TD.

Conclusions: Several factors were associated with variation of treatment patterns for hypertension. Further analyses assessing clinical outcomes associated with varied treatment patterns are urgently needed.

4585 | Drug utilization evaluation of chemotherapy drugs in various cancers in India

Niharika Jupaka

Talla Padmavathi College of Pharmacy, Warangal, India

Background: Cancers have emerged as a leading cause of mortality in recent years. Though a diverse option of chemotherapeutics is available, rational use is key to success in cancer therapeutics. Evaluating the prescribing patterns of chemotherapy drugs for ensuring effectiveness and patient's quality of life.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To describe chemotherapy regimen utilization, effectiveness and evaluate use against national treatment guidelines.

Methods: A prospective observational study was conducted in department of medical oncology in tertiary care hospitals for a period of three months. Patients with various types of cancers and who were willing to fill informed consent form were included for study. The data were collected in a suitably designed data collection form. Most of the drugs prescribed from the Government of India's National List of Essential Medicines (NLEM).

Results: Among150 patients, the most were female (56%) and most commonly in the 61-75 year old age group (32%). The prevalence of cancers and the most frequently prescribed regimens in these cancers were the following: -lung cancer 22% - paclitaxel and carboplatin (51%).-breast cancer 14% - doxorubicin and cyclophosphamide (40%).-ovarian cancer 9.3% - paclitaxel and carboplatin (73%). -stomach cancer8% - oxaliplatin (60%). The only supportive care medication prescribed for every patient was dexamethasone, and the most commonly prescribed anti-emetic drugs were aprepitant(94%) and palanosetron (97%). Use of chemotherapy drugs in this hospital was found to follow National Comprehensive Cancer Network (NCCN) guidelines.

Conclusions: The utilization of anti-cancer drugs in these hospitals was found to be rational and more than 70% of drugs were prescribed from the NLEM. Assessment of pattern of prescribing should be conducted periodically to minimize the untoward effects of cancer treatments as far as possible.

4661 | Deprescribing in older people: Pharmacoepidemiological tools and measures

Katja Taxis[1], Carina Lundby[2], Lisa Pont[3], Wade Thompson[2], Petra Denig[4] and Anton Pottegård[2]

[1]University of Groningen, Groningen, Netherlands; [2]University of Southern Denmark, Odense, Denmark; [3]University of Technology Sydney, Sydney, Australia; [4]University Medical Center Groningen, Groningen, Netherlands

Background: In an ageing society with a high prevalence of people with multimorbidity and polypharmacy, deprescribing is an emerging concept. Deprescribing can be defined as the planned dose reduction or stopping of medication to improve health-related outcomes or reduce the risk of adverse events. Pharmacoepidemiological tools and measures are needed to support and evaluate the implementation of deprescribing.

Objectives: This symposium will provide an overview of concepts, methods and tools for identifying patients in need of deprescribing as well as for assessing determinants and outcomes of implementing deprescribing. The symposium is intended for researchers, clinicians, and policy makers with an interest in drug utilization research and medicine use in complex populations.

Description: In this symposium we will focus on innovative tools and outcome measures needed to support and evaluate deprescribing in various clinical settings. Anton Pottegård will provide an introduction to the concept of deprescribing, highlight challenges ahead and specific areas where pharmacoepidemiology might contribute with important insights. Petra Denig and Wade Thompson will give an overview of screening tools to ascertain the need for deprescribing. This includes the development of an algorithm with artificial intelligence modeling to identify patients in need of deprescribing. Katja Taxis will discuss the value of various outcome measures to evaluate deprescribing interventions, making use of existing databases. This will include how to measure drug burden in patients with multimorbidity. Carina Lundby will discuss how drug utilization studies can be used in deprescribing research. A recent study exploring medication use among Danish nursing home residents will be used as an example of this and include considerations on how findings can be applied in similar populations across countries. It will further include highlighting of potential reasons for trends in medication use as well as considerations on how to facilitate more appropriate medication use in vulnerable populations like the nursing home population. Lisa Pont will present a case study that illustrates several aspects highlighted in the other lectures. The symposium will conclude with an open panel discussion led by questions from participants.

4768 | Implementing the HOUVAST 2.0 intervention in the Dutch primary care, lessons learned from a process evaluation

Stijn Hogervorst

Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Background: Despite the existence of many effective adherence interventions, they are rarely used in routine care. This gap between research and practice calls for more emphasis on the implementation of adherence interventions.

Objectives: This pilot project aims to implement an existing adherence intervention (HOUVAST 2.0) in the Dutch primary care.

Methods: A qualitative process evaluation was conducted as part of a medication adherence pilot project (HOUVAST 2.0). Data were collected through a focus group and four interviews with ten allied GP and pharmacy staff members. Interviews and focus groups were semi-structured using topic lists based on the RE-AIM implementation framework. Interviews were audiotaped and transcribed verbatim. Atlas.ti 8.0 software was used for coding and structuring of themes. A thematic analysis of the data was performed.

Results: Main themes that emerged were 'Training and preparation', 'Appreciation for the intervention' 'Technical barriers to implementation' and 'social barriers to implementation'.

The intervention HOUVAST 2.0 proved engaging for clinicians that used the intervention, but also proved difficult to implement. The main barriers were a suboptimal selection process based on pharmacy refill data, a difficult target population, nurse practitioners' difficulties addressing adherence with patients and the project did not align with goals of GPs.

Conclusions: Implementation of the HOUVAST 2.0 intervention in the Dutch primary care proved challenging. A good established collaboration between GPs and pharmacies, better ICT applications for selecting patients and a training more aimed towards practical

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

communication techniques are important improvements needed for further implementation.

4771 | Antipsychotic treatment changes in incident parkinsonism treated with levodopa

Sibylle de Germay[1], Olivier Rascol[1,2], Jean-Louis Montastruc[1,2] and Maryse Lapeyre-Mestre[1,2]
[1]*Service de Pharmacologie Médicale et Clinique, Centre Hospitalier Universitaire de Toulouse, Toulouse, France;* [2]*CIC INSERM 1436, Centre Hospitalier Universitaire de Toulouse, Toulouse, France*

Background: Neurodegenerative parkinsonisms like Parkinson's disease were treated by dopatherapy to improve motor symptoms caused by dopamine deficit. Psychotic symptoms were found in 40-60% of Parkinson's disease patients. Treating these symptoms by antipsychotics is difficult since these drugs block dopaminergic receptors, leading to worsening motor symptoms. Antipsychotics induce secondary parkinsonisms but their population-attributable fraction of PD was also estimated at 21.7% in a French cohort study. Continuation of antipsychotics after parkinsonism diagnosis leads to a risk of dopaminergic and anti-dopaminergic co-prescriptions.
Objectives: The study aimed to investigate if the start of parkinsonism healthcare went along with changes in antipsychotic use.
Methods: A repeated monthly cross-sectional study was performed between 2006 and 2017, using data of patients with incident levodopa-treated parkinsonism from the French national health database. A six-month lag was introduced before the start of parkinsonism healthcare (defining the diagnosis date) since it is a period of an overall increase in health care consumption. The two years preceding this lag time defined the "pre-diagnosis" period and the two years after the diagnosis defined the "post-diagnosis" period. The number of patients exposed to at least one antipsychotic was measured monthly during the two periods and viewed with streamgraphs.
Results: During the study period, 1,258 patients with incident parkinsonism were identified (mean age 76.6 years ±9.2; 50% of women). During the pre-diagnosis period, 13.6% of patients were exposed to antipsychotics and 14% during the post-diagnosis period. Risperidone was the first used followed by cyamemazine, tiapride and haloperidol. No major changes in terms of antipsychotic classes were observed after the start of dopatherapy, with the exception of a decrease in sulpiride and levomepromazine use. Antipsychotics introduced in the post-diagnosis period were mainly tiapride, risperidone and clozapine. Patients exposed to both antipsychotics and dopatherapy in post-diagnosis period represented 14% of the study population.
Conclusions: This population-based study revealed a high antipsychotic exposure in parkinsonian patients during the "pre-diagnosis" and "post-diagnosis" periods without major changes in terms of antipsychotic classes after dopatherapy beginning. These practices led to a frequent co-prescription of antipsychotics and dopaminergic drugs, reflecting the difficulties encountered by practitioners in treating psychosis associated with neurodegenerative parkinsonism.

4794 | Association between digoxin use and SCD in individuals with the rs10494366 variant of the NOS1AP gene: The Rotterdam study

Negin Soroush, Albert-Jan Aarnoudse, Fereshteh Shokri, Marten Van den Berg, Fariba Ahmadizar and Bruno Stricker
Erasmus University Medical Center, Rotterdam, Netherlands

Background: Digoxin is one of the oldest cardiovascular medications still used to treat heart failure and atrial fibrillation. Due to its narrow therapeutic window, it is associated with life threatening intoxication and arrhythmias, and with QTc-shortening. Common genetic variation in the nitric oxide synthase-1 adaptor protein (NOS1AP) has been associated with QTc interval prolongation and sudden cardiac death (SCD).
Objectives: We investigated whether the rs10494366 variant of the NOS1AP gene modified the risk of SCD in patients using digoxin
Methods: Design: A prospective population-based cohort study **Setting:** The Rotterdam Study (RS). We included data of the three (RS) cohorts, started as of January 1st, 1991 until January 1st 2014. **Exposures**: Digoxin current use on the date of cardiac death in cases and the same day of follow-up in the remainder of the cohort as a time-dependent variable. **Main outcome**: SCD defined as sudden and unexpected death as a result of cardiac causes, according to international criteria. Identification and adjudication of SCD was performed independently, before the start of this study. **Statistical analysis:** We used Cox proportional hazard regression analysis to investigate the associations between NOS1AP rs10494366 variant and incident SCD among digoxin users and non-users. Associations were adjusted for age, sex and BMI, prevalent diabetes, myocardial infarction, baseline hypertension and smoking status (past, current, never).
Results: We included 14,594 individuals, with a mean age of 65.3 (SD 10.3) years. Almost 59% were female. The cumulative incidence of SCD was 9.5% (609 cases) by the end of follow up. Among them, 98 (16%) individuals were exposed to digoxin at the time of death. In model 1 adjusted for age and sex, NOS1AP rs10494366 variant was not associated in the total study population. However, an interaction term of the gene with the daily dose of digoxin was significantly associated with increased risk of SCD (p-value 0.0001). The risk of SCD in current users of digoxin was 4.2 [95% CI 1.3-13.8] for the GG genotype; for the GT genotype, the risk was 2.1 [95%CI 1.1-4.2]; and for the TT genotype was 1.5 [95%CI 0.7-3.2] in fully adjusted models.
Conclusions: NOS1AP rs10494366 variant modified the risk of SCD in users of digoxin. Individuals with the homozygous minor GG allele had a fourfold increased risk of SCD.

4812 | Factors associated with switching from oral glucose-lowering medications to insulin therapy in type 2 diabetes: The Rotterdam study

Payam Peymani[1], Marten van den Berg[2], Bruno Stricker[2] and Fariba Ahmadizar[2]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Department of Clinical Pharmacology & Toxicology, University Hospital Zurich, Zurich, Switzerland; [2]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands

Background: Little is known about factors associated with the decision to switch from oral use to insulin in type 2 diabetes (T2D) patients.

Objectives: Therefore, we investigated factors associated with switching from oral glucose-lowering medications to insulins therapy as a proxy for diabetes progression.

Methods: ***Study design:*** A longitudinal prospective cohort study ***Study Setting:*** Rotterdam Study For this study, we included all pharmacologically treated T2D patients (n=1590). The primary endpoint was switching from oral glucose-lowering medications to insulin therapy. We defined 'switchers' as subjects who switched to insulin therapy (ATC code A10A) with or without continuation of oral glucose-lowering medication. We assessed the association between switching and patients' characteristics including age, gender, body mass index (BMI), waist circumference (WC), smoking, systolic blood pressure (SBP), diastolic blood pressure (DBP), socio-economic status, physical activity, lipids and C-reactive protein (CRP). A modified Cox regression analysis (Fine-Gray model) considering death as the competing risk was used, providing sub-distribution hazard ratio (SHR) and 95% confidence interval (CI).

Results: Mean (SD) age was 67.0 (10.5) years. Almost 56% of patients were females and 41% were obese (BMI≥30 kg/m^2). The frequency rate of switching was 45.1% over a mean follow-up of 4.8±4.2 years. Patients who died during the follow-up study were significantly older than the switchers (p=0.01). Switchers had a higher mean of BMI (p=0.01), and higher systolic blood pressure (SBP) (p=0.01). In univariate analyses age (SHR: 0.96, 95% CI: 0.95 - 0.97), BMI (1.03: 1.02-1.05), WC (1.01: 1.00-1.02), and SBP (1.01: 1.00-1.02) were statistically significantly associated with switching. However, in multivariable adjusted models, the associations were no longer significant except for age.

Conclusions: We showed different individual factors which were associated with switching from oral use to insulin in population with T2D. Our study highlights that insulins added to the standard oral glucose-lowering medication are mainly used in younger T2D patients.

4817 | Preventive effect of antiplatelet salicylates in individuals with type 2 diabetes - The Rotterdam study

Fereshteh Shokri, Negin Soroush, Bruno Stricker and Fariba Ahmadizar

Erasmus University Medical Center, Rotterdam, Netherlands

Background: Antiplatelet salicylates are commonly used for prevention of cardiovascular disease (CVD) in general population. Type 2 diabetes mellitus (T2D) has unfavorable consequences on blood vessels, including macro and microvascular diseases. Although Antiplatelet salicylates are approved agent used to prevent CVD in diabetic patients, there are some patients who do not respond to this medication.

Objectives: We aimed to investigate if low dose antiplatelet salicylates prevent incident CVD by comparing free of diabetes individuals and T2D patients.

Methods: Design: A longitudinal cohort study. Setting: Prospective population-based Rotterdam Study (RS), the Netherlands. We included data of the three (RS) cohorts, starting from March 1997 to January 2015. Exposures: Current use of low dose Carbasalate Calcium or Acetylsalicylic acid (100 mg/day or lower). Main outcome: Incidence of any CVD events defined as a composite endpoint of: myocardial infarction (MI), coronary heart disease (CHD), heart failure (HF), Stroke or CVD mortality during follow-up. Prevalent cases of MI, CHD, HF, and stroke at baseline were excluded from the analyses. Statistical analysis: We applied Cox regression analysis to determine adjusted hazard ratios (HR) and 95% Confidence intervals (CI) for the association of current use of Antiplatelet salicylates and incident CVD among free of diabetes individuals and T2D patients at baseline. We also studied the effect of different Antiplatelet salicylates duration (0, 1-90, 91-365, >366 days) on incident CVD. Associations were adjusted for age, sex, and baseline measurements of BMI, hypertension and smoking status.

Results: We included 8333 individuals free of diabetes, and 1044 with T2D at baseline. Median follow up time was 28 years. In total, At baseline, the mean age (SD) was 64 (9.6) years and 39.7% were men. Mean (SD) BMI was 27.2 (5.5) kg/m^2. The Current use of antiplatelet salicylates was associated with a significantly decreased incidence of any CVD. We found a significant association of antiplatelet salicylates duration of use with incident CVD. longer duration (> 366 days) was associated with significantly increased risk of incident CVD in both free of diabetes [HR=1.44; 95%CI: 1.29-1.61] individuals and T2D [HR=1.38; 95%CI: 1.08-1.76] patients.

Conclusions: Long term antiplatelet salicylates use was not associated with decreased risk of incident CVD among both diabetic and non-diabetic populations. Our study suggests no protective effect of antiplatelet salicylates use, particularly among patients at higher risk of CVD (i.e. type 2 diabetes).

4868 | Impact of the food and drug administration safety warnings and removal of indications for use of oral quinolones

Phuong T. Tran[1,2], Patrick J. Antonelli[2,3], Juan M. Hincapie-Castillo[1,2] and Almut G. Winterstein[1,2]

[1]Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL; [2]Center for Drug Evaluation and Safety, University of Florida, Gainesville, FL; [3]Department of Otolaryngology, College of Medicine, University of Florida, Gainesville, FL

Background: In Nov 2015, concerns of systemic quinolones' risks outweighing benefits led an FDA advisory committee to advise removing

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

indications for acute, uncomplicated urinary tract infection (uUTI), acute sinusitis (AS) and acute exacerbation of chronic bronchitis (AE-COPD). In May 2016, the FDA released a safety communication, requiring label changes, which were implemented in Jul 2016.

Objectives: To assess the impact of oral quinolone (OQ) label changes on utilization in uUTI, AS, AE-COPD.

Methods: This was a trend analysis (Jan 2013 – Nov 2018), using the IBM MarketScan Commercial Claims and Medicare Supplemental Database. For each study month, we assembled 3 cohorts of adults diagnosed with uUTI, AS or AE-COPD who had oral antibiotics (Abx) dispensed within +/-5, +/-14 or +/-5 days, respectively. Patients had to be enrolled -365/+30 days before diagnosis. We excluded patients with conditions that complicate infections (e.g. spinal injury) within -365/+30 days and who hospitalized or had other infections within -90/+30 days. Monthly OQ prevalence was measured as # of OQ per 100 Abx-treated infection episodes. We used interrupted time series to compare the OQ prevalence before and after label changes. Sensitivity analysis used the implementation period from Nov 2015-Jul 2016 to define pre- and post-periods. We used segmented ordinary least-square regression with Newey-West autocorrelation adjustment and controlled for seasonality. We stratified OQ trend by provider types and evaluated shifting treatment pattern to other abx.

Results: In Jan 2013, the OQ prevalence among abx-treated uUTI episodes was 41.21 (40.96; 41.47); among AS 12.05 (11.67; 12.42); and among AE-COPD 34.3 (33.53; 35.16). Before OQ label changes, trends of absolute changes in OQ use prevalence were flat for uUTI -0.08 (-0.09; -0.07); AS -0.06 (-0.08; -0.04); and AE-COPD 0 (-0.05; 0.05). Right after OQ label changes, an immediate absolute reduction was found for uUTI -6.09 (-7.92; -4.26); AS -1.80 (-2.44; -1.16); and AE-COPD -3.41 (-5.66; -1.17). Monthly utilization trends continued to decrease thereafter. Treatment pattern shifted mostly to 1st line Abx (nitrofurantoin in uUTI, amoxicillin/clavulanate in AS; macrolides in AE-COPD), but use of 2nd line or not recommended Abx also increased. OQ prescribing prevalence varied across prescribers, but significant reductions were seen across all provider types.

Conclusions: The label changes had a strong impact on OQ utilization for removed indications. The magnitude of decrease varied by conditions and prescriber specialty.

4916 | Valproate utilisation trends among women of childbearing potential in Ireland between 2014 and 2017: A drug utilisation study using interrupted time series

John Hughes[1], Maeve Mullooly[1], Niamh Buckley[2], Yvonne Looney[2] and Kathleen Bennett[1]

[1]*Royal College of Surgeons in Ireland, Dublin 2, Ireland, Dublin, Ireland;* [2]*Health Products Regulatory Authority, Earlsfort Terrace, Dublin 2, Ireland, Dublin, Ireland*

Background: Use of valproate (VPA) during pregnancy is associated with increased risk of congenital malformations and neurodevelopmental disorders in exposed unborn children. Following an EU-wide safety review in 2014, the European Medicines Agency strengthened the warnings on VPA use in women of childbearing potential (WCBP), which was communicated to healthcare professionals and patient organisations in Ireland.

Objectives: To examine the trends in prevalence of VPA use among women aged 16-44 years in Ireland between 2014 and 2017 and the effect of regulatory intervention on these prevalence trends.

Methods: National pharmacy claims data identified prescriptions dispensed for women aged 16-44 years, and by 10 year age-groups (16-24, 25-34 and 35-44 years), from community pharmacies in Ireland between January 2014 and December 2017. Using annual population estimates, the prevalence rate of VPA use was calculated based on the number of women per month in receipt of VPA per 1000 eligible women in Ireland. Segmented regression analysis of interrupted time series was used to examine slope changes in monthly prevalence rates of VPA use before and after regulatory intervention (pre- and post-December 2014).

Results: Overall, the rate of VPA use among those aged 16-44 years from January 2014 (2.06/1000) to December 2014 (2.06/1000) was stable, however, there was a non-significant overall decrease in subsequent months to December 2017 (1.80/1000; p=0.077). Analysis stratified by age-groups found that the post-intervention decrease was only significant in the youngest 16-24 year age-group, where the rate of VPA use between January 2014 and December 2014 remained stable (1.60/1000), but was seen to decrease in the months following regulatory intervention (1.20/1000 as of December 2017; p=0.009).

Conclusions: There is evidence that changes in use of VPA among WCBP, particularly those aged 16-24 years, were observed following targeted regulatory intervention. Future research should examine the impact of the 2018 EU-wide safety review on VPA use in this cohort.

4943 | Low-dose aspirin use for primary or secondary prevention of cardiovascular diseases in patients with type 2 diabetes

Payam Peymani[1], Najmeh Maharlouei[2], Azra Izanloo[3], Amir Hooshang Mohammadpour[4], Abbas Rezaianzadeh[5] and Fariba Ahmadizar[6]

[1]*Department of Clinical Pharmacology & Toxicology, University Hospital Zurich, Zurich, Switzerland;* [2]*Health Policy Research Center, Institute of Heath, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran;* [3]*Razavi Cancer Research Center, Razavi Hospital, Imam Reza International University, Mashhad, Islamic Republic of Iran;* [4]*Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran;* [5]*Department of Epidemiology, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran;* [6]*Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands*

Background: Whether Low-Dose Aspirin (LDA) is indicated for primary or secondary prevention of cardiovascular diseases (CVD) in population with type 2 diabetes mellitus (T2DM) remains unclear.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Moreover, if gender plays a role in LDA indication has not been studied.

Objectives: To compare the indication of LDA use for primary and secondary prevention of CVD in patients with T2DM.

Methods: *Study Design:* Cross-sectional analysis *Study Setting:* The large prospective population-based Kharameh Study in Iran that includes 10,688 individuals aged 40 to 70 years *Data Analysis:* We included 1,607 patients with T2DM. Chi-square test was applied to compare prevalence rate of LDA indicated as <100 mg/daily in diabetic patients with CVD (secondary prevention) and without CVD (primary prevention); CVD defined as presence of myocardial infarction, myocardial ischemia, chronic heart disease, heart failure or stroke. In gender-stratified analysis, we further studied the effect of gender on this indication.

Results: Prevalence rate of T2DM was higher among women (71.3%) compared to men. Mean (SD) age was 58.6 (7.2) years; mean (SD) body mass index was 27.1 (4.1) and CVD was prevalent as 21.0%. Prevalence rate of T2DM patients on LDA use was 22.4%, with no significant difference between men and women (p=0.47). 59.3% of diabetic patients were using LDA for secondary prevention of CVD, shown as statistically significantly (p<0.001) higher rate compared to those taking LDA for primary prevention (12.6%).

Conclusions: LDA is most common for secondary prevention of CVD in patients with T2DM. Gender has no effect on this indication. Given that LDA is used to prevent CVD, longitudinal studies are needed to clarify the efficacy and safety of this indication in patients with T2DM.

5001 | Utilization of oral anticoagulants in patients with venous thromboembolism

Geetha Iyer[1,2], Ajinkya Pawar[1], Chandrasekar Gopalakrishnan[1], Helen Tesfaye[1], Kristyn Chin[1], Joshua J. Gagne[1,2] and Katsiaryna Bykov[1]
[1]Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [2]Harvard T H Chan School of Public Health, Boston, MA

Background: Introduction of direct-acting oral anticoagulants (DOACs) has transformed the treatment of venous thromboembolism (VTE). Real-world data offer valuable insight into how anticoagulants are utilized in clinical practice and may aid in understanding reasons for changes in therapy.

Objectives: To 1) evaluate prescribing patterns of oral anticoagulants in patients with VTE, 2) assess measures of adherence and persistence, and 3) identify clinical events that precede discontinuation or switching.

Methods: We used claims from US Medicare and IBM MarketScan Commercial databases (2010 – 2017) to characterize patients initiating oral anticoagulant within 90 days of discharge from VTE hospitalization (index event). We plotted trends in oral anticoagulation initiation and compared profiles of patients initiating warfarin vs. DOACs (rivaroxaban, dabigatran, apixaban and edoxaban) over time. Patterns of anticoagulant discontinuation (≥ 30 days treatment gap) and switches, proportion of days covered (PDC) during the 365 days after initiation, and time on anticoagulant therapy (median and interquartile range, IQR) were assessed. We also identified clinical events in the 30 days preceding changes in therapy.

Results: 234,020 patients (Medicare - 153,063; MarketScan - 80,957) initiated an oral anticoagulant after their index VTE; 100% initiated warfarin in 2010 and 27% initiated warfarin, 33% rivaroxaban, and 37% apixaban in 2017. Patients initiating warfarin were more likely to have hypertension, diabetes mellitus, anemia, and history of kidney disease compared to those initiating DOACs. Median duration of treatment was 172 days (IQR 76 - 326) and 167 days (IQR 80 - 278) in Medicare and MarketScan, respectively, and was similar regardless of whether the index event was provoked. Patients with pulmonary embolism as the index event persisted longer on treatment than those with deep vein thrombosis. The overall 365-day PDC with any oral anticoagulant was 0.55 ± 0.30 in Medicare and 0.51 ± 0.29 in MarketScan. Approximately 25% discontinued and 9% patients switched anticoagulant therapy within a year. Switching to another anticoagulant was preceded by codes for VTE diagnostic procedures, atrial fibrillation, or ischemic stroke among 30% of MarketScan and 32% of Medicare patients.

Conclusions: Most patients with VTE continued anticoagulant treatment for approximately 6 months and clinical reasons for modifying anticoagulant therapy were identified in a third of patients. Information on why and how treatments are adapted in clinical practice is crucial for generating valid evidence on drug safety and effectiveness.

Drug Utilization Research -> Health policy and governance

57 | Methods to evaluate the effects of policy changes during the opioid crisis

Juan M. Hincapie-Castillo[1], Amie J. Goodin[1], Gerald J. Dal Pan[2], Mina Tadrous[3]
[1]University of Florida, Gainesville, FL; [2]Food and Drug Administration, Silver Spring, MD; [3]University of Toronto, Toronto, ON, Canada

Background: Attempts to mitigate the opioid abuse epidemic in North America have resulted in an abundance of policies aimed mainly towards control of drug supply. Drug utilization research (DUR) tools are useful in assessing these policies; however, the framing of research questions for evaluation throughout the continuum of the health policy process requires further considerations for correct causal inference and for successful translation of results to stakeholders. Lessons learned from the evaluations of opioid policies can inform future studies in other areas.

Objectives: We aim:

1). To provide an overview of the health policy process as applied to the rapidly evolving challenges of the opioid crisis.

2). To assess strengths and limitations in both established and emerging novel policy evaluation methods, and accompanying measurement challenges for opioid-related research.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3). To examine applications of these methods in current studies estimating effects of drug-related policies using examples from the US and Canada.

Overall, this symposium will benefit researchers and policymakers interested in learning strategies for addressing methodologic challenges when designing a policy evaluation.

Description: The symposium will be divided among four panel speakers, with 20 minutes each. The opioid crisis will serve as the motivating case throughout the symposium, where a sampling of the multitude of policies and respective methodological considerations are woven throughout each presentation. First, Amie Goodin will introduce policy theory through the lens of a legal epidemiology framework to set the stage for planning evaluations in the context of the opioid crisis. Juan Hincapie-Castillo will then give an overview of DUR policy evaluation methods that can be applied to specific research questions using real-world data, where methodological challenges in evaluating policy implemented at the health-system, state, and/or national levels are addressed. Gerald Dal Pan will then discuss measurement challenges in policy evaluation when estimating opioid utilization as well as the outcomes associated with the opioid and related poly-substance abuse epidemic. Lastly, Mina Tadrous will provide applied examples of Canadian policy evaluations, outlining the unique challenges associated with traditional (e.g., time series strategies, difference-in-differences techniques) and emerging novel policy evaluation methods (e.g., the potential for dynamic compartmental modeling techniques, structural break models and machine learning applications). The session will conclude with a 10-minute Q&A from panel members.

2400 | Inequities in primary care attachment among people receiving opioid therapy

Tonya Campbell[1], Richard Glazier[1,2,3], Laura Robertson[2], Diana Martins[2], J. Michael Paterson[1,3], David Juurlink[1,3,4], Muhammad Mamdani[1,3,5] and Tara Gomes[1,2,3]

[1]ICES, Toronto, ON, Canada; [2]St. Michael's Hospital, Toronto, ON, Canada; [3]University of Toronto, Toronto, ON, Canada; [4]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]Unity Health Toronto, Toronto, ON, Canada

Background: Qualitative evidence has indicated that people in Ontario, Canada who use opioids for managing chronic pain, or for opioid agonist therapy, may experience difficulties securing a primary care provider (PCP) and may seek care in an emergency department (ED) as a substitute.

Objectives: To compare rates of re-attachment to primary care and ED visits for people receiving opioid therapy relative to people with no recent opioid exposure.

Methods: In this population-based cohort study, we identified Ontarians whose enrolment with a PCP was terminated between January 2016 and December 2017, and classified individuals as opioid agonist therapy (OAT) recipients, chronic pain-related opioid therapy (COT) recipients, or people without recent opioid exposure. Our primary outcome was the rate of primary care re-attachment, defined as attachment to an enrolment model, community health centre, or fee-for-service physician. Our secondary outcome measured the rate of ED visits during the period without primary care attachment. Cox and Poisson models were used to compare outcomes between the groups exposed to opioids and the group unexposed.

Results: We identified 1,759 OAT recipients, 3,891 COT recipients, and 150,890 opioid unexposed individuals whose PCP enrolment was terminated. At 1-year follow-up, OAT recipients had a lower rate of primary care re-attachment (adjusted Hazard Ratio [aHR] 0.54; 95% CI 0.49-0.59), and COT recipients had a similar re-attachment rate (aHR 0.96; 95% CI 0.92-1.01), compared to opioid unexposed individuals. When considering enrolment models alone, both groups had a lower re-attachment rate compared to people without opioid exposure (OAT recipients: aHR 0.35; 95% CI 0.31-0.41, COT recipients: aHR 0.86; 95% CI 0.81-0.91). Relative to opioid unexposed individuals, the rate of ED visits was greater among OAT recipients (adjusted rate ratio [aRR] 1.23; 95% CI 1.16-1.30) and COT recipients (aRR 1.37; 95% CI 1.31-1.43), during the period without attachment.

Conclusions: Compared to the opioid unexposed individuals, people who use opioids face inequities in primary care attachment, particularly to enrolment models. Furthermore, the higher rates of ED visits among these individuals may indicate unmet health needs. Barriers to accessing primary care among people using opioids must be addressed by clinicians and policymakers.

2550 | Ability of primary healthcare records to assess medicinal products discussed by the pharmacovigilance risk assessment committee

Robert Flynn[1,2], Karin Hedenmalm[1], Tarita Murray-Thomas[3], Alexandra Pacurariu[1], Peter Arlett[1], Hilary Shepherd[3], Puja Myles[3] and Xavier Kurz[1]

[1]European Medicines Agency, Amsterdam, Netherlands; [2]University of Dundee, Dundee, United Kingdom; [3]Clinical Practice Research Datalink, London, United Kingdom

Background: The EU's Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for protecting patients by ensuring the safety of marketed medicines. The European Medicines Agency (EMA) supports such evaluation by analysing routinely collected Primary care Health Records (PHRs) to assess drug utilisation, risks of medicines and effectiveness of risk minimisation measures.

Objectives: To evaluate the capture of exposure to medicines discussed at PRAC in four established PHR databases.

Methods: Four PHR databases were searched for substances discussed at consecutive PRAC meetings from September to November 2018: IQVIA Medical Research Data (IMRD) - France, IMRD - Germany, IMRD - United Kingdom and the Clinical Practice Research Datalink Aurum. Data extracted were: number of prescriptions, number of patients with at least one prescription, whether a Centrally (CAP) or Nationally (NAP)

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Authorised Product and authorisation date. Exposures were assessed up to 31 August 2018. To estimate the number of substances each database could meaningfully assess adverse events, we calculated the numbers of patient exposures required to detect a statistically significant event associated with a theoretical relative risk of 2.0, with adverse event rates taken from the Summary of Product Characteristics frequency categories. This was based on a hypothetical comparison of two proportions using a 2-sided Fisher test with $\alpha = 0.05$, power = 0.90 and equal numbers of exposed/comparator patients.

Results: There were a total of 128 drug substances (or classes): 83 CAPs (64.8%) and 45 NAPs (35.2%). Of CAPs, 6 (7.2%) had been authorised for < 2 years, 20 (24.1%) for 2-5 years and 57 (68.7%) for > 5 years. Where marketed (n = 41), all NAPs had been authorised for > 5 years. No individual database was able to detect a doubling in effect size for the majority of CAPs for *common* (1/100), *uncommon* (1/1000), *rare* (1/10000) or *very rare* (1/100000) events, or NAPs for *uncommon*, *rare* or *very rare* events. An analysis of pooled allowed the detection of an *uncommon* adverse event associated with a doubling of risk for 26.5% of CAPs and 60.0% of NAPs. For events that were *rare* or *very rare* the proportion was lower (CAPs: 4.8% and 0%; NAPs: 40.0% and 11.1%). Coverage was worse for "orphaned" substance.

Conclusions: More advanced and recently authorised medicinal products had less coverage in the available databases compared to more established, nationally licensed products. To enable better informed regulatory decisions there is a need to access complementary data sources, particularly capturing exposure in specialist care settings.

2575 | Program churn among children enrolled in North Carolina medicaid

Alexander Breskin[1], Rushina Cholera[2], David Anderson[2], Suzanne Landi[1], Aaron McKethan[1,2] and Charlene Wong[2]
[1]*NoviSci, Durham, NC*; [2]*Duke University, Durham, NC*

Background: Retaining eligible children in public insurance is of rising concern as pediatric Medicaid/CHIP enrollment has declined in recent years. Any gaps in coverage, even short ones, lead to unmet healthcare needs for children. This coverage "churning" is also costly for public programs. Understanding program churning will be critical to prevent widening of health disparities as North Carolina (NC) is poised to implement dramatic payment and care delivery reforms, including the value-based Integrated Care for Kids model.

Objectives: To describe rates and disparities in Medicaid coverage churning among NC children.

Methods: Children enrolled in NC Medicaid on January 1, 2016 (N=1,196,127) were included and followed until December 31, 2018. We used the Kaplan-Meier estimator to calculate the probability of continuous enrollment and the time to reenrollment among those with a coverage gap of ≥1 month. Children who reenrolled within 6 months of disenrollment were assumed to have been continuously eligible for coverage and were classified as having experienced churning. Disparities in churning were assessed by demographic characteristics.

Results: 90.4% of children remained continuously enrolled for 1 year, 81.3% for 2 years, and 73.6% for three years. Adolescents ages 16-18 were less likely to remain continuously enrolled for 2 or 3 years (60.2-73.4%) compared to younger children. Among children who experienced a coverage gap (N= 315,217), 17.0% churned (i.e., reenrolled within 6 months), 9.2% reenrolled within 7-11 months, and 73.8% did not reenroll for one year or more. Of the White children who experienced a coverage gap, 13.8% (95% CI: 13.6, 14.0) reenrolled within 6 months compared to 17.7% (95% CI: 17.4, 18.0) of Black children and 23.0% (95% CI: 22.7, 23.3) of Hispanic/Latinx children. Program churning was higher in children living in urban areas (20.4% [95% CI: 20.1, 20.7]) compared to those living in rural (17.4% [95% CI: 17.1, 17.6]) and suburban (17.8% [95% CI: 17.5, 18.2]) areas.

Conclusions: Most Medicaid insured children remained continuously enrolled for at least a year with almost 75% experiencing 3 years of continuous enrollment. Among children who experienced a coverage gap, 17% churned with reenrollment within 6 months. Higher rates of churn among minority children and children living in urban areas can inform how the allocation of limited resources to reduce coverage instability.

2577 | Utilization of hydroxyprogesterone during the second and/or third trimester among pregnancies with live birth deliveries in the sentinel distributed database

Huei-Ting Tsai[1], Mayura Shinde[2], Austin Cosgrove[2], Jie Li[1], Christina Chang[1], Christine Nguyen[1], Corinne Woods[1], Joy Kolonoski[2], Tiffany Woodworth[2] and David Moeny[1]
[1]*U.S. Food and Drug Administration, White Oak, MD*; [2]*Harvard Pilgrim Health Care Institute, Boston, MA*

Background: Makena®, hydroxyprogesterone caproate (HPC) injection, is indicated for reducing the risk of preterm birth in women with a singleton pregnancy who had a prior singleton spontaneous preterm birth. The U.S. FDA approved Makena on February 3, 2011 under accelerated approval, contingent upon post-marketing confirmation of clinical benefit, such as improvement in neonatal mortality and morbidity. The confirmatory trial failed to confirm Makena's efficacy. An analysis of drug utilization of HPC, including Makena, in pregnant women was undertaken to inform the landscape of HPC use for deliberations at the FDA's Advisory Committee meeting on Makena.

Objectives: To assess the utilization of HPC in pregnancy in the U.S.

Methods: We identified pregnant women aged 10-54 years, with a live birth from January 1, 2008 through April 30, 2018, and with continuous medical and drug insurance coverage for at least 301 days prior to a live birth delivery in the Sentinel Distributed Database (SDD). The exposures of interest included use of injectable HPC (Makena and its generics) and compounded HPC from bulk power during the 2nd or 3rd trimesters. We assessed three obstetrical

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

conditions of interest as potential reasons for use: (1) history of preterm delivery, (2) preterm labor in the current pregnancy, and (3) cervical shortening in the current pregnancy. We evaluated the temporal trend of HPC use over the study period. Among pregnancies with injectable HPC use, we calculated the percentage of those with diagnoses for each related obstetrical condition; and the percentage of pregnancies with diagnoses for any of three related obstetrical conditions.

Results: We identified a total of 3,451,121 live-birth pregnancies (among 2,912,911 women) between 2008 and 2019 in the SDD. Of these pregnancies, 16,535 showed use of injectable HPC during the 2nd or 3rd trimesters. The yearly proportion of pregnancies with injectable HPC use increased over the study period from 0 in 2010 to 13 per 1,000 pregnancies in 2018; use of compounded HPC decreased from 4 to 0.25 per 1,000 pregnancies over the same time. Of 16,535 pregnancies with injectable HPC use, 6,443 (39%) had recorded history of preterm delivery and 12,060 (73%) had at least one related obstetrical condition.

Conclusions: We found modest use (about 1.3% in 2018) of HPC during the 2nd or 3rd trimesters of live-birth pregnancies in SDD. A high percentage (73%) of pregnancies with injectable HPC use had at least one obstetrical indication of interest.

2617 | Prescribing trends of direct acting antivirals for the treatment of hepatitis C in Ontario

Mina Tadrous[1], Kate Mason[2], Bernadette Lettner[3], Mary Guyton[2], Zoë Dodd[2], Jeff Powis[3], Diana Martins[4] and Tara Gomes[4]
[1]Women's College Hospital, Toronto, ON, Canada; [2]South Riverdale Community Health Centre, Toronto, ON, Canada; [3]Toronto Community Hep C Program, Toronto, ON, Canada; [4]Ontario Drug Policy Research Network, Toronto, ON, Canada

Background: The ease and effectiveness of direct acting oral antivirals (DAAs) treatments provide opportunity to expand treatment for chronic hepatitis C (HCV). Reimbursement mechanisms for DAAs have changed on two occasions since these drugs were added to Ontario' publicly funded drug formulary. Whether these changes have appreciably modified prescribing patterns and increased access to DAAs is unknown.

Objectives: The purpose of this study was to summarize the utilization of DAAs in Ontario between 2012 and 2018, and describe changes in prescribing physician specialties. A secondary objective was to describe the characteristics of people who received treatment through public reimbursement in 2018.

Methods: We conducted a repeated cross-sectional study for DAAs reimbursed by the public drug program in Ontario from January 1, 2012 to December 31, 2018. We measured the quarterly number of users, overall and by prescriber specialty. Characteristics of those receiving DAA treatments in 2018 were examined overall and by prescriber specialty.

Results: A total of 27,116 individuals received a publicly-funded DAA prescription between Q1-2012 and Q4-2018. Nearly two-thirds (n=17,813; 65.7%) of all DAAs were prescribed by gastroenterologists, hepatologists or infectious disease specialists. Only 9.6% of DAA recipients were treated by general practitioners. Utilization of DAAs had three major phases of increased uptake: (1) the introduction of DAAs to Ontario's public drug formulary as a prior authorization benefit in Q1-2015; (2) expanded listing of DAAs as limited use products on the formulary in Q1-2017; and (3) the introduction of newer DAAs in Q2-2018. In 2018, 2,538 unique individuals received publically funded DAAs. The majority were over age 50 (59.8%), male (63.8%) and living in urban (88.8%) neighborhoods of lower socioeconomic status (41.7% in lowest income quintile neighborhoods). There were important differences among patients who received treatment from gastroenterologists/hepatologists (GH). For example, patients who received treatment from a general practitioner (GP) or infectious disease specialist (IDS) were more likely to have a mental health diagnoses (GP: 77.7%; IDS: 71.2% v GH: 41.6%) and be receiving opioid agonist therapy (GP: 54.5%; IDS: 51.6% v GH: 12.4%).

Conclusions: HCV elimination guidelines call for an expansion of the range of who delivers HCV treatment. Changes in the listing criteria of DAAs in Ontario's public drug program has led to increased uptake of these agents. However, there does not appear to be increased prescribing of DAAs among.

2622 | Impact of two recent major drug shortages on drug utilization

Mina Tadrous[1], Katie Suda[2] and Tara Gomes[3]
[1]Women's College Hospital, Toronto, ON, Canada; [2]University of Pittsburgh, Pittsburgh, PA; [3]Unity Health Toronto, Toronto, ON, Canada

Background: Over the last decade the number of drug shortages has dramatically increased in Canada and worldwide. **Between 2015 to 2017, there were over 1,000 reported drug shortages** and the annual number appears to be increasing. Two recent major shortages occurred impacting access to bupropion and valsartan- two very commonly used treatments.

Objectives: To measure the impact of product shortages on drug utilization of two recent drug shortages in Ontario Canada.

Methods: We conducted a repeated cross-sectional study of bupropion and valsartan between July 1, 2012 and March 31, 2019. Both drugs experienced a significant drug shortage in 2018 and 2019, respectively. Using the public claims data in Ontario. We analyzed the quarterly number of drug claims for each of these medications. We analyzed all drugs including those impacted and not impacted by the specific shortage. We reported the number of claims quarterly for each drug class before and after the drug shortage occurred.

Results: We found that the number of claims for bupropion did not significantly decrease after the drug shortage was reported in Q1-2018, with the number of claims only slightly plateauing at 236,017 claims and no significant reduction in the trend. In contrast, valsartan claims dropped dramatically from 191,732 claims after the shortage occurred to 56,548 claims in Q1-2019, a 71% reduction.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Our results highlight the variable impact of shortages on utilization. Although both drug shortages were prolonged in their limitation of products the extent and number of products affected may greatly influence the impact of the drug shortage. This work highlights potential differences in drug shortages that should be used to inform policies to help curb the growing problem.

2634 | Estimating the impact of prescribing limits on prolonged opioid use following surgery

Jessica C. Young[1], Nabarun Dasgupta[1], Virginia Pate[1], Til Sturmer[1], Brooke A. Chidgey[2] and Michele Jonsson Funk[1]
[1]*University of North Carolina, Chapel Hill, NC;* [2]*University of North Carolina School of Medicine, Chapel Hill, NC*

Background: In response to concerns about opioid addiction, some states now limit the days supplied (DS) for initial postoperative prescriptions. However, few studies have examined the impact of these policy changes on prolonged opioid use in the population.
Objectives: To a) examine the gradient of risk of prolonged postsurgical opioid use based on the initial prescription duration, and b) estimate the potential impact of varying prescribing limits on risk of prolonged postsurgical opioid use.
Methods: We used a 20% random sample of Medicare claims (2007-2016) to identify opioid naive patients undergoing invasive surgery. Prolonged use was defined as at least 1 Rx in each of 3 consecutive 30-day windows immediately following surgery. We calculated 90-day risk of prolonged use comparing patients at a given DS level to patients receiving longer initial prescriptions. Adjusted risk differences (aRD) were obtained via standardized mortality ratio weights (adjusted for demographics, surgical characteristics, baseline medication use and comorbidities), comparing patients with a Rx greater than a given prescribing limit versus those at the limit. Estimated number of averted cases was also quantified.
Results: We identified 749,269 patients who received a perioperative opioid (median DS=5, mean age=73yr, 44% male). The overall risk of prolonged use was 14.0 (95%CI: 13.7, 14.3) per 1000 exposed patients, increasing with days supplied (14.7 for >2 days to 34.4 for >15 days). Among patients with >2 DS (n=615,490; 92%), we estimated 3.3 (1.0, 5.6)/1000 additional cases of prolonged opioid use compared to those receiving 2 DS. Among patients receiving >7 days (n=143,408; 22%), a common limit in state laws, the aRD was nearly null (-0.1/1000). At 15+ days (n=21,382; 3%), we estimated 3.5 (-0.6, 7.6)/1,000 additional cases compared to those receiving exactly 15 days. The estimated number of potentially averted cases of prolonged opioid use ranged from 10,144 (2 days) to 373 (15 days).
Conclusions: We illustrate a method to examine potential impacts of prescribing limits. While risk of prolonged postsurgical opioid use increased as patients received larger initial DS, the number of prolonged use cases theoretically preventable by prescribing limits differed by orders of magnitude depending on the number of patients above the proposed limit. While most laws focus on DS limits, results for quantity and dosage dispensed show similar trends and will also be presented, along with procedure specific (knee arthroplasty, hernia repair, cholecystectomy) results.

2646 | Strategies to approach the judicialization of health technology in Latin America and Caribbean

Sueli Miyuki Yamauti and Luciane Cruz Lopes
University of Sorocaba, Sorocaba, Brazil

Background: The judicialization of health technology in Brazil is a phenomenon that concerns public institutions, as it is growing, cumulative and increases inequities. In the literature, there are several suggested strategies to approach it. On the other hand, several strategies were implemented in Brazil. However, it is not known what type of arrangements for the health system they used in their implementation and whether there are similarities with those suggested in the literature.
Objectives: To analyze the feasibility of implementing the proposed strategies to approach the judicialization of health technology in Latin America and the Caribbean in the Brazilian context.
Methods: Comparative cross-sectional analysis among the 45 strategies proposals to approach the judicialization of health technology in the public sector, extracted from the literature review by Pinzón-Flórez et al. with the 78 strategies already implemented in Brazil, identified and categorized by Yamauti et al. as to the correspondence between them. The strategies were classified according to six World Health Organization's health system arrangements.
Results: Eight strategies proposed in the study by Pinzón-Flórez et al. are consistent with the Brazilian government's policies or programs; 27 are similar in terms of the activities developed by the strategies implemented in some Brazilian context and; 10 have no analogy with the strategies implemented in Brazil. The 78 strategies implemented work using at least two arrangements for health systems and 96.2% of them belong to the service delivery arrangement.
Conclusions: The proposed strategies to approach the judicialization of health technology in Latin America and the Caribbean are feasible to be implemented both in the form of government policies or programs and as institutional strategies in the Brazilian context. However, the strategies implemented are complex, encompass various health system arrangements and require a legal apparatus along with a public health system that has an integrated service delivery. These characteristics must be evaluated before implementing them in other contexts.

2688 | Impact of hydrocodone rescheduling on opioid prescribing by dentists in the United States, 2012-2017

Connie H. Yan[1], Colin Hubbard[1], Gregory S. Calip[1], Lisa K. Sharp[1], Charlesnika T. Evans[2,3], Susan Rowan[1], Jessina C. McGregor[4], Allen Campbell[5], Walid F. Gellad[6,7] and Katie J. Suda[6,7]
[1]*University of Illinois at Chicago, Chicago, IL;* [2]*Northwestern University Feinberg School of Medicine, Chicago, IL;* [3]*Hines VA Hospital, Hines, IL;*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[4]Oregon State University, Corvalis, OR; [5]IQVIA Institute for Human Data Science, Durham, NC; [6]University of Pittsburgh, Pittsburgh, PA; [7]VA Pittsburgh Healthcare System, Pittsburgh, PA

Background: Dentists are amongst the top specialty prescribers of opioids, accounting for approximately 6.4% of all outpatient opioid prescriptions in the United States (US). In 2014, the US Drug Enforcement Administration (DEA) rescheduled hydrocodone-containing products (HCP) from schedule III to II, introducing more restricted prescribing and dispensing regulations, as a means to reduce opioid prescribing.

Objectives: To evaluate the impact of the HCP rescheduling regulation on dental prescribing of opioids in the US.

Methods: An interrupted time-series analysis examined monthly opioid prescriptions of five oral opioid classes (products containing hydrocodone, tramadol, codeine, oxycodone, morphine or fentanyl, and other) using the IQVIA Longitudinal Prescription Data from 2012 to 2017. Ordinary least-square regression models, with Newey-West standard errors to handle autocorrelation and heteroscedasticity, were used to examine the changes in prescription volume, dentist- and US population-based prescribing rates, quantity and days' supply dispensed, and morphine milligram equivalents (MME), across the opioid classes in the 33 months prior to index (regulatory change in October 2014) compared to the 39 months after index (post-period).

Results: From 2012 to 2017, dentists prescribed approximately 70 million opioid prescriptions, of which 68.9% were HCP, 18.3% codeine, 8.6% oxycodone, 3.9% tramadol, and 0.4% other. At index, HCP immediately decreased by 103,527 prescriptions, with increases in prescriptions for codeine (69,796), oxycodone (16,651), and tramadol (16,289). All changes were significant at $p<0.0001$. In the post-period, HCP (4,520 prescriptions/month), oxycodone (672.1), tramadol (108.3), and other (31) opioid prescriptions significantly declined each month ($p<0.0001$), except for codeine (49.5; $p=0.7588$). Similar trends were observed for dentist- and population-based prescribing rates across all opioids. In the post-period, monthly mean quantity and days' supply dispensed, and MME significantly declined across all opioids ($p<0.0001$). For HCP in 2012 compared to 2017, average quantity dispensed per prescription decreased by 11% (18.4 pills vs. 16.3), days' supply decreased by 8% (3.5 days vs. 3.2), and MME decreased by 8% (36.2 MME vs.33.4).

Conclusions: US dentists' prescribing of HCP declined after the DEA rescheduling, but may have consequently increased prescribing of other opioids, including high potency agents. Understanding the impact of this regulation is important to develop strategies to ensure safe and effective prescribing of opioids for dental pain.

3758 | Impact of pharmaceutical cost containment policy changes on the use of antidepressants in Japan

Shinobu Imai[1,2], Anna Kiyomi[1], Munetoshi Sugiura[1], Kiyohide Fushimi[3] and Karolina Andersson Sundell[4]

[1]Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan; [2]National Hospital Organization Headquarters, Tokyo, Japan; [3]Tokyo Medical and Dental University Graduate School, Tokyo, Japan; [4]University of Gothenburg, Gothenburg, Sweden

Background: In the last two decades, many countries have been affected by the global financial crisis. At the same time, pharmaceutical expenditures have increased exponentially. The use of antidepressants and the associated expenses have grown in many countries, mainly because of the introduction of emerging pharmaceutical classes of antidepressants with a better risk-benefit profile compared to the conventional milder antidepressants, which require extended use for treating depression and anxiety.

Objectives: In this study, we analysed the changes in the trends of using antidepressants upon introduction of new guidelines, safety information, cost containment policies and approval of original brand drugs and generic drugs, with the overarching aim of assessing the Japanese generic drug promotion policy.

Methods: Time series analysis was performed using the seasonal autoregressive integrated moving average (ARIMA) modelling method along with the intervention analysis. Sales data of the selected drugs, including SSRIs, SNRIs and other antidepressants, from April 2002 to March 2016 were collected from IQVIA. Altogether, eight interventions were analysed, including three policy changes (P1, P2 and P3), three published guidelines (GL1, GL2 and GL3), and two safety information (SI1, SI2). Based on the status of the patent, we classified the drugs into three categories: drugs that are no longer protected by a patent (LP), new substances (OT), and generic drugs (GE).

Results: The use of SSRI/SNRI peaked by 2008 and reached a plateau. However, the introduction of SI1 in 2006 and SI2 in 2009 resulted in a significant downward shift in the use of SSRI/SNRI and an upward shift in other antidepressants. According to the stratification of the use of SSRI/SNRI by patent status, i.e., LP, OT, or GE, the use of LP drugs started to decline since 2008; instead, the use of OT drugs started to increase since 2012. When milnacipran, the first generic drug of SSRI/SNRI was introduced in 2008, there were a significant downward shift in the use of LP drugs. However, the share of GE was lower than the share of OT by the end of study period.

Conclusions: We describe the trends in usage of antidepressants during this decade. Introduction of safety information had a negative impact on the use of SSRI/SNRI, which was substituted by other antidepressants. We also described the situation in which there was a switch from the use of LP to OT drugs.

3823 | Establish a model for mapping Chinese indication with ICD-10-CM in Taiwan: Using antipsychotics as examples

Chien Chou Su[1,2], Ching-Lan Cheng[1,2,3,4], Yi-Wei Wu[3] and Yea-Huei Kao Yang[2,3,4]

[1]National Cheng Kung University Hospital, Tainan, Taiwan; [2]Health Outcome Research Center, National Cheng Kung University, Tainan,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Taiwan; [3]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [4]School of Pharmacy, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background: In Taiwan, the labelled indications of pharmaceutical products are approved in Chinese language by Taiwan Food and Drug Administration (TFDA), which are known to be described variably for one single active pharmaceutical ingredient. Meanwhile, the National Health Insurance (NHI) reimbursement scheme of pharmaceutical preparations is implemented based on the labelled indications by TFDA. However, the claims of pharmaceutical reimbursement are required to submit using the International Classification of Disease (ICD). Therefore, when evaluation on the prescribing compliance with reimbursement scheme is needed, a mapping system of Chinese indications with ICD codes should be established in advance.

Objectives: To establish a mapping system between indication and ICD-10-CM for TFDA approved antipsychotics (APs), and evaluate the validity of ICD-10-CM mapping with indication by reviewing electronic medical records.

Methods: *Design and setting*: The mapping process was performed by dictionary-based and keywords matching method. The dictionary-based method was to define the same concept between Chinese indications and English medical terminologies by researchers in advance, and converted the Chinese indications into English indications. These converted indications were linked to SNOMED CT system by keywords matching, and further mapped with ICD-10-CM. *Statistical analysis*: we selected risperidone as the index drug for examining the validity of ICD-10-CM mapping of indication. Sensitivity and positive predictive value (PPV) for ICD-10-CM were evaluated by reviewing electronic medical records in a medical center.

Results: The mapping rate was 99.9%. In this mapping system, there were 784 pharmaceutical licenses approved by TDFA. Among the matched ICD-10 CM, there were 65.5% belonged to mental and behavior disorders, 1.6% diseases of the nervous system, 7.7% factors influencing health status and contact with health services, 6.5% symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, and the others was 18.7%. The rate of this mapping system, the sensitivity and PPV of risperidone prescriptions and indications in the electronic medical records were 94.6% and 80.8%, respectively.

Conclusions: The mapping strategy for linking Chinese indications to ICD-10-CM via SNOMED CT can be employed for the other pharmaceutical products, which may support utilization evaluation of the reimbursement scheme in Taiwan NHI.

3911 | Serious adverse events with high-cost drugs accessed through litigation in Brazil

Ricardo Eccard da Silva[1], Elisângela da Costa Lima[2], Maria Rita C.G. Novaes[3] and Claudia Garcia Serpa Osorio-de-Castro, 21041-210[4]

[1]Brazilian Health Surveillance Agency (Anvisa), Brasília, Brazil; [2]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; [3]University of Brasília, Brasília, Brazil; [4]Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

Background: Serious and/or rare conditions with high social impact and risk of death are usually treated with high-cost drugs/medicines either recently brought to market or still undergoing trials for later licensing. Brazilian patients have legal right to access unlicensed drugs undergoing clinical research, if there is evidence of efficacy and safety.

Objectives: This study investigated the occurrence of serious adverse events related to very high-cost medicines from clinical studies and obtained by patients though health litigation.

Methods: A descriptive study using secondary data investigated unlicensed medicines obtained through lawsuits from 2010 to 2017, costing more than 1 million Brazilian reais (BRL), adjusted by the Brazilian Consumer Index to July 2017. Data sources were the Brazilian Health Surveillance Agency Registry (DATAVISA) and Adverse Events in Clinical Studies (NotivisaEC) Databases. Medicines were categorized by the Anatomical Therapeutic Chemical classification to level 03 and events by the WHO Adverse Drug Reaction Terminology. The study received ethical approval by the UnB IRB.

Results: In the period, 812 drugs in clinical studies were obtained thorough litigation. 44 (5.4%) were related to 1248 serious events. Total Brazilian Government expenditure was 3.2 billion BRL. Class L04A (n=7) presented greater expenditures (over 1.8 billion BRL). 861 (69%) took place in clinical trials, 250 (20%) in expanded access programs and 100 (8%) in compassionate use programs. 37 of all serious events (6%) were associated with post-trial drug provision. 196 deaths occurred and L01X was the most involved category (49.5%). Most other serious events (n=419) and aftereffects (n=42) were related to L01X.

Conclusions: Very high-cost drugs paid for by the government and obtained through health litigation were related to deaths and serious adverse events in Brazil.

3944 | Citizenship status and the prevalence, treatment, and control of cardiovascular disease risk factors in United States, 2011-2016

Jenny S. Guadamuz[1], Ramon Durazo-Arvizu[2], Martha L. Daviglus[1], Gregory S. Calip[1], Edith A. Nutescu[1] and Dima M. Qato[1]

[1]University of Illinois at Chicago, Chicago, IL; [2]Loyola University Chicago, Chicago, IL

Background: The adult immigrant population has doubled from approximately 19 million in 1990 to 42 million in 2017. However, noncitizens encounter significant barriers to healthcare access and disproportionately face structural factors (e.g., poverty and residence in underserved communities) that adversely impact health. Therefore, citizenship status may contribute to disparities in cardiovascular disease (CVD) and its risk factors.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To estimate the prevalence, treatment, and control of high cholesterol, hypertension, and diabetes by citizenship status.

Methods: Analyses of the National Health and Nutrition Examination Survey (2011-2012 to 2015-2016), including 16,986 adults (≥20 years). Citizenship status was categorized as US-born citizens, foreign-born citizens, or noncitizens. CVD risk factor prevalence (age-standardized), treatment, and control were defined per national guidelines and determined using serum/examination values and prescription-medication inventories.

Results: Fifty-five percent (54.6%) of US adults had high cholesterol (41.7%), hypertension (33.7%), or diabetes (13.2%); however, limited differences were observed across citizenship status. Noncitizens had considerably lower treatment rates of high cholesterol (16.4% vs. 45.5% and 43.3%), hypertension (60.3% vs. 81.1% and 79.6%), and diabetes (51.2% vs. 69.5% and 66.6%) than US-born and foreign-born citizens (all $P<.001$). These treatment disparities were consistent across racial/ethnic groups. Noncitizens were more likely to be uninsured or lack a usual source of care (52.2% and 34.5%) than US-born (13.6% and 14.3%) and foreign-born citizens (16.2% and 14.6%) (all $P<.001$). Therefore, adjusting for healthcare access characteristics attenuated treatment disparities based on citizenship status. Among adults treated for CVD risk factors, there were no significant differences across citizenship status in the control of high cholesterol (38.1%) and hypertension (71.1%), but diabetes control rates were lower among noncitizens (35.3%) than among US-born (51.2%) and foreign-born citizens (46.9%) ($P<.001$).

Conclusions: Efforts to prevent CVD, the leading cause of death among immigrants, should address the undertreatment of high cholesterol, hypertension, and diabetes by ensuring access to healthcare among noncitizens.

3950 | Impact of branded generics on the price of anti-dementia products in South Africa

Ilse Truter

Nelson Mandela University, Port Elizabeth, South Africa

Background: The Single Exit Price (SEP) for medicines was introduced in South Africa in 2004 with the aim to promote the transparent pricing of medicines. The SEP consists of the manufacturer price, the logistics fee and value added tax (15%), but excludes the dispensing fee. The SEP is periodically reviewed. In addition, generic substitution is compulsory in South Africa in an attempt to lower medicine prices.

Objectives: The aim was to use the SEP, which was introduced to standardise the pricing of medicines in South Africa, to analyse price differences of anti-dementia products.

Methods: The SEPs of four anti-dementia products in the Anatomical Therapeutic Chemical (ATC) group N06D on the South African market were extracted from the Database of Medicine Prices as on 22 January 2020. The Defined Daily Dose (DDD) was used as the standard dose, where possible, for comparative purposes.

Results: Six trade name products of memantine were available on the South African market in January 2020 (one originator and five branded generics) in one dosage strength (10 mg). The DDD of memantine is 20 mg. The price of the originator was R29.85/DDD, compared to an average price of R9.20/DDD for the branded generics (the price of the least expensive branded generic was R8.48/DDD). The film-coated branded generic tablets were slightly more expensive (R9.26/DDD) compared to the normal tablet (R9.11/DDD). Fourteen trade name products for donepezil 5 mg were available. The SEP for the originator was R25.65, compared to an average SEP of R10.99 for the 5 mg tablet (seven branded generics) and R9.81 for the 5 mg film-coated branded generic tablets (six branded generics). The price of the 10 mg originator tablet was R27.42, compared to an average of R11.44 for the 10 mg tablet (six branded generics) and R10.03 for the 10 mg film-coated tablet (seven branded generics). The price per DDD for the branded generics was on average 60% of the price per DDD of the originator (R38.47). Galantamine only had one branded generic, which was on average 60% of the price of the originator for the 8 mg, 16 mg and 24 mg tablets. Rivastigmine was only available as an originator tablet in a dosage strength of 3 mg (the price per DDD (9 mg) was R77.33/DDD.

Conclusions: Despite efforts to standardise and make medicine prices transparent in South Africa, there are still huge price differences, and recently many new branded generics became available on the market. The question can be asked whether prescribing according to active ingredients (INN prescribing) would not have been a better option in a country with a resource-constrained health care system, instead of the introduction of multiple branded generics.

3986 | Unblocking the barriers of access to direct-acting antiviral-based hepatitis C treatment in China: Lessons learnt from Tianjin City

Peiwen Zhang[1], Ran Guo[1], Jun Lian[1], Mengjia Zhi[1], Chengzhen Lu[2], Weishen Wu[3], Lihong Wang[4], Polin Chan[5], Zhongdan Chen[6], Jing Sun[1] and Yuanli Liu[1]

[1]Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [2]Tianjin No 2 People's Hospital, Tianjin, China; [3]Tianjin Center for Disease Control and Prevention, Tianjin, China; [4]Tianjin Healthcare Security Administration and Settlement Center, Tianjin, China; [5]HIV, Hepatitis and STI Unit, Division of Communicable Diseases, World Health Organization, Manila, Philippines; [6]Hepatitis/TB/HIV/STI, World Health Organization, Office of the WHO Representative in China, Beijing, China

Background: The high price is a critical barrier of access to new therapies of direct-acting antiviral (DAA) for hepatitis C for both the patients and the society. Many countries continue to face the challenge of financing such expensive medicines. Such examples include both high-income and middle-income countries. Existing evidence about the efforts of China to address this challenge is limited. To our

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

knowledge, this is the first detailed description of a novel financing model and comprehensive analysis of its impact on patient financial burden of hepatitis C treatment in China.

Objectives: To examine the evolution of approaches to navigating patients barriers of access to DAAs based treatment of hepatitis C in Tianjin city, China.

Methods: Review of publicly available literature, including published and grey literature. Conduct on-site data extraction and critical informant interview. The patient financial burden of hepatitis C treatment was analyzed. The financial burden of hepatitis C patients with different treatment models and health insurance financing models was measured by calculating the number of annual income to cover patient out-of-pocket (OOP) expenditure for the standard treatment course accordingly.

Results: Tianjin is the first area to pilot a capitated provider payment program for the treatment of hepatitis C. Through which, the retirees, employees and residents spend 0.7, 1.0 and 5.6-6.8 months of their salary and disposable income for the treatment respectively, the financial burden of patients were much relieved. By the end of March 2019, the first-year pilot program had 876 hepatitis C patients registered the new insurance coverage and treated in Tianjin.

Conclusions: The study showed that even in the developing country, the financial barriers of access to new hepatitis C treatment for patients could be unblocked with government commitment and novel financing models. International experiences demonstrated that centralized bulk procurement is a good leverage for price negotiation, primarily when using innovative payment approaches. To re-produce the initial success of Tianjin, continued efforts are needed for stronger strategic price negotiation, preferably at central level. The case of Tianjin brings implications to the other areas of China and even other developing countries that, government commitment, novel financing model and pooled procurement are critical elements of stronger purchasing power and better secure of treatment.

4062 | Medication calculation errors with moderate, severe and fatal patient outcomes: Findings from the Norwegian incident reporting system

Alma Mulac[1], Katja Taxis[2], Ellen Hagesæther[3] and Anne Gerd Granas[1]
[1]*University of Oslo, Oslo, Norway*; [2]*University of Groningen, Groningen, Netherlands*; [3]*Oslo Metropolitan University, Oslo, Norway*

Background: In 2016 and 2017, almost 40% of medication-related safety incidents reported from Norwegian hospitals were due to wrong dose errors. Dosage errors caused by miscalculations are of special interest, as there is currently little understanding of why these errors happen.

Objectives: By extracting all calculation errors with moderate, severe and fatal patient outcomes, this study examines the types of errors and their causes.

Methods: We retrospectively evaluated 3,372 medication-related incident reports submitted to Norwegian Incident Reporting System over a 2-year period for reports describing calculation errors. Medication errors were reported from 64 Norwegian hospitals in 2016, and 55 hospitals in 2017. Incident reports consisted of categorical data (e.g., patient age, incident date, day of the week) and free-text data (incident and causes description, patient consequences, prevention measures, and caseworker's comments). We selected calculation errors associated with moderate harm, severe harm and death. Errors associated with no or mild patient harm were excluded. The data were classified according to the NCC MERP Index for Categorizing Medication Errors and analyzed in SPSS. The main outcome measures were administration route, drugs and drug classes involved, calculation error enablers, mechanisms, and contributing causes.

Results: In total, 68 calculation errors with moderate, severe or fatal patient outcomes were analyzed. 30 % of miscalculations were due to conceptual errors, 26 % due to math errors and 26 % were 10- or 100-fold overdosages. Morphine was the most frequently reported medication related to calculation errors. Opioids, IV-solutions, cardiac and antibacterial therapy were the most frequently reported drug classes. The major contributing factors were procedures not adhered to (38%) and lack of double-checks. A knowledge deficit was detected in 59% of the cases. Majority of errors were reported by nurses (49%) and physicians (24%). Children (0-4 years) and elderly (75-79 years) were most at risk for calculation errors.

Conclusions: Calculation errors causing moderate, severe and fatal patient harm occurred mostly due to a lack of conceptual understanding of numbers, fractions and measurements/units. The preparation of injectable drugs should be given particular attention to prevent calculation errors and patient harm.

4209 | Utilization and expenses of traditional Chinese patent medicines in cancer treatment: A retrospective study on outpatients' prescriptions

Erdan Luo, Tianqi Zhang and Ying Bian
University of Macau, Macao, Macao

Background: Traditional Chinese Patent medicines (TCPMs) were increasingly used as a complementary treatment for cancer in China, while studies about the expenses of anticancer TCPMs were limited.

Objectives: To figure out the characteristics of utilization and expenses of TCPMs in cancer treatment.

Methods: Outpatients' prescriptions were collected from traditional Chinese medicine department of a large-scale cancer center in south China in 2017. The frequencies and rates of prescribing TCPMs were measured, and reimbursed expenses were analyzed based on China's National Basic Medical Insurance Drug Catalog (NBMIDC).

Results: A total of 23673 prescriptions with TCPMs were collected among outpatients diagnosed with cancer, mainly including nasopharynx, breast, lung, liver, cervix uteri, colorectal and stomach cancer. There were altogether 81 kinds of TCPMs used in cancer treatment. The most common prescribed drug was Lingzhibaozi, accounting 17.97% of all the anticancer TCPMs, followed by Fulingduotang (11.73%), Huazhenghuisheng (10.02%), Huaier (9.84%), Fufangzaogong (4.68%),

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Fufangbanmao (4.57%) and Anduolin (4.46%). With the instructions of immunomodulating for cancer patients, the prescribing rates of Lingzhibaozi and Fulingduotang were both accounted 10% to 40% in most cancers. Fufangbanmao was prescribed mostly in thyroid (37.94%), laryngeal (29.77%), and oral cancer (24.44%). Anduolin was prescribed mostly in ovary (17.74%) and endometrial cancer (17.86%). The average expense of TCPMs was 1084.21 RMB per prescription, which was much higher than that of Chinese herbal medicines. Noticeably, the overall ratio of self-paid TCPMs expenses accounted for 62.94%. The two top used drugs, Lingzhibaozi and Fulingduotang, which cost 1365.48 and 1244.09 RMB per patient in average, were both at patients' own expenses. While the expenses were partially covered for Fufangbanmao, Huazhenghuisheng, Huaier and Anduolin, whose self-paid ratios were depended on the reimbursement regulations in NBMIDC and types of patients' insurance.

Conclusions: The utilization of TCPMs varied in different cancers. Lingzhibaozi and Fulingduotang were widely prescribed in most cancers, while the usage of Fufangbanmao and Anduolin concentrated on head and neck cancer, and gynecologic cancer respectively. The overall expenses and self-paid ratios of anticancer TCPMs were both high. Though NBMIDC was controlling the use of TCMPs by reimbursement regulations, it is noteworthy to monitor the overuse of self-paid TCPMs to prevent the potential economic burden in cancer treatment.

4254 | Real world data to identify target population for new CAR-T therapies

Valeria Belleudi[1], Francesco Trotta[2], Filomena Fortinguerra[2], Francesca Romana Poggi[1], Odoardo Olimpieri[2], Enrica Santelli[1], Ilaria Cozzi[1], Paola Michelozzi[1] and Antonio Addis[1]

[1]Lazio Regional Health Service, Rome, Italy; [2]Italian Medicines Agency-AIFA, Rome, Italy

Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma often refractory to currently available treatments (immuno-chemotherapy/cell-stem-transplantation-ASCT). Recently, have been approved new cell therapies for patients failing two conventional treatments, CAR-T (Chimeric-Antigen-Receptor-T-cell), committing payers in planning and implementing their use.

Objectives: To define, using Real World Data (RWD), a reproducible procedure that allows estimation of the target population for CAR-T therapy.

Methods: Through the integration of electronic healthcare data (EHD), we identified patients with an incident diagnosis of non-Hodgkin's Lymphoma (NHL) during 2010-2015, resident in Lazio, aged≥ 20 years. The cases with DLBCL were followed tacking into account pathological anatomy (PA) report, up to 3 years. To be defined relapsing after two treatment lines (R2), patients must have had new chemotherapy and/or NHL hospitalization after ASCT or at the end of the second chemotherapy. R2-rate was extended to the population without PA.

Results: NLH incident patients were 7,384, 68% of which with PA record and, 29% of these had DLBCL codes. Patients who relapsed after two treatment lines were 47 (39%) in the subgroup of patients with transplant and 138 (41%) in that with second chemotherapy treatment. Patients in the two subgroups were very different in terms of age and comorbidity. Applying R2-rate (13.7%) to the DLBCL incident case, we estimated 45 patients eligible for CAR-T.

Conclusions: This study shows how RWD allows estimation of a target population with new advanced therapies. This approach is rigorous, transparent and verifiable over time with respect to the individual opinions of experts.

4394 | The rise and fall of prescription fentanyl

Shelley A. Jazowski[1], Stephen W. Patrick[2] and Stacie B. Dusetzina[2]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Vanderbilt University School of Medicine, Nashville, TN

Background: The United States Department of Justice and state attorneys general have increasingly scrutinized the role of pharmaceutical marketing practices in the creation and spread of the opioid epidemic. Following accusations of misleading promotion regarding prescription fentanyl's safety and appropriate use, the manufacturer of one such product (Subsys) agreed to multi-million dollar settlements in 2015.

Objectives: To evaluate the association between legal settlements and changes in the promotion and use of Subsys and other transmucosal immediate-release fentanyl (TIRF) products.

Methods: We used general payments files from the Centers for Medicare and Medicaid Services Open Payments Database and Medicare Part D Prescriber Public Use files from 2013-2017 to identify promotional (non-research) payments and prescription fills (≥11) for TIRF products: Subys (fentanyl sublingual spray), Fentora (fentanyl buccal tablet), Abstral (fentanyl sublingual tablet) and Lazanda (fentanyl nasal spray). Data for Fentora, Abstral and Lazanda were combined and analyzed separately. We used segmented regression to evaluate the association between legal settlements and quarterly promotional spending and descriptive statistics to assess annual utilization trends.

Results: Promotional spending on Subys increased $206,074 per quarter, reaching over $2.5 million in payments in Q2-2015. Immediately following legal settlements, payments abruptly declined by $1,773,576 million ($p<0.0001$). Promotional spending continued to decline each quarter, with payments equaling $136,647 in Q4-2017; a 95% decrease from the quarter preceding legal settlements. Similar trends were observed for other TIRF products.

Prescription fills for Subsys more than tripled between 2013 (4,034) and 2015 (12,667), whereas claims for other TIRF products decreased 6% to 2,455 fills in 2015. Use of Subsys declined by 46% in 2016 and an additional 55% in 2017. Similarly, prescription fills for other TIRF products decreased 5% and 29% in 2016 and 2017, respectively.

Conclusions: Promotional payments significantly decreased for TIRF products, indicating that legal settlements modified the promotional practices of Subsys' manufacturer and may have indirectly changed the marketing of other TIRF products. We also observed decreases in Subsys utilization in 2016 and 2017 perhaps suggesting that prescribers responded to promotional changes, legal concerns or both.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4424 | Development and testing of a digital observational tool to monitor bar code medication administration

Alma Mulac[1], Rune Kristiansen[2], Synne Margrethe Nielsen[1], Yvonne Andersson[3], Sandra Rut Eikeland[4], Katja Taxis[5], Ellen Hagesæther[6] and Anne Gerd Granas[1]

[1]*University of Oslo, Oslo, Norway*; [2]*Hospital Østfold Kalnes, Sarpsborg, Norway*; [3]*Hospital Pharmacies Enterprise South Eastern Norway, Oslo, Norway*; [4]*Hospital Pharmacies Enterprise South Eastern Norway, Sarpsborg, Norway*; [5]*University of Groningen, Groningen, Netherlands*; [6]*Oslo Metropolitan University, Oslo, Norway*

Background: Bar Code Medication Administration (BCMA) technology, i.e., scanning barcodes on medicines and patients' wristbands, has the potential to reduce medication administration errors, but are sometimes used incorrectly due to poor implementation and technology limitations. BCMA technology, however, affects workflow and changes the way nurses interact with patients and colleagues. Consequently, unsafe acts such as routine violations of procedures, skill-based errors or interruptions may occur. Creative workarounds are common, and unsafe practice still exists. Additionally, there is a lack of standardized methodology for measuring the implementation grade of the technology and for measuring administration errors in BCMA.

Objectives: Our aim was to develop and test a digital observational tool to collect real-world data on how BCMA technology is used in a hospital setting. The objectives were to test the digital tool while observing medication administration and get a better insight in (un) safe practices and medication administration errors.

Methods: We developed a digital online registration tool. The categories we wanted to record during observations were discussed, tested, and evaluated in a pilot in a hospital setting. This involved the themes: the use of BCMA, unsafe practices during medication administration, the errors of preparation or labeling in the trolley, information on scanned /overrides of medications, technological discrepancies during observation, the use of inpatients private medications, medication errors and field notes. The data was collected on handheld tablets.

Results: Two researchers observed nurses for 7 days, at two medical wards, as they administered medications to 30 patients. We found that the tool captured unsafe practices and errors, and provided detailed and structured data on the use of BCMA. We performed a thorough evaluation with 8 inter-professional panel-members, and extracted the most suitable categories, with the focus on the processes supporting BCMA, and excluded categories related to details of the therapy, such as drug, dose, strength, indications, and interruptions. To accommodate data registration during observation, most questions were designed as drop-down lists. In addition, a free text option was available for registering qualitative observations.

Conclusions: Our digital observational tool was successful in recording how nurses use BCMA. The tool can be used to capture technological challenges with the system, as well as documenting medication administration errors, workarounds, and violations of procedures.

4454 | Accelerated vs regular approval, differences in study characteristics of lung cancer treatments approved by the US Food and Drug Administration

Tatiane Ribeiro[1], Lewis Buss[1], Sanni Ali[2,3] and Moacyr Nobre[1,4]

[1]*Department of Preventive Medicine, Faculty of Medicine, University of São Paulo, Sao Paulo, Brazil*; [2]*Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom*; [3]*Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom*; [4]*Clinical Epidemiology and Research Support Team, São Paulo Heart Institute (InCor), Sao Paulo, Brazil*

Background: Lung cancer is the leading cause of cancer death globally. The accelerated pathway is a program used for faster drug approval by the US Food and Drug Administration (FDA) and it allows approval based on surrogate endpoints.

Objectives: To assess differences between accelerated vs regular pathway approvals made by the FDA for lung cancer treatment, from 2006 to 2018, in terms of study design, sample size, effect size and outcome measures.

Methods: Two independent researchers reviewed the @DrugsFDA in the FDA's online bulletin that includes all approvals for lung cancer drugs. The data collected included: study type (RCT or single-arm), sample size (<200 vs ≥200 patients), the primary outcome (overall survival or surrogate endpoint) and effect size (large vs not large; Risk ratio, RR ≥ 2 was considered large). Accelerated pathway approvals were identified on the FDA website. Study characteristics were compared between accelerated and regular approvals. The absolute number differences were presented and a 2-sided P value .05 was used to assess statistical significance by Fisher's exact test.

Results: From 2006 to 2018, the FDA approved 31 new drugs and supplemental indications for lung cancer, totaling 37 studies: 13 via accelerated and 24 via the regular pathway. Proportionally more approvals via the accelerated pathway were based on single-arm trials (85% vs 21% p<0.001) and small sample sizes (69% vs 29% p=0.036). Surrogate outcomes were more frequent among accelerated approvals (92% vs 58% p=0.057). Large effect size (RR ≥ 2) was not different between the pathways (38% vs 25% p=0.27).

Conclusions: Single-arms, small sample size and surrogate endpoints are associated with low quality of evidence and we find that it's more prevalent in the accelerated pathway for lung cancer approval. However, a larger effect size was not observed in the accelerated pathway approvals.

4490 | Association of formulary exclusions and restrictions for opioid alternatives with opioid prescribing among medicare beneficiaries

Tanvi Rao[1], Zippora Kiptanui[2], Paul Dowell[2], Corey Triebwasser[3], G. Caleb Alexander[4] and Ilene Harris[2]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]IMPAQ International, LLC, Washington, DC; [2]IMPAQ International, LLC, Columbia, MD; [3]IMPAQ International, LLC, Wellesley, MA; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Background: While there are many pharmacologic alternatives to opioids, it is unclear whether the structure of Medicare Part D formularies discourages their use.

Objectives: (1) To quantify the coverage of opioid alternatives and the prevalence of prior authorization [PA], step therapy [ST], quantity limits [QL] and tier placement for these drugs; and (2) to test whether these formulary exclusions and restrictions are associated with increased opioid prescribing to older adults, at the county level.

Methods: Design, Setting, and Participants: County-fixed effect models estimated using a panel of U.S. counties over the 50 U.S. states and the District of Columbia over calendar years 2015 and 2016. The sample included 2721 counties in 2015 and 2671 counties in 2016 with sufficient data on Medicare Part D formulary design and opioid prescribing. **Main outcomes and measures:** County-level opioid prescribing rate (number of opioid claims divided by the number of overall claims) and counts of excluded opioid-alternatives and opioid-alternatives with PA/ST/QL and high-tier placements.

Results: We examined 30 non-opioid analgesics across over 28,000 Medicare plans. On average, Medicare plans did not cover 7% of these drugs (interquartile range [IQR] 10%). Among covered non-opioids PA and ST were uncommon, with fewer than 5% impacted by PA and 0% by ST. On the other hand, 13% of covered non-opioids had quantity limits (IQR 10%) and 22% were in high-cost tiers (IQR 38%). Increases in the number of non-opioids excluded on Medicare plans in a county were associated with increased opioid prescribing (effect size relative to mean, 2.2-3.7%; $P<0.01$). Conversely, increases in the number of opioids not covered on Medicare plans in a county was found to be associated with decreased opioid prescribing (effect size relative to mean, 0.8-1.5%; $P<0.02$). None of the utilization management strategies (PA/ST/QL) examined, nor high cost tier placements of non-opioids, were statistically associated with increased opioid prescribing.

Conclusions: Restricting access to pharmacologic alternatives to opioids may contribute to increased opioid prescribing.

4563 | Triptans-utilization study for regulatory action on medication-overuse headache: Using nation-wide claim database in Japan

Sono Sawada, Haruka Shida, Kazuhiro Kajiyama, Mikiko Kubo, Yoko Takaashi, Chieko Ishiguro and Yoshiaki Uyama
Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan

Background: Under the universal care service in Japan, almost all medical claims submitted electronically are aggregated as the National Database (NDB). As of March, 2018, the NDB covered more than 95% of claims. Using this database, the Pharmaceutical and medical device agency (PMDA), the Japanese regulatory agency, has been conducting several drug-utilization studies for the purpose of drug-safety assessment. One of these studies will be reported here. There was the concern on triptans, a class of migraine medication, overuse-induced headache from Japanese and foreign spontaneous reports, however, no data were available regarding the situation in clinical practice in Japan.

Objectives: To identify the total number of patients who were prescribed triptans from 2010/8 to 2016/3 in Japan and the proportion of patients suspected of overusing the medication among them.

Methods: Drug claims obtained from hospitals, clinics, dental clinics, and outpatient pharmacies during the period of 2010/8 to 2016/3 were used as a data source. At first, we identified the total number of triptan-prescribed patients and the number of patients who were suspected of triptan-overuse and calculated the proportion of them among the total patients. A case of "possible addicts" was defined as a patient with at least one of the following criteria; 1) for four and more continuous months, the total amount of prescribed triptans in a single month exceeded 10 times more than the maximum single dose. 2) The total amount of prescribed triptans in a certain month exceeded 10 times more than the maximum single dose multiplied by X months ($X \geqq 4$) and the next prescription was recorded within X months. We also defined "probable addicts" by replacing the term "the maximum single dose" with "the maximum daily dose". These definitions were established on the basis of the definition of "Triptan-overuse headache" in the International Classification of Headache Disorders 3rd edition(ICHD-3).

Results: A total of 2,078,556 patients with triptans prescription were included for analysis in this study. Of those, 102,871 (4.95%) and 16,426 (0.79%) patients were identified as "possible addicts" and "probable addicts", respectively.

Conclusions: Based on the results in this study as well as the situation in foreign counties, the MHLW, the Ministry of Health, Labour and Welfare, and PMDA have decided to require the marketing authorization holder of triptans products to put the important precautions about medication-overuse headache on their package inserts.

4595 | Hormone replacement therapy (HRT) and risk of breast cancer: Nested case-control studies using QResearch and clinical practice research datalink (CPRD)

Yana Vinogradova[1], Carol Coupland[1] and Julia Hippisley-Cox[2]
[1]University of Nottingham, Nottingham, United Kingdom; [2]University of Oxford, Oxford, United Kingdom

Background: HRT can relieve often life-changing menopausal symptoms for many women, but the Women's Health Initiative (WHI) and many smaller studies reported increased breast cancer risk associated with its use. Most studies were, however, underpowered to investigate different HRT preparations and the WHI included only two. A recent Lancet meta-analysis pooled results from numerous, rather heterogeneous studies, and has reported higher than expected risks.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To quantify breast cancer risks associated with different HRT treatments.

Methods: Two separate studies used the QResearch and CPRD primary care databases containing UK general practice records, representative of the general population. Overall between 1998 and 2018, 98,611 women aged 50 to 79 had a primary breast cancer diagnosis. Each case was matched by birth year and practice to up to 5 controls, alive and registered at the time of case diagnosis (index date). Exposure to different HRT treatments was based on prescriptions other than in the year before the index date. Duration of use (long-term, ≥ 5 years; short-term, 1 to <5 years) and recency of use (current, <5 years before the index date; past, ≥ 5 years) were both investigated. Conditional logistic regression was used to calculate odds ratios adjusted for smoking, ethnicity, body-mass index and co-morbidities associated with increased risk of breast cancer or use of HRT. Separate analyses were run for each database and the results combined using meta-analysis techniques.

Results: Overall, 33,709 (34%) cases and 134,391 (31%) controls had used HRT. Compared to no use, long-term current use was associated with increased risks of breast cancer for oestrogen-only therapy (odds ratio 1.15, 95% confidence interval 1.09 to 1.21) and oestrogen-progestogen therapy (1.79, 1.73 to 1.85). For combined progestogens, increased risk was highest for norethisterone (1.88, 1.79 to 1.99) and lowest for dydrogesterone (1.24, 1.03 to 1.48). Past oestrogen-only use and past short-term oestrogen-progestogen use were not associated with increased risk. However, the risk associated with past long-term oestrogen-progestogen use remained increased (1.16, 1.11 to 1.21).

Conclusions: This observational study covering all common HRT treatments in the UK is the largest consistent study done and provides reliable population-based risk estimates. While echoing the pattern of the Lancet meta-analysis findings, our estimates appear lower and more in line with earlier studies. They should assist any patient and their doctor when selecting appropriate therapy.

4734 | Comparing opioid regulations globally across regions with different levels of opioid utilisation

Teng-Chou Chen[1], Björn Wettermark[2], Douglas Steinke[1], Gillian Caughey[3], Mina Tadrous[4], Veronika Wirtz[5] and Li-Chia Chen[1]

[1]Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom; [2]Department of Pharmacy, Uppsala University, Uppsala, Sweden; [3]Registry of Senior Australians, South Australian Health and Medical Research Institute and Division of Health Sciences, University of South Australia, Adelaide, Australia; [4]Women's College Hospital, Toronto, ON, Canada; [5]School of Public Health, Boston University, Boston, MA

Background: The enactment of policy to control opioid prescribing has been associated with decreased opioid utilisation and related-harms. However, strictly limited access to opioids can potentially lead to unmet needs of pain management.

Objectives: This study aimed to identify the variation in opioid policies across global jurisdictions with different levels of opioid utilisation to explore the feasibility of conducting a cross-national comparison (CNC) study investigating the impacts of policies on opioid-related issues.

Methods: A cross-sectional survey included participants by purposeful sampling from March to November 2018. Experts with interests in CNC studies comparing opioid utilisation were invited to participate at the Drug Utilisation Research Special Interest Group (SIG) of the International Society for Pharmacoepidemiology in 2017. Information related to controlled drug schedules, regulations and the most commonly used opioid in each region were collected by a face-validated electronic survey. Regions were defined as geographic areas with unique regulations and were categorised according to their level of opioid consumption using the Adequacy of Consumption Measure. Descriptive statistics were applied to present the frequency of answers for the individual items included in the survey.

Results: Overall, 35 responses from 22 regions were received, and 5, 8 and 9 regions had opioid consumption categorised as more than adequate, moderately adequate or less than moderate, respectively. All 22 regions had control substance regulations, with the majority of opioids listed as controlled substances, but 11 regions did not list tramadol as a controlled substance. Most regions restricted the access to opioids by limiting the amount and duration of a prescription (n=10) or authorising certain pharmacies to supply prescription opioids (n=5). Among the 5 regions with more than adequate opioid consumption, oxycodone or codeine with paracetamol were the most commonly used opioid preparations. In contrast, tramadol was the most commonly used opioid among the 9 regions with opioid consumption categorised as less than moderate.

Conclusions: There is a variation in national regulations regarding opioid prescribing, and regions had higher opioid consumption were tend to prescribed stronger opioids. Despite tramadol being the most commonly used opioid in regions with less opioid consumption, there was no consensus about its classification as a controlled substance. Further CNC studies should investigate the impacts of regulations on opioid prescribing.

4846 | Over 2000 seniors initiate second-line osteoporosis pharmacotherapy monthly in Ontario - Impact of drug policy change and call for research

Natalia Konstantelos, Nancy He, Kaley N. Hayes and Suzanne M. Cadarette

University of Toronto, Toronto, ON, Canada

Background: Osteoporosis is a brittle bone disease characterized by low bone mineral density and increased fracture risk. Oral bisphosphonates are the primary drugs used to treat osteoporosis in Canada. However, not all patients tolerate oral bisphosphonates or continue to lose bone on therapy. These patients may benefit from switching to more potent second-line treatment options: annual

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

infusion of zoledronic acid or biannual denosumab injection. All residents over the age of 65 can access drugs listed on the Ontario Drug Benefit (ODB) formulary. Zoledronic acid was added to the ODB formulary in 2006 and denosumab was added in 2012, yet both were restricted to women meeting high fracture risk criteria, and special authorization was required that limited coverage in men. Coverage for both drugs broadened February 2018 to include men and women with fewer restrictions.

Objectives: To estimate the impact of the 2018 policy change on the number of seniors initiating second-line osteoporosis therapy in Ontario.

Methods: We identified Ontario residents aged 66 or more years initiating denosumab or zoledronic acid, 2016/02 - 2019/12. Interrupted time series analysis (segmented linear regression with autoregressive error models) was used to examine the impact of the policy change (2018/02) on the monthly number of new users of each therapy, accounting for seasonality, non-stationarity, and autocorrelation. Analyses were completed by sex for denosumab, yet combined for zoledronic acid due to small sample size.

Results: We identified 85,893 denosumab (mean age 79, SD=8.2; 88% women) and 1040 zoledronic acid (mean age 74, SD=6.3; 84% women) initiators during the study period. The monthly number of initiators was stable over the 2 years pre-intervention with an average of 33 men and 1,405 women starting denosumab, and 18 seniors starting zoledronic acid. A significant immediate increase in denosumab use (477% men; 21% women), and zoledronic acid (25%) occurred at the time of the policy change. The number of initiators exceeded predicted values post-policy change with a relative increase of 62% (n=40) for zoledronic acid, and 62% for denosumab (men: 177%, n=357; women: 44%, n=1959) with a post-intervention monthly average of 408 men and 1826 women and starting denosumab, and 27 starting zoledronic acid.

Conclusions: After broadening coverage, over 2000 seniors start second-line therapy monthly in Ontario. Better understanding of the characteristics of patients initiating denosumab vs. zoledronic acid as well as the relative benefits and harms of these therapies in the real-world is needed.

4883 | Impact of meningioma risk minimization campaign on cyproterone acetate use in France

Camille Morival[1], Marine Penichon[2], Clément Mathieu[2], Natapy Attoumi[1], Louis Letinier[1], Amandine Gouverneur[1], Antoine Pariente[1] and Julien Bezin[1]

[1]Bordeaux Population Health Research Center, Team Pharmacoepidemiology, UMR 1219, Inserm, University of Bordeaux, Service de Pharmacologie Médicale, Pôle de Santé Publique, CHU de Bordeaux, Bordeaux, France; [2]Bordeaux Population Health Research Center, Team Pharmacoepidemiology, UMR 1219, Inserm, University of Bordeaux, Bordeaux, France

Background: Cyproterone acetate (CA) is a synthetic progesterone derivative with anti-androgenic properties. In France, it is commonly used in hormone related disorders resulting in androgenization in the woman, and is indicated in prostate cancer and reduction of drive in sexual deviations in men; off-label use for contraception and acne has been evidenced. A risk of meningioma was reported among users of high cumulated doses of CA since 2007 which led to risk minimization campaign by French Health Authorities after 2011.

Objectives: This study aimed at describing the impact of national health policies on the use of cyproterone acetate in France.

Methods: We analysed data from the nationwide monthly drug claim database for the 01/01/2010 to 30/09/2019 time period. Monthly reimbursed amount of CA were derived from the information of refunded packages and expressed in terms of defined daily doses (DDD). Key dates of the risk minimization campaign and communication concerning the meningioma risk were identified from Health Authorities' websites. Briefly, the ain dates were : addition of meningioma as a contraindication in the SmPC in 2011; results of the national pharmacovigilance survey in March 2014; creation of the scientific committee in charge of the risk minimization campaign at the French national drug authority and results of a pharmacoepidemiology risk study in June 2018; risk communication to patients and health professionals from August to November 2018. Change point analysis was used to identify potential changes in monthly CA claims. The analysis was stratified according to the two CA dosage available in France (50mg;100mg).

Results: For 100mg CA and 50mg CA, the monthly amount of reimbursed DDD evolved from 329,640 and 706,290 DDD in January 2010 to 39,900 DDD and 152,610 DDD in September 2019, respectively. Graphically, CA 100mg decreased continuously over the study period, whereas CA 50mg decreased especially after July 2018 which correspond to the beginning of the public risk communication. The change point analysis evidences a significant 55.1% decrease starting from March 2015 in the monthly amount of reimbursed DDD for 100mg CA, and a significant 35.5% decrease starting from September 2016 for that of 50mg CA.

Conclusions: Cyproterone acetate 100mg amount of use changed following the risk signal identification. In contrast, cyproterone acetate 50mg amount of use change concomitantly to the establishment of the risk minimization campaign in France. However, change point analysis method identified earlier significant change in the use of cyproterone acetate 50mg.

4892 | Ecuador's administrative data sources for drug utilization research

Mónica Tarapues[1], Carlos Durán[2], Belén Mena[1], Patricia Granja[3], Lisiane Leal[4], Monique Elseviers[5] and Luciane Cruz[6]

[1]UCE, Quito, Ecuador; [2]Ghent University, Ghent, Belgium; [3]PUCE, Quito, Ecuador; [4]McGill University, Montreal, QC, Canada; [5]Ghent University, Ghent, Belgium; [6]University of Sorocaba, Sao Paulo, Brazil

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Health-related administrative sources of information are currently a source in pharmacoepidemiological research. Along the years, different databases have been developed to manage medical and pharmacy records that are now electronically reported with the possibility of establishing record linkage systems. However, in LA countries as Ecuador little is known about the availability of the information and its application in drug utilization research.

Objectives: The aim of this study is to outline the main characteristics of administrative data sources of Drug Utilization (DU) from Ecuador.

Methods: A network of health experts, liaising with national data providers and academic experts in Pharmacoepidemiology & DU research conducted a website search in government institutions. Researchers independently screened eligible data sources to identify public, health-related administrative data in Ecuador. From each source of information, we collected information on accessibility, coverage (national, regional, municipality, organization multi-site), data provider (public health, private sector, both), type of data sources (wholesaler, pharmacy records, electronic health records, other), setting (ambulatory, hospital, both), covered periods. Descriptive analysis was performed.

Results: The Ecuadorian Institute of Social Security and the Ministry of Health are the main public healthcare providers in Ecuador. For DU research, we identified 4 data sources, which are not publicly and conveniently accessible on line; all of them reported data from ambulatory and hospital settings, but only in 2 are possible to separate; 3 include only data from the public sector. One data source receive notifications of adverse events and technical complaints related to the use of medicinal products. Data source from the social security institute include clinical data as well as dispensing registries. The last includes the patients´ record number, gender, age, date of dispensing, name and code of the drug, the number of dispensed units and the actual price per unit.

Conclusions: Dispensing registries are the main data source of DU data in Ecuador. Transparency and public accessibility of the data is a major weakness of the Ecuadorian DU data sources. Unfortunately, current information is limited and segmented. Latin American and Ecuadorian researchers, as policy makers as well, must pressure to improve the quality and transparency of DU data.

4990 | Ondansetron in pregnancy: Patterns of usage and characteristics of patients in UK general practice

Jim Slattery Slattery[1] and Hedvig Nordeng[2]
[1]*European Medicines Agency, Amsterdam, Netherlands;* [2]*University of Oslo, Oslo, Norway*

Background: Hyperemesis gravidarum (HG) is not a labelled indication of ondansetron in the UK but Royal College of Obstetricians and Gynaecologists guidance suggests that it is safe and effective as a second line treatment for nausea and vomiting & HG in pregnancy. Recent studies from the US, where exposure is common in pregnancy (possibly 9%), have suggested a possible association of in-utero exposure to ondansetron with cardiac defects and oral cleft in the child. The potential clinical significance of these findings for the UK can be informed by measurements of ondansetron usage.

Objectives: To determine treatment patterns for ondansetron in pregnancy and to characterize the target population.

Methods: The study population consists of 717007 pregnancies that can be matched to a live birth within an IMRD-UK registered GP practice between 2005 and September 2018. In-utero exposures to ondansetron were described with respect to year of birth, dosage and timing within the pregnancy and the temporal relationship to first line anti-emetics recommended by the RCOG was examined. The characteristics of exposed mothers in terms of age, smoking, clinical diagnoses and exposures to other forms of medication were contrasted with unexposed mothers. Odds ratios were calculated for each characteristic.

Results: Prescription rates for ondansetron during pregnancy steadily increased over the study period from 0.04% in 2005 to 1.99% in 2018. First trimester exposure increased from 0.01% to 1.11% over the same period. In addition to other anti-emetics (antihistamines) and therapies to treat the sequelae of HG (Oral rehydration, vitamins and nutrients), use of ondansetron was disproportionately associated with antipsychotics (OR=13.1 compared to unexposed), antidepressants (OR=2.0), antibacterial (OR=2.0) and drugs for constipation (OR=1.9). Associated clinical events other than nausea or vomiting included gastrointestinal hemorrhage (OR=7.8), emergency hospital admission (OR=4.6) and thyrotoxicosis (OR=4.3).

Conclusions: Although UK use of ondansetron for nausea in pregnancy has increased in recent years it is not yet close to levels of use in the US. Formal etiological studies of association with birth defects in UK, and probably EU, data will face challenges due to low exposure, rare outcome events and a target treatment population with many distinctive clinical features that may require adjustment in statistical models. None-the-less, the continued increase in usage suggests that such analyses should be carried out.

5014 | Key evidence supporting prescription opioids approved by the U.S Food and Drug Administration, 1997-2018

James Heyward[1], Thomas J. Moore[2], Jennifer Chen[3], Kristin Meek[1], Peter Lurie[4] and Caleb Alexander[1]
[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [2]*Institute for Safe Medication Practices, Alexandria, VA;* [3]*Johns Hopkins School of Medicine, Baltimore, MD;* [4]*Center for Science in the Public Interest, Washington, DC*

Background: Despite increased scrutiny of U.S. Food and Drug Administration (FDA) regulation of opioids, no study has yet assessed the evidence thresholds applied to new approvals of opioid analgesics.

Objectives: (1) To characterize the quality of safety and efficacy data in New Drug Applications (NDA) for opioid analgesics approved by the FDA between 1997 and 2018.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: We conducted a cross-sectional analysis of NDAs using ClinicalTrials.gov, FDA reviews and peer-reviewed publications. Patient populations of interest were acute and chronic pain patients enrolled in pivotal trials (the main trials considered for drug marketing approval) of FDA-approved opioid analgesics. We assessed key characteristics of each NDA including: number, size and duration of pivotal trials; trial control; use of enriched enrollment randomized withdrawal designs (EERW); and systematically measured outcomes from pooled safety analyses.

Results: Of 48 NDAs, most were for new dosage forms (n=25, 52.1%) or new formulations (n=9, 18.8%); only 1 (2.1%) was for a new molecular entity. Among products supported by at least one pivotal trial, eight approved acute pain products had a total of 19 Phase III trials with a median treatment duration of 2 days (interquartile range [IQR] 1, 3) enrolling a median of 329 (IQR 199-456) patients, and twenty-one opioids approved for chronic use included 28 Phase III trials with a median duration of 84 (IQR 25-84) days, enrolling a median of 298.5 (IQR 174-525) patients. Seventeen of these twenty-one opioids (81%) were approved based on EERW designs. Among the 42 NDAs subject to safety data requirements, 15 (35.7%) included pooled safety reviews that reported systematic assessment of the development of drug tolerance (including 14/33 NDAs for chronic use, 42.4%), 8 (19.0%) reported systematic assessment of study drug diversion, and 7 (16.7%) reported systematic measurement of non-medical opioid use. While all but one of 48 NDA's approved were for previously approved moieties, analysis of available NDA's for referent products yielded similar findings.

Conclusions: Between 1997 and 2018, the FDA approved opioids based on Phase III trials of short and intermediate duration, often in narrowly defined pain populations among patients able to tolerate the drug. Systematic collation of important safety outcomes was rare.

5040 | Pain management curricula within health professional schools in the United States: A landscape analysis

James Heyward[1], Beth Hogans[2], Jacob Christopher[1] and Caleb Alexander[1]

[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [2]*Johns Hopkins School of Medicine, Baltimore, MD*

Background: Given the ongoing opioid epidemic in the United States, even as chronic pain persists, pain management preparedness for health professionals is vitally important.

Objectives: To assess the current state and future of pain education in U.S. health professions schools utilizing (1) literature review; (2) appraisal of accreditation documents; and (3) conduct of key informant interviews.

Methods: A National Institute on Drug Abuse (NIDA)-commissioned study using three-pronged analyses of pain education at health professional schools in the U.S., including allopathic and osteopathic medical, nursing, physician assistant, pharmacy, and physical and occupational therapy. Our approach consisted of a formal review and synthesis of the peer-reviewed literature focusing on studies describing the content, medium, setting, and other characteristics of pain education programs in the U.S.; analysis of information presented by professional accreditation organizations, especially guidelines and competencies for programs; and in-depth key informant interviews with educational leaders in diverse health professions. We performed iterative analysis and synthesis of the information from these data-gathering approaches.

Results: Thirty-one publications were included in our review of the recent literature, most focused on medical education; five examined interprofessional education. Of the accreditation organizations contacted, half maintained information regarding curriculum standards - this information was limited to general standards for clinical preparedness, and was not sufficiently detailed for further study. Key informants included six curriculum leaders from varied health professions. Despite recommendations and guidelines, pain management preparation was inconsistent across programs, professions, specialties and disciplines. Teaching was often fragmented and bootstrapped; and competed with many other topics, barriers to implementation of coordinated curricula were prominent. We observed innovation and change, including novel programs incorporating multimodal pain-care strategies, interdisciplinary and interprofessional programming, and coordination with substance abuse training.

Conclusions: Despite considerable activity in the health professional training programs examined, barriers prevent programs from offering consistent, comprehensive, longitudinal, and high-quality pain management training. At present, accreditation standards and oversight organizations do not support critically needed improvements in pain management preparedness.

5058 | Drug use research in Peru: Is real-world data available?

Yesenia Rodríguez[1], Maribel Salas[2], Lisiane Leal[3], Monique Monique[4] and Luciane Cruz Lopes[5]

[1]*Institute of Health Technology Assessment and Research (IETSI), Lima, Peru;* [2]*Daiichi Sankyo, New Jersey, NJ;* [3]*Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada;* [4]*University of Ghent, Ghent, Belgium;* [5]*University of Sorocaba, São Paulo, Brazil*

Background: Drug utilization research (DUR) is being progressively demanded by health authorities and payers to assess the impact on the benefit-risk of drugs in the real-world setting. DUR is used to provide evidence-based data to inform policies and make decisions. Health System in Peru is based on Integrated Health Networks, and it is administered centrally by the Ministry of Health. No mapping has been conducted until now to describe the existing data sources for DUR in Peru.

Objectives: To map and describe data sources publicly accessible for DUR in Peru

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: Experts in Peru's Health Care System and academic Pharmacoepidemiology experts were invited to ensemble a network. A manual search of data sources providing information about medication use in the website from Peruvian institutions (government, academic, private) was made. In addition, we developed a systematic review of scientific literature using PubMed and LILACs to retrieve studies or documents (Bulletin, etc.) that used such data sources in Peru. Working in pair team of reviewers independently screened eligible studies and data. The data sources collected information on accessibility, geographic granularity, sector, type, and setting. Data were analyzed in a descriptive manner.

Results: From seven data sources identified, only one was publicly available. The process for obtaining data was not clear for the other data sources. Four had national granularity; five were from the Public health system. Each data source presented different source types: health care providers and Marketing Authorization Holders. The setting of data source was both hospital and ambulatory care and most of them had less than 10 years of coverage. Two data sources have individual-level data on adverse drug reactions and prescriptions. From the systematic review developed, we found two studies, one was derivate from the National Health Care survey (ENSUSALUD 2016) and the other from the Drug Integrated System (SISMED) of the Ministry of Health of Peru

Conclusions: The National Health Care survey conducted in 2016 was the only data source available. In general, the overall context of data sources for DUR in Peru is unknown. Few studies were conducted so far and internal initiatives and partnerships with universities seem to be a good strategy to improve drug utilization research in Peru.

5118 | Data sources for health care decision making in Mexico: Challenges and strength (Mexican Working Group on DUR)

Diana Gomez[1], Svetlana Doubova[2], Anahí Dreser Mansilla[3], Juan Carlos Sanchez Salgado[4], Lucila Castro Pastrana[5], Yared Santa Ana Tellez[6], Elena Ibarra Cazares[7], Isabel Hernández Lira[8], Lisiane Leal[9], Maribel Salas[10], Monique Elseviers[11] and Luciane Cruz Lopes[12]

[1]Universidad Autonoma del Estado de Morelos, Cuernavaca, Mexico; [2]Mexican Institute of Social Security, Mexico City, Mexico; [3]Instituto Nacional de Salud Pública, Cuernavaca, Mexico; [4]Immunology and Advanced Science Institute, Mexico City, Mexico; [5]Universidad de las Américas, Puebla, Mexico; [6]Utrecht University, Utrecht, Netherlands; [7]Universidad Autónoma Metropolitana, Mexico City, Mexico; [8]National Cancer Institute, Mexico City, Mexico; [9]McGill University, Montreal, QC, Canada; [10]University of Pennsylvania, Philadelphia, PA; [11]Ghent University, Belgium, Belgium; [12]University of Sorocaba, São Paulo, Brazil

Background: Access to consistent and validated information on drug utilization is crucial to inform decision making, both at the national policy level as well as in health care settings. However, this information is not always available or appropriate. Research on reliable data sources, and the development of a national inventory of such data sources contributes to prompt public health decisions.

Objectives: The aim of this descriptive study was to develop an inventory of the data sources for drug utilization research (DUR) in Mexico, highlighting databases potential strengths and limitations for decision-making

Methods: A Mexican working group on drug DUR that included health professionals, national data providers, and academic experts in the research fields of pharmacoepidemiology, health economics, and health systems research, research conducted an internet search of the institutional and governmental Mexican websites. The collected information from various data sources included accessibility, geographic granularity (national, regional, municipality, organization multi-site), type of the health sector (public, private, or both) and the data sources (pharmaceutical wholesale suppliers, pharmacy records, electronic health records, other), setting (ambulatory, hospital, or both), years available, and type of data aggregation. We performed a descriptive analysis of the databases.

Results: Ten databases were identified, of which only 30% were publicly available, and 70% had restricted access; 90% reported national data; 40% included data from both public and private sectors; 30% were from pharmacy records, 40% from patient records. Eight databases contained separate information from both hospital and ambulatory settings. Information on the data granularity (individual or aggregate level data) was uncertain in 40%.

Conclusions: There are diverse data sources for DUR in Mexico, but access is still a barrier for researchers. To facilitate DUR in Mexico, access to the databases should be public (easy and transparent). The existing databases represent useful and inexpensive resources to provide timely information primarily about medicines volumes, drug-drug and drug-diseases interactions and other prescription errors, as well as on outcomes of healthcare (e.g. adverse drug events, including death). The existing databases constitute a good source of "real-world" health care data to guide health policy, however the creation of new databases, as well as the conjunction of them, is an important task to be undertaken in México.

Drug Utilization Research -> Other

44 | Access to insulin: A success story from the Sudan

Isam Eldin Mustafa

National Health Insurance Fund, Khartoum, Sudan

Background: Diabetes Mellitus (DM) is a global health concern where one in ten people are living with diabetes and half of the people who need insulin lack access to it. The economic burden of DM in Sudan is high where the prevalence of the disease is over 10%. Over 36% of the total expenditure of diabetes in children is spent on insulin in Sudan which represent 23% of the household income. The fluctuation of the exchange rate since referendum in 2011 is significant. The National Medical Supplies Fund (NMSF) developed a policy for procurement and pricing of insulin by signing a long-term contract with the supplier and subsidizing it by increasing prices of products with low prices and high consumption.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: 1. 1. To determine the impact of procurement and pricing policy on the price of mixed human insulin. 2. 2. To identify the affordability of insulin for insured and noninsured population in Sudan
Methods: A comprehensive review of the procurement documents of NMSF from 2011 until 2018 was performed. The affordability of patients to insulin price was done following the World Health Organization/Health Action International Methodology.
Results: The tender price of mixed human insulin in 2011 was 3.2 Euros (3.54 US$) which is fixed until 2019. The patient's price since 2011 until 2019 is 40 Sudanese Pounds(SDG), while the exchange rate in 2011 was 1US$ = 2.7 SDG, 5.4 SDG in 2012, 6.5 SDG in 2015, 15.8 SDG in 2016, 45 SDG in 2018. The worker of the lowest wage needs to work 1.5 days to purchase 10 ml 100 IU/ ml of insulin if is not insured, while the insured patient has to work 0.38 day.
Conclusions: The cross subsidy that the NMSF implements to reduce the price of insulin beside the long contract with the supplies of single source products have great impact on the reducing the economic burden of insulin. Further study to determine the adherence to insulin and predict the future sustainability of the supply of subsidized insulin is badly needed.

2329 | Pattern and risks perception of medical drugs use among adults in rural and urban communities, Southwest, Nigeria

Waheed Adedeji[1,2], David M Dairo[1,2], Patrick Nguku[3] and Fatai A. Fehintola[1,2]
[1]University College Hospital, Ibadan, Nigeria; [2]University of Ibadan, Ibadan, Nigeria; [3]Nigerian Field Epidemiology and Laboratory Training Program, Abuja, Nigeria

Background: Inappropriate drug use can result in untoward consequences including drug resistance, adverse drug reactions and death. Antimalarial, antibacterial, analgesics, and sedatives are among the commonly abused and inappropriately used drugs. There is a paucity of data on drugs use pattern and risks perception in the communities.
Objectives: To determine the pattern, risks perception and predictors of medical drugs use among adults in the rural and urban communities, Southwest, Nigeria.
Methods: A cross-sectional study was carried out among 999 adults aged 18 years and above, selected by multistage sampling. The questionnaires, adapted from previous studies, were pretested and interviewer-administered. The pattern of medical drugs used, prescribers, sources of drugs acquisition, and perception of drug risks were obtained. Risk perception was rated each for the commonly used drugs/drug classes and herbal concoction and ranked. The level of significance was set at 5%.
Results: The median (range)% prevalence of drug use [rural vs urban] were: lifetime, [57.3(16-79)vs 59(19.5-82.9)], current, [30.7 (7.4-62.3) vs 31.6(10.4-69.3)] and past use, [21.2 (9-30.0)]. Drugs used were majorly self-prescribed, median(range)%: 54.5(50-73.8) vs 61.9 (50.9-82.4), and obtained from patent medicine store, median(range)%: 71.3(67.2-79.3) vs 70.5(60.8-80.5). Most commonly used drugs were: artemether/lumefantrine, 227(78.3%) vs 210 (63.8%), Ampiclox^{R}, 94(43.5%) vs 126(53.2%), paracetamol, 283 (64.5%) vs 343(70.4%) and chlorpheniramine, 23(36.5%) vs 36(43.4%). The prevalence of antimalarial monotherapy was 21.7 vs 36.2%. More than half (51.2%) had low risk perception, and no difference in risk perception between rural and urban communities (x^2=0.5, p=0.51). Factors predictive of lifetime drugs used, odd ratio (95% CI) were: antimalarial [educational level, 2(1.4-2.8), presence of health facilities 0.5(0.3-0.9), male 0.6 (0.4-0.8), long distance to health facility, 1.7 (1.1-2.6)]; antibacterial[educational level,1.8(1.3-2.4), old age, 0.5 (0.3-0.9), medical illness, 1.68(1.04-2.7)]; analgesics {distance to health facility, 0.6(0.4-0.9), married, 0.51(0.3-0.8)}; and sedatives [educational level, (1.1-2.2), medical illness 2.1(1.3-3.3), alcohol 2.2,(1.5-3.3)].
Conclusions: The pattern of drugs use was similar in both communities. Drugs were mostly self-prescribed and obtained from patent medicine store. The risk perception of drugs was low. Factors predictive of drugs used were educational level, distance to the health facility, medical illness, and alcohol intake.

2330 | Real-world data analysis of potential drug-drug interactions in Greek community pharmacies

Georgios Poulentzas[1], Panagiotis Nikolaos Lalagkas[1], Lampros Tsiolis[1], Dimitra Hadjipavlou-Litina[1], Eleftherios Berberoglou[2], Antonios Douros[3,4,5], Christos Kontogiorgis[2] and Theodoros Constantinides[2]
[1]Aristotle University of Thessaloniki, Thessaloniki, Greece; [2]Democritus University of Thrace, Alexandroupolis, Greece; [3]McGill University, Montreal, QC, Canada; [4]Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [5]Institute of Clinical Pharmacology and Toxicology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Germany, Germany

Background: Drug-drug interactions may lead to severe clinical outcomes concerning patients' health, thus posing a serious threat to various fields of Public Health. To date, they have been significantly understudied in Greece.
Objectives: The goal of this study was to determine the prevalence of potential drug-drug interactions (pDDIs) and shed light on the factors responsible for the growth of this problem.
Methods: For this cross-sectional study, anonymous e-prescription data for the years 2012 -2017 were randomly obtained from 5 community pharmacies in Thessaloniki, the second-largest city in Greece. The sampling process was as follows: for each year patients were chosen by increasing identification number based on the coding of the pharmacies, ensuring randomized selection, and their e-prescription history was found. This process was repeated until 1.000 patients using 2 or more medicines concurrently for 3 or more months were gathered for each year. The study group assumed concurrent use of the medications if they were dispensed within a time period of 30 days. Using the online Drug Interaction Checker (www.drugs.com/drug_interactions.html), pDDIs were categorized depending on their clinical significance into major, moderate, and minor. Prevalence was

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

calculated as "Number of patients with at least one pDDI/Total number of patients" and logistic regression was used in order to identify the factors associated with increased risk of potential drug-drug interaction existence.

Results: During the study period, we collected e-prescription data of 8.320 patients, distributed in all 6 years. The overall prevalence of major pDDIs was 12.5% (45.4% for moderate pDDIs). The most common major pDDIs were those between calcium-channel blockers and statins (29.5% of pDDIs) followed by anticoagulant and PPIs (10.7% of pDDIs). The most common potential adverse effect of the assessed pDDIs (8.2%) was major myopathy. After adjustment, statistically significant associations seem to exist between risk of major pDDIs and number of administered drugs (Odds ratio 5.72, 95% CI: 4.87 - 6.72).

Conclusions: The prevalence of pDDIs in this study is higher than what has been reported in other European countries, with polypharmacy being the main contributing factor. Therefore, given that pDDI prevalence is considered a quality marker of prescribing practices, our data argue for a need for improvement in that area in Greece.

2343 | Women are started on a lower daily dose of metoprolol than men irrespective of dose recommendations

Linda C. Hendriksen[1,2], Paul D. van der Linden[2], Katia M.C. Verhamme[1], Bruno H. Stricker[1] and Loes E. Visser[1,3]

[1]Erasmus Medical Center, Rotterdam, Netherlands; [2]Tergooi Hospital, Hilversum, Netherlands; [3]Haga Teaching Hospital, The Hague, Netherlands

Background: In a pharmacokinetic study of metoprolol, women had a two times higher maximal concentration in the blood and a significantly higher area under the curve than men after 100 milligrams (mg) twice daily. However, current guidelines do not distinguish dosage advices for women and men.

Objectives: This study was conducted to evaluate whether physicians prescribe the same starting dose of metoprolol for women and men under real-life circumstances. To see if differences occurred after the start of metoprolol, the dosing regime was followed up to 10 prescriptions.

Methods: A cohort analysis was performed in the Rotterdam Study (RS) and results were replicated in the Integrated Primary Care Information (IPCI) database - A Dutch GP database. The study population comprised all patients aged ≥18 years starting on metoprolol. The primary outcome was the mean daily dose in mg of the first metoprolol prescription. The secondary outcome was the dose regimen, expressed as the mean daily dose in mg per prescription up to 10 prescriptions. Data were analysed using an independent-samples t-test to compare the mean daily dose of metoprolol for both sexes per prescription. A linear regression analysis on the first prescription was used to adjust for age and in the RS also for indications.

Results: In total, 1,263 women and 870 men were included from the RS. The mean daily dose of the first prescription was significantly lower in women than in men; 61.1 mg and 65.9 mg respectively. Women received a 4.8 mg (95% CI -7.8, -1.8) lower dose. For both sexes, dosages increased over time and the difference remained statistically significant for the first three prescriptions. In total 23,074 women and 19,562 men were included from the IPCI database. Also in this database, the mean daily starting dose of metoprolol was significantly lower in women than in men; 57.3 mg and 62.0 mg respectively. The dose of the first prescription was 4.6 mg (95% CI -5.3, -4.0) lower in women. Dosages increased over the 10 prescriptions for both women and men and the difference in dose remained statistically significant. The dose of the first prescription was statistically significantly lower in women after adjustment for age in the RS and the IPCI database and after adjustment for indications in the RS.

Conclusions: In real life, women received a lower starting dose of metoprolol than men despite the absence of sex-adjusted dosage recommendations in guidelines. Furthermore, both women and men received lower dosages than recommended. This might mean that prescribers start at a lower dose because they fear that women are more prone to adverse reactions.

2397 | The association between dental opioid prescription characteristics and the risk of long-term use and overdose

Tonya Campbell[1], Diana Martins[2], Mina Tadrous[1,3,4], David Juurlink[1,4,5], J. Michael Paterson[1,4], Muhammad Mamdani[1,4,6], David Mock[4] and Tara Gomes[1,2,4]

[1]ICES, Toronto, ON, Canada; [2]St. Michael's Hospital, Toronto, ON, Canada; [3]Women's College Hospital, Toronto, ON, Canada; [4]University of Toronto, Toronto, ON, Canada; [5]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [6]Unity Health Toronto, Toronto, ON, Canada

Background: Dental pain is a common indication for opioid initiation, with a recent study indicating that 22% of people in Ontario, Canada who initiated opioid therapy between April 2015 and March 2016 were prescribed by a dentist. However, little is known regarding the risks of these medications when prescribed by dentists.

Objectives: To examine the association between initial dental opioid prescription characteristics and the risks of long-term use and harm.

Methods: We conducted a population-based cohort study of Ontario residents initiating opioids prescribed by a dentist between October 2014 and September 2016. The primary exposure was the average daily opioid dose dispensed at initiation, in morphine milligram equivalents (MME). Secondary exposures were the prescription duration (days supplied) and the formulation dispensed on initiation (immediate-release or long-acting). The primary outcome was continued opioid use at one year, and the secondary outcome was opioid toxicity within one year. Logistic regression was used to estimate the association between the initial prescription opioid characteristics and continued use, and opioid toxicity incidents were summarized using descriptive statistics.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Among 384,079 individuals initiating opioids prescribed by dentists, 1,810 (0.5%) remained on therapy for at least one year, and 152 (0.40 per 1,000 person-years) experienced an opioid toxicity incident. Compared to a daily dose of 20MME or below, an initial daily dose greater than 90MME was associated with a 67% increase in the odds of continued use (aOR 1.67; 95% CI 1.08 to 2.60). Relative to a duration of 3 days supplied or less, a duration greater than 14 days was associated with an almost threefold increase in the odds of continued use (aOR 2.87; 95% CI 1.86 to 4.41). In the secondary analysis, opioid toxicity rates increased with increasing daily dose initiated, and almost one-quarter of events (22.4%) occurred within the six weeks after initiation.
Conclusions: While persistent opioid use and toxicity occurred infrequently among dental patients newly receiving opioids, judicious opioid prescribing, including lower daily doses and shorter prescription durations following dental procedures may serve to reduce the risks of long-term use and opioid-related harms.

2423 | Psychotropic medication use in former ICU patients with mental health problems: A prospective observational follow-up study

Debbie G.A. Janssen[1], Joep Jonker[2], Diederik van Dijk[3], Eibert R. Heerdink[2,3,4], Toine C.G. Egberts[2,3] and Arjen J.C. Slooter[3]
[1]*Primary Healthcare Institute, Ministry of Defense, Utrecht, Netherlands;* [2]*Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands;* [3]*University Medical Center Utrecht, Utrecht, Netherlands;* [4]*HU University of Applied Sciences, Utrecht, Netherlands*

Background: An increasing number of patients with critical illness survive an admission to the intensive care unit (ICU) because of advancements in critical care. However, approximately 50-70% of these survivors develop mental health problems sometime after ICU discharge. Little is known on 'whether' and 'how' these patients are being treated.
Objectives: To describe the extent to which patients with mental health problems after admission to an Intensive Care Unit (ICU) initiate and use psychotropic medication.
Methods: All adult patients who stayed in the ICU of the University Medical Center Utrecht for 48 hours or more between 2013 and 2017, alive after 1 year and not admitted to the ICU with brain injury, were eligible. Questionnaires that included the Hospital Anxiety and Depression Scale (HADS), the Impact of Event Scale (IES/IES-R), and psychotropic medication use, were used to identify components of mental health problems, i.e. depression, anxiety and posttraumatic stress disorder (PTSD).
Results: Of the 1328 former ICU patients, 24.3% (n=323) had developed any of the mental health problems mentioned above. Of this group, 29.7% (n=96) used psychotropic medication one year after ICU discharge versus the 10.6% (n=107) of patients without these problems (OR 3.17, 95% CI 2.29-4.38). They were further 3.31 (95% CI 2.03-5.40) times more likely to initiate psychotropic medication (12.1% vs 3.7%) after ICU admission. Similar patterns were observed for individual groups of psychotropics: antidepressants, antipsychotics and benzodiazepines.
Conclusions: Former ICU patients with mental health problems were almost three times more likely to use and initiate psychotropic medication than former ICU patients without these problems, although only one third of the patients were treated with psychotropic medication. Future research should investigated whether mental health problems are properly diagnosed and treated in former ICU patients.

2495 | Older adults with colorectal cancer receive higher opioid dose

Sean P. Fleming, Tham T. Le and Julia F. Slejko
University of Maryland Baltimore, Baltimore, MD

Background: Initiatives to curb inappropriate opioid prescribing are known to have unintended consequences on exempt patient populations. This impact is not well understood among adults with colorectal cancer (CRC), which is prevalent across the lifespan though most common among older adults.
Objectives: To determine factors associated with opioid receipt and dose among adults with CRC by age group.
Methods: We performed a retrospective cohort study derived from a 10% random sample of enrollees within IQVIA™ Adjudicated Health Plan Claims Data from 2006-2015. The index date was the first CRC claim (ICD-9-CM codes 153xx-154xx) among individuals 18-64 years old continuously enrolled 12 months before and after the index. Opioid receipt was defined as any opioid prescription post-index. Baseline covariates were defined in the 12 months pre-index. A multivariable logistic model was used to examine the odds of opioid receipt, adjusting for pre-index opioid receipt, sex, Charlson Comorbidity Index, chronic pain, mental illness, concomitant psychoactive medication use, and CRC-related treatments. Morphine equivalent daily dose (MEDD) was calculated as (Quantity*Strength*Conversion Factor)/ Total Days Supplied. A multivariable generalized linear model with a Gamma distribution and log-link was used to examine MEDD post-index.
Results: Of 8,737 subjects, 51.63% (n=4,511) were 55 to 64 years, 34.53% (3,017) 45 to 54 years, 10.53% (920) 35 to 44 years, and 3.31% (289) ≤35 years. Overall, 34.54% received an opioid pre-CRC with a median (IQR) days supply of 10.0 (30.0) and MEDD of 8.3 (21.5). Post-CRC, 54.90% received an opioid with a median (IQR) days supply of 13.0 (40.0) and MEDD of 15.0 (34.4). Compared to individuals 55 to 64 years, the odds of opioid receipt were greater but not statistically significant among individuals aged ≤35 years (odds ratio (OR) 1.02; 95% Confidence Interval (CI): 0.77-1.35), 35 to 44 years (OR 1.03; 95% CI: 0.87-1.21), and 45 to 54 years (OR 1.07, 95% CI: 0.96-1.19). The average marginal effect (AME) associated with age under 35 years was -5.10 MEDD (95% CI: -10.83- -0.63), 35 to 44 years (-5.81; 95% CI: -9.18- -2.44), and 45 to 54 years (-2.09; 95% CI: -3.97- -0.21).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Opioid receipt did not differ between age groups post-index, yet the oldest age group had a significantly higher MEDD. This is concerning as older adults are more sensitive to medications, thus more likely to experience adverse events such as respiratory depression. Further research on the determinants of opioid dose may specify whether the observed associations are clinically justified or signals of potential age disparities in the treatment of pain in CRC.

2513 | Pain severity and analgesics use in the community-dwelling older population: A drug utilization study from Germany

Thi N.M. Nguyen[1,2], Dana C. Laetsch[1], Li-Ju Chen[1,2], Walter E. Haefeli[3], Andreas D. Meid[3], Hermann Brenner[1] and Ben Schöttker[1,2]

[1]*German Cancer Research Center (DKFZ), Heidelberg, Germany*; [2]*University of Heidelberg, Heidelberg, Germany*; [3]*Heidelberg University Hospital, Heidelberg, Germany*

Background: Chronic pain is common in the older population and a significant public health concern. However, comprehensive studies on analgesics use in this age group from Germany are scarce.

Objectives: This study aims to give a comprehensive overview on the prevalence of overall analgesics use and the prevalence of use of the most common therapeutic groups of analgesics in community-dwelling older adults from Germany.

Methods: A cross-sectional study was carried out using data from a German cohort of 2038 community-dwelling adults aged 63-89 years. Descriptive statistics and logistic regression models were applied to assess the utilization of analgesics by age, sex, pain severity, pain duration and locations.

Results: One out of four (25.0%) study participants was suffering from high intensity or disabling pain (grades II-IV). However, less than one out of four (22.9%) used any analgesic drugs, and about half (50.5%) of those still reported to suffer from high intensity or disabling pain (grades II-IV) despite the intake of analgesics. Among analgesics users, occasional non-steroid anti-inflammatory drugs (NSAIDs) use was the most frequent pain therapy (in 43.6% of user), followed by metamizole (dipyrone) use (16.1%), regular NSAIDs use (12.9%), strong opioids use (12.7%) and weak opioids use (12.0%). In multivariate logistic regression models, higher age, higher pain severity, longer pain duration, abdominal pain and back pain were statistically significantly associated with opioids use. Metamizole use was also statistically significantly associated with higher pain severity but inversely associated with pain duration.

Conclusions: A significant number of older German adults are affected by high intensity and disabling chronic pain despite receiving analgesics. Long-term studies are needed to compare the effectiveness and safety of different treatments for chronic pain in older adults.

3719 | St John's Wort: Utilization during pregnancy and pregnancy outcomes

Wiebke Schaefer, Nadine Wentzell and Ulrike Haug

Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany

Background: Pregnant women may be prone to using complementary and alternative medicine, such as St. John's Wort (St. John's) for the treatment of mild depressive disorders. However, little is known about the utilization of St. John's during pregnancy. In Germany, high-dose preparations of St. John's can be reimbursed by statutory health insurances, enabling to study exposure to St. John's based on German claims data.

Objectives: To characterize pregnancies exposed to high-dose preparations of St. John's and to describe the outcomes of these pregnancies.

Methods: Using the German Pharmacoepidemiological Research Database (GePaRD) with data on ~1.5 million pregnancies between 2006 and 2016, we identified pregnancies with exposure to high-dose St. John's via outpatient dispensations. We characterized these pregnancies regarding the timing of dispensation of St. John's preparations, the use of other antidepressants in the year before or during pregnancy, concomitant use of potentially interacting drugs, as well as the relative frequency of pregnancy outcomes compared to all other pregnancies.

Results: We identified 496 pregnancies with dispensation of a high-dose St. John's preparation in at least one trimester. Of these, 386 (78%) had a dispensation during the first trimester only, and 16 pregnancies (3%) had a dispensation in all trimesters. About one third already had a dispensation of St. John's in the year before pregnancy. In 21% of all pregnancies exposed to St. John's, the mothers had a dispensation of other antidepressants in the year before pregnancy and 12% during pregnancy (9% in the first trimester). Concomitant use of potentially interacting drugs during pregnancy was infrequent, with less than 1% of all pregnancies being exposed to such drugs in one of the trimesters. Compared to the rates previously published for all pregnancies in GePaRD, pregnancies exposed to St. John's less frequently resulted in live birth (89% vs. 94%), while the rates for induced abortions/stillbirths and ectopic pregnancies were about two times higher (7.9% vs. 3.8% and 2.0% vs. 1.4%, respectively). All non-live births except for one stillbirth occurred in pregnancies exposed during the first trimester only.

Conclusions: Our results suggest that St. John's is used as an alternative to other antidepressants in some pregnancies, but is also newly dispensed for treatment during pregnancy. Further investigations are needed to explore potential reasons why the rates for non-live births were higher among pregnancies exposed to St. John's compared to other pregnancies.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3732 | Antidepressant use among adults patients in primary care in Brazil: Results of a national survey

Natalia P.B. Torres, Juliana Alvares Teodoro, Augusto AfonsoGuerra Junior and Francisco A. Acurcio
Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Background: Antidepressant medicines are widely prescribed. In the last years, international population-based studies have identified growth in their use. Considering the limited number of studies on this topic in Brazil, it is important to investigate and describe characteristics of their use, providing information about a middle-income country.
Objectives: To estimate the prevalence of antidepressant use and identify its associated factors among adults in primary care of the Brazilian National Health System (NHS).
Methods: This study is part of the National Survey on Access, Use and Promotion of the Rational Use of Medicines in Brazil - Services, a cross-sectional and evaluative study, consisting of information collection from a representative sample of cities, primary health care services and patients in the five regions of Brazil. Patients were interviewed in primary health care services, with a specific questionnaire. An estimate of 1,800 patients would be interviewed by region of the country. At the end, 8,803 interviews were conducted, from July to December 2014. The outcome considered was use of any antidepressant in the past 30 days. We performed a descriptive analysis of the population and the antidepressants used. The association between antidepressant use and demographic, socioeconomic, clinical and lifestyle-related characteristics was evaluated using logistic regression model.
Results: The prevalence of antidepressant use was 6.8% (95% CI 6.2 - 7.3). Most users who self-reported previous diagnosis of depression (70.6%) and who were extremely depressed/anxious (75.6%) did not report antidepressant use, suggesting underuse. The most commonly drugs used were fluoxetine, amitriptyline and venlafaxine. After all adjustments, the multivariate analysis found that the use of antidepressants is more likely in females, who self-reported depression and anxiety/depressive status, that practices polypharmacy and use psychotropics, have alcohol abstinence, a higher socioeconomic status and being of the white ethnicity/race.
Conclusions: The prevalence of antidepressant use observed in Brazil is lower than in USA and some European countries. The factors associated with its use are consistent with the literature. The findings suggest that there may be inequity in access to drug treatment for depression in the Brazilian NHS. Although patients have a universal right to health in Brazil, the inequities found, especially for non-white individuals and those from lower social classes, show that it is necessary to improve actions to ensure access to treatment of depressive disorders by primary care users.

3748 | Variations in long-term opioid use definitions in observational research: A systematic review of studies using routinely collected data

Juliana de Oliveira Costa, Claudia Bruno, Navya Baranwal and Sallie-Anne Pearson
Centre for Big Data Research in Health, Sydney, Australia

Background: Opioid treatment guidelines do not recommend long-term (LT) use due to the development of tolerance and risk of dependence. However, there is no consensus on the definition of LT opioid use, creating challenges for measurement in real-world settings.
Objectives: To catalogue the definitions and terminology relating to LT opioid use and the rationale for definitions in observational research using routinely collected data.
Methods: We conducted a systematic review of observational studies evaluating LT opioid use from routinely health administrative data sets or electronic health records. We searched MEDLINE and Embase and conducted hand searches for studies published between January 2000 and July 2019. Two independent reviewers screened abstracts for 4,056 articles and 205 full-text manuscripts. We also evaluated study reporting using selected items from the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) checklist.
Results: We included 128 studies; most were from the US (82%), published between 2016 and 2019 (67%), used pharmacy dispensing data (86%) and had nationwide data coverage (46%). Common terminology included "Long-term use" (28%), "Chronic use" (21%), "Chronic therapy" (11%) and "Long-term therapy" (9%). We identified 85 different definitions of LT opioid use, most commonly 90 days of cumulative or continuous use within a year (22%). To derive definitions, studies generally combined one measure of duration, such as supply days/days of use (67%), episode length (22%), fills in 3-months (5%) with additional criterion (40%); continuity between the fills (25%), number of fills (13%), defined daily doses/ morphine milligram equivalents (5%), other (8%). Definitions were mostly based on previous publications (63%), clinical judgment (15%), or empirical data (3%); 10% of studies tested more than one definition. LT opioid use was not clearly defined in 21 studies and 38 studies did not specify the opioids evaluated.
Conclusions: While there is an increasing interest in evaluating LT opioid use due to its clinical and economic burden, there is a large variability in definitions used and poor reporting of the rationale and implementation of the definitions, impacting on research reproducibility.

3819 | Biologic use and persistence for Crohn's disease after intestinal resection in the United States 2002-2018

Joehl T. Nguyen[1], Edward L. Barnes[2], Swetha Srinivasan[1] and Alan C. Kinlaw[1]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC;* [2]*University of North Carolina School of Medicine, Chapel Hill, NC*

Background: Patients with Crohn's Disease (CD) are often treated with surgical resection but postoperative recurrence leading to repeat resection remains common. Biologic therapy is a recommended

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

prophylactic strategy in patients with CD, but data are limited on real-world use and outcomes in the postoperative setting.

Objectives: To describe baseline characteristics and postoperative biologic treatment patterns for patients with CD after intestinal resection.

Methods: Using IBM Watson Health MarketScan data 2002-2018, we identified patients with diagnosis of CD at intestinal resection, and excluded patients with prior resections during a 2-year baseline period. We identified claims for anti-tumor necrosis factor-α, anti-integrin, and anti-interleukin 12/23 agents. We used bivariate analysis to assess whether baseline covariates were associated with biologic use within 6 months after surgery. We used Kaplan-Meier-based cumulative incidence to estimate 6-month risk of treatment discontinuation (with 95% confidence intervals, CI), defined as switching or stopping biologic therapy outside the FDA-labeled treatment frequency (including a 30-day grace period). The last day of the allowable gap period was defined as the discontinuation date among patients who were non-persistent on their postoperative biologic.

Results: Among 5373 patients who had surgery for CD, 1547 (28.8%) patients received a biologic within 6 months after surgery. 50.9% were female and 72.3% had received a partial colectomy or ileocolic resection at baseline. Compared to patients who did not initiate biologics within 6 months after surgery, these patients were younger (mean age 36 vs 41 years), more commonly from the South and West regions, and had similar prevalence of colonoscopy prior to surgery (78.3%). Most patients who used biologics within 6 months after surgery were treated with infliximab (38.5%) and adalimumab (55.3%), while 5.2% of patients were treated with vedolizumab. The 6-month risk of discontinuation for patients treated with infliximab, adalimumab, and vedolizumab was 18.4% (95% CI 15.2%-21.6%), 31.6% (95% CI 28.4%-34.8%), and 19.8% (95% CI 10.8%-28.8%), respectively. 36.3% of non-persistent patients received a colonoscopy after surgery and before discontinuing their initial postoperative treatment.

Conclusions: Patients on postoperative adalimumab were more likely to discontinue their prescribed therapy through 6 months compared to infliximab and vedolizumab. Further analyses should examine postoperative treatment channeling for CD, including combination therapy with non-biologics.

3865 | Are aclidinium and aclidinium/formoterol used according to their approved indication in Europe? Results of a multicountry drug utilization postauthorization safety study

Elena Rivero-Ferrer[1], Anna Julia Witzleb[2], Morten Olesen[3], Estel Plana[1], Jaume Aguado[1], Nuria Saigi-Morgui[1], Annalisa Rubino[4], Sami Z. Daoud[5], Alejhandra Lei[6], Susana Perez-Gutthann[1], Tania Schink[7], Nina S. Kristiansen[3], Anton Pottegård[3] and Cristina Rebordosa[1]

[1]RTI Health Solutions, Barcelona, Spain; [2]Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany; [3]University of Southern Denmark, Odense, Denmark; [4]AstraZeneca, Cambridge, United Kingdom; [5]AstraZeneca, Gaithersburg, MD; [6]AstraZeneca, Barcelona, Spain; [7]Leibniz Institute for Prevention Research and Epidemiology-BIPS, Bremen, Germany

Background: Aclidinium bromide was approved in the European Union for the treatment of chronic obstructive pulmonary disease (COPD) in adult patients in 2012 and aclidinium/formoterol in 2014. A drug utilisation study in three European countries is part of the pharmacovigilance plan.

Objectives: To evaluate the potential indication of aclidinium, and aclidinium/formoterol, and characteristics of new users of study medications in Denmark, Germany, and the United Kingdom (UK).

Methods: Cohorts in the Danish National Health Databases (2015-2017), the German Pharmacoepidemiological Research Database (2015), and the UK Clinical Practice Research Datalink (CPRD GOLD, 2015-2017) included new users treated with long-acting muscarinic antagonists (LAMA) (aclidinium, aclidinium/formoterol, tiotropium, other LAMA), long-acting beta2-agonists (LABA), or LABA/inhaled corticosteroids (LABA/ICS). On-label was defined as use in adults with a diagnosis of COPD with or without asthma. Off-label use was defined as use in patients aged < 18 years or use in patients with a recorded diagnosis of asthma without a COPD diagnosis. Absence of a recorded diagnosis of COPD and asthma was classified as unknown indication.

Results: There were 4,871 users of aclidinium and 2,153 users of aclidinium/formoterol in the UK, 2,836 users of aclidinium and 2,586 of aclidinium/formoterol in Denmark, and 9,961 users of aclidinium and 10,069 users of aclidinium/formoterol in Germany. Among users of aclidinium, a COPD diagnosis was present in 89% of users in the UK, 87.4% in Germany, and 56.0% in Denmark. For aclidinium/formoterol, this percentage was 90.5% in the UK, 92.8% in Germany, and 57.7% in Denmark. There was no or minimal paediatric use. Among users of aclidinium, diagnosis of asthma with no COPD diagnosis occurred in 5.0% in the UK, 5.4% in Germany, and 8.8% in Denmark. For aclidinium/formoterol, it occurred in 3.2% in the UK, 2.6% in Germany, and 3.0% in Denmark. The indication was unknown in 6% of users of aclidinium in the UK, 7.2% in Germany, and 35.0% in Denmark. For aclidinium/formoterol, this percentage was 6.3% in the UK, 4.6% in Germany, and 39.2% in Denmark.

Conclusions: Aclidinium and aclidinium/formoterol are prescribed mainly according to the approved indication. Based on recorded diagnoses, it cannot be ruled out that a patient may have had childhood asthma that later resolved or evolved to asthma-COPD syndrome in adulthood. Paediatric use was anecdotal. The high proportion of 'unknown indication' in Denmark is driven by the lack of primary care diagnoses.

3879 | Trends in first opioid prescribing in more than 600000 opioid-naïve and cancer free patients in Sweden - Drugs, doses, and diagnoses

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Carola Bardage, Maria Grünewald, Paulina Tuvendal and Rickard Ljung
Swedish Medical Products Agency, Uppsala, Sweden

Background: Opioids play an important role in health care as analgesics; during and after surgical procedures, in severe acute pain and cancer pain. Treatment with opioids can pose a risk of addiction. In the United States, opioid dependence in an increasing proportion of the population is one of the biggest public health problems. Therefore, there is reason to follow the prescription of opioids over time in Sweden This is to pay attention to the medical care of these drugs and urge caution and proper use in accordance with product information, treatment recommendations and guidelines.
Objectives: The objective was to describe the prescribing of opioids, indications for treatment, who prescribed, what is prescribed, and any risk factors for future overconsumption and dependence.
Methods: This cohort study used individual data of unique users of opioids linked from several national-coverage health data registers to evaluate time trends to assess first time prescription of opioids by drug type, doses, and diagnoses, in adults aged 18-64 years in Sweden. All patients with a first prescription of an opioid in 2012 to 2015 were studied and the date of the first prescription was defined as their index date. Patients with any prescription of an opioid within 6.5 years prior to index date were excluded. Any patient with a record of a cancer, except non-melanoma skin cancer, prior to or 3 months after index date was excluded.
Results: A total of 617,568 patients aged 18-64, 50 % men, were prescribed opioids for the first time. One third of the prescriptions were from specialized out-patient care (33 %) and primary care (28,3 %), respectively. Dental care accounted for 9 % of all first prescriptions. The fixed combination of codeine and acetaminophen was the most commonly prescribed opioid with 322 818 patients (52 %), followed by tramadol (120 271, 19 %) and oxycodone (104 418, 17 %). From 2012 to 2015 tramadol as first prescribed opioid dropped from 26 % to 14 % and oxycodone increased from 10 % to 24 %. Fracture of the lower leg was the most common indication in in-patient care and dorsalgia in specialized out-patient care for the first prescription of an opioid. The prescribed amount of opioid, with respect to the analgesic effect (when comparing morphine equivalents) was equivalent regardless of the opioid prescribed.
Conclusions: Exploring trends in opioid prescriptions to opioid naïve cancer free patients in Sweden from 2012 to 2015 does not show an increase in opioid use. There has been a shift from tramadol to oxycodone, but codeine in fixed combination with acetaminophen is by far the most commonly prescribed opioid.

4001 | Prevalence of chronic drug use in pediatrics: Comprehensive overview based on German claims data

Oliver Scholle[1], Antje Neubert[2], Oliver Riedel[1], Irmgard Toni[2] and Ulrike Haug[1,3]

[1]*Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany;* [2]*Universitätsklinikum Erlangen, Erlangen, Germany;* [3]*University of Bremen, Bremen, Germany*

Background: The frequency and type of drug prescriptions in children and adolescents require careful monitoring given the uncertainties and risks associated with pediatric drug use. Existing studies in this field using large health care databases, however, focused on any drug use (i.e., at least one prescription of a certain drug) while recurrent drug use may even be more relevant for monitoring.
Objectives: To provide a comprehensive overview of frequencies and types of recurrent drug prescriptions in children and adolescents in Germany in 2016.
Methods: We used the German Pharmacoepidemiological Research Database (GePaRD)—a claims database covering ~17% of the German population. We identified children and adolescents aged 0-17 years with continuous insurance coverage in 2016 and assessed the prevalence of recurrent prescriptions (≥3 prescriptions of the same drug/therapeutic subgroup in 2016) based on ATC codes. We stratified the analyses by age and sex.
Results: Among 1.5 million children and adolescents included overall, the prevalence of recurrent drug prescriptions was 102 per 1,000 in girls and 87 per 1,000 in boys. For comparison, the prevalence of any drug prescriptions was more than five times higher. Among girls, the prevalence of recurrent drug prescriptions ranged between 43 (<2 years) and 207 per 1,000 (13-17 years). In 2-12-year-old girls, systemic antibiotics (ATC subgroup J01) had the highest prevalence of recurrent use (2-5 years: 66 per 1,000; 6-12 years: 31 per 1,000). In girls aged 13-17 years, sex hormones (ATC subgroup G03) had the highest prevalence of recurrent use (146 per 1,000). Furthermore, unlike other age and sex groups, this subgroup showed a prevalence above 10 per 1,000 for levothyroxine. Among boys, the prevalence of recurrent drug prescriptions ranged between 61 (<2 years) and 98 per 1,000 (13-17 years). In 2-5-year-old boys, systemic antibiotics had the highest prevalence of recurrent use (73 per 1,000). In older boys (6-17 years), psychoanaleptics (ATC subgroup N06) showed a higher prevalence than antibiotics. Methylphenidate was the most frequently prescribed recurrent drug among boys aged six years and older (6-12 years: 23 per 1,000; 13-17 years: 26 per 1,000).
Conclusions: This description of recurrent drug prescriptions provides important insights on chronic drug exposure in children and adolescents and highlights marked differences between age and sex groups. The high prevalence of three or more antibiotic prescriptions in preschoolers and of levothyroxine in girls aged 13-17 years are striking and require further consideration.

4008 | Feasibility of studying the use of tissue-agnostic cancer drugs in population-based European health databases

Xabier Garcia de Albeniz[1], Nuria Riera Guardia[1], Lia Gutierrez[1], Shahram Bahmanyar[2], Patrick Blin[3], Cécile Droz[3], Miriam Heinig[4],

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Marie Linder[2], Nicholas Moore[3], Renate Schulze-Rath[5], Janet Sultana[6], Gianluca Trifirò[6], Wei Wei Zhang[7] and Jihong Zong[7]
[1]RTI-Health Solutions, Barcelona, Spain; [2]Centrum för Läkemedelsepidemiologi, Karolinska Institutet, Stockholm, Sweden; [3]University of Bordeaux, Bordeaux, France; [4]Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Bremen, Germany; [5]Bayer AG, Berlin, Germany; [6]Università degli Studi di Messina, UNIME, Messina, Italy; [7]Bayer US LLC, Whippany, NJ

Background: Tissue-agnostic cancer drugs, indicated based on tumour biology rather than its anatomic origin, represent a state of the art in cancer therapeutics. Larotrectinib is an oral inhibitor of three kinases (TRKA, TRKB, TRKC) active in several tumours. Larotrectinib is approved by the US FDA and by the EMA as monotherapy in patients with solid tumours that have an *NTRK* gene fusion without an acquired resistant mutation, that are metastatic, or where surgical resection is likely to result in severe morbidity, or that have no satisfactory alternative treatment options or that have progressed following treatment.

Objectives: To assess the feasibility of conducting a drug utilisation study of larotrectinib using various European data sources.

Methods: We developed a feasibility assessment form with questions targeted to assess the data availability on expected use of larotrectinib and other cancer drugs, tumour diagnosis and its status when a drug is started, and biomarker testing, specifically *NTRK* fusion and tests results. Researchers from seven European databases contributed; we present the results from six: German Pharmacoepidemiological Research Database (GePaRD), Swedish National Health Registers (SNHR), Norwegian Health Databases and Registers (NHDR), System National de Données de Santé (SNDS), Italian Health Databases of Caserta/Palermo (IHD), and Public Health England (PHE).

Results: All databases allow a characterization of demographics, comorbidities, and health care utilization, as well as oral cancer drugs dispensed by ambulatory pharmacies. Full information on oral cancer drugs dispensed by a hospital pharmacy (likely for larotrectinib) is available in all except SNDS and GePaRD. For SNDS only, data of new expensive cancer drugs are available, while in GePaRD, the information available is the administration of a drug in a hospital. No database contains information on specific genetic tests or their results, except for PHE. PHE has information on the most common tests run for somatic genetic alterations, as well as a field ("other") for less common tests. Except for IHD, all databases are linkable to cancer registries, although due to data protection laws involving a burdensome effort, linkage in GePaRD may not be feasible.

Conclusions: Only PHE contains all elements to evaluate the use of larotrectinib in routine practice. Nevertheless, PHE recency, a lag time up to 5 years for 100% completeness, and the lack of published research on cancer with genetic alterations should be considered. The custodians of the rest of the databases are not aware of plans to add tumour genetic information.

4034 | The one percent: Screening Danish nationwide drug utilisation data for patterns of misuse

Lars Christian Lund, Mette Reilev, Anton Pottegård and Jesper Hallas
University of Southern Denmark, Odense, Denmark

Background: Measures of inequality, e.g. the Gini coefficient and income shares, are frequently used when analysing economic data but have rarely been applied to drug utilisation. Large inequalities in drug utilisation have previously been shown to be a marker of drug misuse. Using these measures in large-scale health databases may thus identify drugs with an unsuspected misuse potential.

Objectives: To describe and screen the Danish population's drug use for inequal drug use patterns.

Methods: Data from the Danish national prescription registry filled by patients aged 40+ during 2018 were analysed. Drugs administered intravenously or without a defined daily dose were excluded. As measures of inequality, we calculated the Gini coefficient, the fraction of all drug use consumed by the 1% most intensive users (1-percentile ratio) and the mean DDD used per day. The Gini coefficient measures statistical dispersion, with a coefficient of 1 representing total inequality while 0 represents total equality. Signals were sorted in descending order according to Gini coefficient and 1-percentile ratio.

Results: 43,890,792 prescriptions filled by 2,474,195 individuals were analysed. The three drugs with the highest Gini coefficient were methylprednisolone (0.88), docusate sodium for rectal administration (0.81) and oxycodone (0.80). The highest 1-percentile ratio was found for methylprednisolone (0.39), cyclizine (0.23) and loperamide (0.22). The median daily DDD consumed in the highest percentile was 3.2 for methylprednisolone, 2.8 for oxycodoone, 1.2 for cyclizine and 1.1 for loperamide.

Conclusions: The uneven distribution of methylprednisolone use was expected and is justified by the drug's clinical application in emergency immunosuppression.

The signals for loperamide and cyclizine were unexpected and warrant further investigation. When taken in supratherapeutic doses, loperamide acts as an opioid agonist. Misuse of loperamide is an emerging problem in the nordic countries but has hitherto been assumed to be restricted to over the counter sale of the drug. Cyclizine has a sedating effect and is hallucinatory when taken in large doses. It is likewise sold over the counter, suggesting that the true magnitude of misuse might be even larger.

4079 | Patterns and trends of idarucizumab use in an Italian region: A probabilistic record-linkage approach in a real-life setting

Niccolò Lombardi[1], Valentina Brilli[1], Giada Crescioli[1], Alessandra Bettiol[1], Ippazio Cosimo Antonazzo[2], Giampiero Mazzaglia[2], Stefano Fumagalli[1], Guido Mannaioni[1], Alfredo Vannacci[1] and Rosa Gini[3]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]University of Florence, Florence, Italy; [2]University of Milano-Bicocca, Monza, Italy; [3]Regional Agency for Healthcare Services of Tuscany, Florence, Italy

Background: Idarucizumab is a specific reversal agent for dabigatran, a direct oral anticoagulant. In 2015, idarucizumab was approved in Europe to quickly restore coagulation and it is currently subject to additional safety monitoring. The drug is administered only during inpatient or emergency care: in such settings, its use is poorly captured by most real-world databases.

Objectives: To retrieve individual level information on idarucizumab use from an Italian record-linkage claims database in order to describe main characteristics of users.

Methods: Italy has a regional-based, universal coverage healthcare system. Healthcare delivered to each inhabitant of Tuscany, an Italian region, is registered in a record-linkage claims database (RLCD). This information can be traced at individual level using an encrypted identification code, except in the case of medicines administered in Inpatients or Emergency Care (IEC), where only date and ward of administration are recorded. All person-years (PYs) exposed to dabigatran from January 2015 to December 2018 were calculated from RLCD, using defined daily doses (DDDs) to estimate duration of each recorded dispensation. Idarucizumab use during the study period was identified from IEC, and incidence rate was calculated over PYs of dabigatran use. To identify subjects treated with idarucizumab, emergency admissions and hospital discharge records were probabilistically linked to dabigatran users, matching date and ward of admission as retrieved from RLCD. A further selection was made by a manual check of the diagnoses compatible with the indications of use of idarucizumab. Linked users were described in terms of indication and followed-up for 30 days to assess mortality.

Results: During the study period, 26,821 PYs of dabigatran use were observed, and 112 administrations of idarucizumab were recorded, corresponding to 4.2 (95% CI: 3,4-5,0) per 1,000 PYs. Overall, 103 idarucizumab administrations (92.0%) were linked to at least one patient, while 50 (44.6%) were uniquely linked to 47 patients. Most of them were men (55.3%), aged ≥80 years (68.1%). Indications were emergency surgical procedures and life-threatening bleeding in 17 (36.1%) and in 30 subjects (63.9%), respectively. Overall, 30-days mortality was 17.0% (N=8).

Conclusions: This analysis demonstrates the potential of the Tuscany database in retrieving patient-level information on idarucizumab use and sets the stage for post-marketing surveillance on its safety profile in a real-life setting.

4096 | Dispensing practices of antibiotics by community pharmacies in two districts of Nepal

Nisha Jha[1], Sunil Shrestha[2] and Pathiyil Ravi Shankar[3]

[1]KIST Medical College, Kathmandu, Nepal; [2]Nepal Cancer Hospital and Research Center, Kathmandu, Nepal; [3]Oceania University of Medicine, Apia, Samoa, Samoa, Samoa

Background: Use of antibiotics as an over the counter medicine is very common in Nepal. In a developing country like Nepal, the implementation of the existing antibiotic use guidelines is very difficult. Various factors contribute to irrational use of antibiotics including self-medication, irrational prescribing and dispensing.

Objectives: To evaluate the antibiotic dispensing practices of community pharmacies and the association, if any, between the educational qualification, experience, professional license and the location of the pharmacy with the antibiotic dispensing practices.

Methods: Design: A cross sectional prospective study

Setting: Community pharmacies of two districts of Nepal. Inclusion criteria: Community Pharmacies registered at Department of Drug Administration of Nepal and willing to participate in the study. Exclusion criteria: Community pharmacies not willing to participate in the Study. Study site and duration: Study was conducted in Kathmandu and Lalitpur districts from October 2018 to November 2018 among the community pharmacies listed in different directories. The sample size was 78 with a 5% margin of error, 95% confidence level, and 50% response distribution and random sampling method was used. Data was collected using a questionnaire. Written informed consent was obtained. The data was analyzed using SPSS for Windows.

Results: Out of 78 pharmacies, 12 (15.4%) were unregistered and 54 (69.2%) were located in Kathmandu district. Antibiotics dispensed without a prescription were 67 (85.9%). Fifty-two (66.7%) pharmacists did not ask for prescription before dispensing antibiotics. The practice of brand substitution was seen in 43 cases (55.1%). Antibiotics per prescription was three in 51 cases (65.4), followed by two antibiotics in 27 (34.6%) and this was significant in the pharmacies near hospital and periphery. Advice regarding completing the course of antibiotics were given by 59 (75.6%) pharmacies and insufficient number of antibiotics dispensed were 23 (29.5%). Nine pharmacists (11.5%) replaced prescribed antibiotics with cheaper brands. Azithromycin 69 (88.5%) was the most commonly dispensed antibiotic followed by amoxycillin 68 (87.2%).

Conclusions: Dispensing antibiotics without a prescription is seen in majority of pharmacies which can be a big threat towards using antibiotics rationally. The findings of this study may necessitate re-evaluation of the guidelines framed for improving safe and rational use of antibiotics.

4151 | Statin use and melanoma recurrence

Chrystelle Kiang[1], Anne Fia Grann[2,3], Uffe Heide-Jørgensen[2], Thomas P. Ahern[4], Timothy L. Lash[1,2], Henrik Toft Sørensen[2] and Deirdre P. Cronin-Fenton[2]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Emory University, Atlanta, GA; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Department of Clinical Oncology, Aarhus, Denmark; [4]University of Vermont, Burlington, VT

Background: The use of statins to lower risk of cardiovascular disease is well established, but there is evidence that statins have positive pleiotropic effects including the reduction of cancer recurrence. In addition to inhibiting the synthesis of cholesterol, statins can prevent the synthesis of isoprenoids and reduce cancer cell proliferation. Lipophilic statins are more readily available in extrahepatic tissue than hydrophilic statins, so the pleiotropic effects could differ by type of statin.

Objectives: To investigate whether an association exists between post-diagnostic statin use and melanoma recurrence among melanoma patients, and whether it differs by type of statin.

Methods: We conducted a prospective cohort study of residents in Denmark diagnosed with localized or regional melanoma between 1997 and 2009 using the Danish Cancer Registry. Prescription data for lipophilic and hydrophilic statins was obtained from the Danish National Prescription Registry. Melanoma recurrence, defined as tumor growth in the same organ, near the site of the original tumor, or metastases to a distant organ, was obtained from the Danish National Pathology Registry. We followed patients from 90 days after melanoma diagnosis until December 31 2011. We modeled statin exposure as a time-varying exposure updated daily and lagged by one year. We used Cox regression to estimate the association between any statin use and melanoma recurrence, adjusting for cancer stage, sex, age, and potentially confounding co-medications: aspirin, NSAIDs, vitamin K coagulants, steroids, diuretics, ACE-inhibitors, and beta-blockers. We considered statins overall, and separately according to lipophilic versus hydrophilic statins.

Results: Of 12,906 melanoma patients, 2,241 (17%) were statin users. Users of any statin experienced fewer recurrences than non-users, with a 5-year adjusted hazard ratio (aHR) of 0.80 (95% confidence interval 0.65, 0.98). Most prescriptions were for lipophilic statins (80%) and the aHR associating melanoma recurrence and lipophilic statin use was 0.78 (95% CI 0.63, 0.98). The aHR associating melanoma recurrence and hydrophilic statin use was 0.82 (95% CI 0.53, 1.26).

Conclusions: In this cohort of Danish melanoma patients, use of any statin was associated with a reduced risk of melanoma recurrence.

4188 | Polypharmacy at the time of opioid overdose in older adults on long-term opioid therapy

Nazleen F. Khan, Katsiaryna Bykov and Joshua J. Gagne
Brigham and Women's Hospital, Boston, MA

Background: The opioid epidemic is a pressing public health concern that affects patients of all ages, including older adults. In 2017, opioid overdose was responsible for nearly 9,000 deaths among individuals aged 55 and older in the US. Polypharmacy is also common in older adults who take opioids and may further contribute to overdose events. However, little is known about the prevalence of polypharmacy at the time of overdose in older adults who use opioids long-term.

Objectives: To identify patterns of concurrent opioid and non-opioid medication utilization at the time of overdose among long-term opioid users ≥ 65 years of age.

Methods: We used data from 2014 through 2017 from a large US commercial insurance database to conduct a descriptive study of opioid and non-opioid prescription use among older long-term opioid users who experienced an overdose. The source population consisted of patients with at least 180 days of continuous enrollment and 90 days of continuous opioid use prior to their first overdose at age 65 or older in the database between January 1, 2015 and December 31, 2017. Comorbidities were assessed in the 180 days prior to and including the overdose date. Opioid overdose was defined as an event resulting in an emergency room visit or hospitalization based on International Classification of Diseases codes. We assessed the number of active non-opioid prescriptions on the overdose date and most common non-opioids and opioids active on the overdose date. Active medications were defined as prescriptions with a dispensing date and days' supply that overlapped with the overdose date.

Results: We identified 499 older adults on long-term opioid therapy who experienced an overdose between 2015 and 2017. Mean age at the time of overdose was 73.4 years, 66.3% were female, and 94.4% had a diagnosis for a chronic pain condition (osteoarthritis, rheumatoid arthritis, postherpetic neuralgia, diabetic neuropathy, fibromyalgia, back or neck pain, other arthritis, and/or other neuropathy). On the overdose date, 80.4% of patients had active prescriptions for four or more non-opioid medications, and 98.8% had active dispensings for one or more non-opioids. Gabapentin (29.7%), levothyroxine (20.6%), and furosemide (19.2%) were the most common active non-opioids on the overdose date.

Conclusions: Polypharmacy is common on the overdose date among older adults on long-term opioid therapy and frequently involves drugs that could interact with opioids to increase overdose risk. Interventions may focus on dispensing opioid antagonists or deprescribing other medications to reduce the potential for drug-drug interactions.

4194 | Effects on seizure activity of co-prescribing anti-epileptic drugs and antidepressant medications among African Americans with epilepsy

Courtney L. Schlusser[1], Regine Haardoerfer[2] and Nancy J. Thompson[2]
[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Emory University, Atlanta, GA

Background: People with epilepsy (PWE) often experience comorbid depression, a known risk factor for seizure activity. To treat comorbid epilepsy and depression, PWE are co-prescribed anti-epileptic drugs (AEDs) and antidepressants. The risk of seizure activity may decrease

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

when depression is reduced through antidepressant medication utilization.

Objectives: To determine the effect of concomitant use of AEDs and antidepressants on seizure activity among African Americans with epilepsy in a southeast hospital system.

Methods: Data were obtained from medical records of African American adults with an epilepsy diagnosis who sought services at an inner-city hospital in the southeast. We identified 126 patients who had a seizure event between 2010-2015, were prescribed an AED, and visited the hospital system every 90 days. Medical visits every 90 days served as a proxy for medication refill data. A case-crossover study design was used to assess effects of co-prescribing antidepressants with AEDs on seizure activity. In this design, cases served as their own controls using 2:1 matching. Analyses involved generalized estimating equations (GEE) to account for repeated measures with differing time periods of antidepressant medication use: 3 months and 6 weeks. We estimated the odds of seizure activity after adjusting for gender, age, and marital status.

Results: Overall, nearly half of the patients were male (48%), and the majority were single (62%) with a mean age of 48 years (SD=16.5). In this sample, there is a low proportion of patients who were prescribed antidepressants (5%). The results of the GEE model suggest that the odds of having a seizure are nearly half for patients who have been co-prescribed an antidepressant with an AED for 6 weeks (OR=0.44; 95%CI: 0.42, 0.45) after adjusting for age, gender, and marital status. The odds of seizure activity further decrease for those who have been co-prescribed the medications for 3 months (OR=0.39; 95%CI: 0.38, 0.40).

Conclusions: Antidepressants, when co-prescribed with AEDs, may have a protective effect on seizure activity. This result suggests that treating depression among PWE decreases seizure activity. However, this result may be a result of selection bias conditioning on hospital system visits every 90 days, assuming that prescriptions are being filled regularly. Additionally, this study had access to medical visits of one hospital system, and is missing data on all other medical visits outside of the system. These results present opportunities for future research and interventions to reduce seizure frequency.

4198 | Cutaneous adverse drug reactions to antiretroviral therapy among HIV-infected patients in a Nigerian teaching hospital

Abdulwasiu A. Busari[1], Kazeem A. Oshikoya[2], Divine-Favour C. Imoh[1] and Ibrahim A. Oreagba[1]

[1]*College of Medicine, University of Lagos, Lagos, Nigeria;* [2]*Lagos State University College of Medicine, Ikeja, Lagos, Nigeria*

Background: Cutaneous adverse drug reactions (CADRs) are common in HIV infected patients than the general population. Antiretroviral therapy (ART) induced CADR are associated with increasing morbidity and mortality. Despite the benefit of ART, they are limited by CADRs, especially at initiation of therapy.

Objectives: The study aimed to determine the prevalence, pattern of and factors predicting CADRs among HIV-infected patients receiving ART at the Lagos University Teaching Hospital (LUTH) in Nigeria.

Methods: A total of 450 HIV-infected patients on ARTs and attending APIN (AIDS Preventions Initiative in Nigeria) clinic at LUTH were studied over 3 months. Data were captured with a self-designed pro forma. Demographics clinical details, prescribed ART, as well as pattern and severity of CADRs experienced by the patients were extracted. Data were analyzed using SPSS version 20.0. The demographic, Univariate analysis of the variables were compared for patients with and without CADRs. Covariates predicting CADR were determined using multiple logistic regression. Any p value <0.05 was considered to be statistically significantly.

Results: Of the 450 patients evaluated, (121: 26.9%) were male. The median (interquartile range) age was 40 (36-48.65) years. CADRs was reported in (22;5.4%) patients, which were mild (32%), moderate (52%), and severe (8%). The pattern of CADR reported include maculopapular rash (55.3%) urticarial rash (19.6%), fixed drug eruption (7.1%), and angioedema (3.5%). Steven Johnsons syndrome (SJS) (7.1%) and Toxic Epidermal Necrolysis (TEN) (3.5%) were the severe forms of CADRs reported. Suspected drugs for the CADRs are nevirapine (80.4%) zidovudine (7.1%), cotrimoxazole (1.8%), and isoniazid (1.8%). Female gender (OR=0.1, CI =0.03-0.72, p= 0.017) and use of nevirapine (OR=10.2, CI = 4.1-25.5, p=0.001) were the independent risk factors for CADRs.

Conclusions: Use of nevirapine was associated with CADR, necessitating a shift from nevirapine based to dolutegravir based ART. A higher risk of CADRs in female patients would require monitoring of ART use in this gender.

4240 | (In) appropriate LAMA prescribing in asthma patients: A cohort analysis (the Alpaca study)

Christina Hoeve[1], Esme Baan[1], Maria de Ridder[1], Leis Demoen[2], Lies Lahousse[1,3], Guy Brusselle[1,2] and Katia Verhamme[1,2]

[1]*Erasmus University Medical Center, Rotterdam, Netherlands;* [2]*Ghent University Hospital, Ghent, Belgium;* [3]*Ghent University, Ghent, Belgium*

Background: Although long-acting muscarinic antagonists (LAMA) are only indicated as add-on therapy in asthmatic patients, there are concerns of monotherapy use.

Objectives: To study the prevalence of LAMA monotherapy and its potential association with severe asthma exacerbations (SAE) in patients with asthma.

Methods: A cohort study (2007-2017) in the IPCI primary care database, in asthma patients aged 6-50, using LAMA during follow-up. Respiratory prescriptions were retrieved from the electronic medical records based on ATC code. Asthma treatment periods were categorized as LAMA mono, double (LAMA+ICS), or triple therapy (LAMA

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

+ICS+LABA). Patients characteristics (age, sex, history of exacerbations, and comorbidities) were collected at the start of each treatment period. A Poisson regression analysis was performed to calculate the relative rate (RR) of SAE, adjusting for patient characteristics.

Results: From a total of 66,508 asthma patients, 1,238 (1.9%) LAMA users were identified, with a median age of 41 years and 65.9% females. From a total of 3,596 LAMA treatment periods, 1,390 (38.7%) were considered LAMA mono therapy, 553 (15.4%) double therapy and 1,653 (46.0%) triple therapy. In all patients using LAMA, the RR of SAE during monotherapy compared to double therapy was 1.6 (p=0.42). When excluding patients who ever used triple therapy the RR increased to 5.7 (p=0.02).

Conclusions: This observational study shows that LAMA is frequently prescribed as monotherapy (i.e. without concurrent ICS) which is associated with an increased risk of exacerbations. This emphasizes the need to check for ICS use when prescribing LAMA to asthmatic patients.

4265 | Identification of clinical cases to educate pharmacists on medication-related problems leading to hospital readmissions after discharge

Selma En-nasery - de Heer[1,2], Elien B. Uitvlugt[3], Patricia M.L.A. van den Bemt[4], Bart J.F. van den Bemt[5,6], Pierre M. Bet[1,2], Eleonora L. Swart[1], Fatma Karapinar[7] and Jacqueline G. Hugtenburg[1,2]

[1]Amsterdam UMC, VU University Medical Center, Amsterdam, Netherlands; [2]VU University Medical Center, Amsterdam, Netherlands; [3]OLVG Hospital, Amsterdam, Netherlands; [4]University Medical Center Groningen, Groningen, Netherlands; [5]Sint Maartenskliniek, Nijmegen, Netherlands; [6]Radboudumc, Nijmegen, Netherlands; [7]OLVG, Amsterdam, Netherlands

Background: Despite the introduction of various measurements aimed at facilitating correct prescribing, the number of medication-related admissions in the Netherlands is not declining. Therefore, it is important to identify medication-related readmissions and educate pharmacists on medication-related problems (MRPs) that may occur after hospital discharge. Cases regarding preventable hospital readmissions could give insight to pharmacists to identify MRPs around hospital discharge.

Objectives: To select cases of preventable medication related readmissions due to transitions in care, that can be used to train pharmacists to possibly prevent MRPs, improve the information transfer between healthcare providers and to adequately inform patients on their medication and its correct use.

Methods: Data of 117 medication-related readmissions were collected and discussed by the research team. 16 potentially preventable re-admissions were selected and assessed in a two round Delphi procedure with nine experts. In the first round the preventability of the medication-related readmissions and their suitability for educational purposes were assessed. Experts also provided written comments on their decision. Consensus was defined as more than 75% agreement between the experts. In the second round, experts gave their opinion on cases for which consensus had not yet been achieved.

Results: After the first round, eight cases were considered suitable as educational material. Four cases were resubmitted. After the second round, two additional cases were also considered suitable after changes. The ten selected cases represent a number of MRPs, such as a prescription error, an error upon discharge and the error of incorrectly continued use after discharge.

Case presentation example: *An 89-year-old woman with a history of insulin dependent diabetes mellitus type II was initially admitted with hypoglycemia. During the hospital stay the patient's insulin dosage was lowered and she was discharged. Within three weeks the patient was readmitted with low consciousness and transpiration. The patient was diagnosed with severe hypoglycemia, caused by administering too much insulin. It appeared that the medication change during the patient's initial hospital admission was not clear. Therefore, the patient continued her old insulin dosage after initial discharge*.

Conclusions: Ten cases were selected by the Delphi panel and can be used as material to train pharmacists and other healthcare professionals to timely identify MRPs that occur after hospital discharge.

4281 | Impact of medication adherence on mortality and cardiovascular morbidity after acute coronary syndrome: Population-based cohort study

Gerard Sotorra-Figuerola[1,2], Dan Ouchi Vernet[1,2], Rosa Morros[1,2,3] and Maria Giner-Soriano[1,2,3]

[1]Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain; [2]Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain; [3]Institut Català de la Salut, Barcelona, Spain

Background: Long-term administration of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) as a secondary prevention improve survival after an acute coronary syndrome (ACS). The adherence to these four pharmacological groups (study drugs) is crucial after ACS.

Objectives: To assess the relationship between the adherences to the four study drugs for secondary prevention and cardiovascular morbidity and all-cause mortality in patients after a first episode of ACS in both sexes.

Methods: Population-based cohort study of adults admitted to hospital with a first episode of ACS during 2009-2016. The data source was SIDIAP (Information System for research in Primary Care [PC]) database, containing anonymized information from electronic health records in PC (Catalonia, Spain). The composite endpoint included: ACS, ischaemic stroke and all-cause mortality. Proportion days covered (PDC) was used to estimate the medication adherence, classifying the patient into adherents (≥85%) and nonadherents (<85%). Time to composite endpoint was analysed by means of nonparametric Kaplan-Meier curves and log-rank test for group comparison.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: 7,152 patients met the inclusion criteria having more than 60 days of follow-up and at least one study drug prescribed. 70.3% were men and the mean age was 70.7 years-old (men: 68.3; women: 76.4). During follow-up (median 2.5 years), 1,139 (22.6%) patients suffered a second ACS, 136 (2.7%) an ischemic stroke and 409 (8.1%) died. For all study drugs, adherent patients had a significant lower probability to have a subsequent cardiovascular event or death than nonadherent patients. Although the observed benefits of being adherent were higher in antiplatelets and statins. In ACEI/ARB and beta-blockers the differences were subtle and disappeared at the end of follow-up. Analysis of adherence to any study drug per sex showed that both men and women had a significant lower probability to suffer a second event or death than nonadherent, although the effect was higher in women.

Conclusions: Adherence to study drugs after a first ACS was associated to lower probability of suffering a new cardiovascular event or death. This effect was higher for antiplatelets and statins. The differences between sexes were slight, although nonadherent women had more probability to suffer a second event or death than men, particularly, at the end of follow-up, probably because women were older.

4293 | Evidence based practice in supplying of over the counter medicines in community pharmacies: A mixed methods study

Nada Alobaid[1], Hind Aboheimed[2], Areej Alhumsi[2], Ghada Aboheimed[2], Nouf Aloudah[2] and Noura Aboheimed[2]

[1]Saudi Food and Drug Authority, Riyadh, Saudi Arabia; [2]Kind Saud University, Riyadh, Saudi Arabia

Background: Despite current studies that showed community pharmacists had a positive attitude toward evidence based medicine (EBM) supply of OTC medicines, there is a lack in EBM practice in community pharmacies.

Objectives: To assess and explore EBM in supplying OTC medicines for three minor ailments: diarrhea, cough, common cold by community pharmacists in Saudi Arabia.

Methods: The study used a mixed methods approach consisted of two parts. The quantitative study which used a mystery shopper approach for 214 randomly selected pharmacies from Riyadh region using 14 questions-Quest Scholar MAC checklist to examine community pharmacists' application of EBM. Secondly, the qualitative study, which encompassed three focus groups with 13 pharmacists from different community practice settings to explore factors affecting EBM practice in supplying OTC medicines from the pharmacist's point of view using theoretical underpinning, designed topic guide.

Results: The analysis showed that only 40% of pharmacists supplied OTC medicines according to EBM. Additionally, logistic regression analysis showed that only two questions asked predicted the correct supply of OTC medicines (Q1:describe your symptoms, Q2:when did the symptoms start?). The two questions has significant p values: 0.022 and 0.023 respectively. The focus groups analysis has identified a range of 29 factors, some were facilitators such as established patient-pharmacist relationship, some were barriers such as conflicts between available evidence, and some were acting as both facilitator and barrier such as patient' awareness and education.

Conclusions: Given the fact that OTC supply is a core function for pharmacists, this study showed a low OTC supply according to EBM. Furthermore, this study identifies several factors explaining this phenomenon. Targeting factors identified in this study might help change this behavior and decrease unwanted events.

4351 | Prediction of COPD treatment nonadherence using real world medicare data

Tham T. Le[1], Danya M. Qato[1,2], Margrét Bjarnadóttir[3], Larry Magder[2], Zafar Zafari[1] and Linda Simoni-Wastila[1]

[1]University of Maryland School of Pharmacy, Baltimore, MD; [2]University of Maryland School of Medicine, Baltimore, MD; [3]University of Maryland College Park, College Park, MD

Background: Nonadherence to treatments for chronic obstructive pulmonary disease (COPD) increases exacerbation risks. Predicting future nonadherence facilitates the identification of nonadherent patients for risk stratification or intervention.

Objectives: To validate prediction models of future nonadherence to COPD maintenance medications in older adults with COPD.

Methods: Design: A retrospective cohort using a 5% sample of Medicare claims from 1/1/2012 to 12/31/2014. **Settings:** This study included beneficiaries: (1) aged > 65 years; (2) had a new COPD diagnosis (index) in 2013; (3) had at least one prescription for COPD maintenance medications within a month from the index; and (4) had 12 months pre- and 12 months post- index continuous enrollment in Parts A, B, and D. We excluded individuals with Medicare Advantage or those who died during the 12-month follow-up. **Predictors:** Measured baseline predictors in the 12 months pre-index included sociodemographic factors, 44 comorbidities (binary), 44 medication use (binary), and proxies for COPD severity (oxygen supplementation and COPD hospitalization). **Main Outcomes:** The primary outcome was nonadherence (defined as proportion of days covered of < 70%) to any inhaled COPD maintenance medications (corticosteroids, long-acting β-agonists, and long-acting anticholinergics, alone or in combination) measured using Part D claims in the 12 months post-index. **Statistical analyses:** The data were randomly divided into the training (70%) and validation (30%) sets. We implemented logistic regression and used positive predictive values (PPV) and Area Under the Curve (AUC) to evaluate prediction performance.

Results: Of 4,416 eligible beneficiaries, 65.4% were female, 85.8% were white, and had a mean age of 77 years. About 32% (n=1,455) of beneficiaries adhered to the COPD maintenance medications. In the validation set: AUC=0.67, sensitivity=93%, and PPV=69% (applying a cut-off=0.5). Using a more conservative cut-off of 0.9 resulted in a PPV of 82% and a sensitivity of 51%. Significant predictors of nonadherence were baseline asthma, COPD hospitalization, and medication use (asthma medications, opioids, anxiolytics, and anticoagulants).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: The logistic regression model shows potential to identify nonadherent patients for intervention, which can label 50% of nonadherent patients with a PPV of >80%. That said, upon test results, less than one out of five patients would mistakenly receive the adherence intervention. For our next steps we will apply other prediction algorithms in a machine learning approach using more years of data.

4360 | Personalized comparisons of flare rates after hydroxychloroquine tapering or discontinuation in systemic lupus

Celline C. Almeida-Brasil[1], Christian A. Pineau[2], Evelyne Vinet[1], John G. Hanly[3], Christine A. Peschken[4], Ann E. Clarke[5], Paul R. Fortin[6], Michal Abrahamowicz[1] and Sasha Bernatsky[1]

[1]McGill University, Montreal, QC, Canada; [2]McGill University Health Centre, Montreal, QC, Canada; [3]Dalhousie University, Halifax, NS, Canada; [4]University of Manitoba, Winnipeg, MB, Canada; [5]University of Calgary, Calgary, AB, Canada; [6]Université Laval, Quebec City, QC, Canada

Background: Hydroxychloroquine (HCQ) is a cornerstone treatment for several autoimmune diseases including Systemic Lupus (SLE). Given unclear risk/benefits in long-term use, patients and physicians struggle with decisions about tapering/stopping HCQ. Although some patients may do well after reducing therapy, others will have potentially life-threatening complications related to SLE flares.

Objectives: To identify factors associated with SLE flare risk after HCQ is tapered or discontinued, and to compare flare rates among high-risk subgroups.

Methods: We analyzed prospective data from 5 Canadian cohorts of SLE patients treated with HCQ, using annual study visits between 1999-2019. We assessed patients from date of HCQ tapering (cohort 1) or discontinuation (cohort 2) until disease flare, defined by therapy augmentation, increase of ≥4 points in the SLE Disease Activity Index-2000 (SLEDAI-2K) or hospitalization for SLE. Multivariable Cox regression was used to identify demographic and clinical factors associated with time to first flare. We compared unadjusted flare rates and 95% CIs stratified by the risk factors. A third cohort of patients remaining on HCQ was used as a control, to assess if the same factors influenced flare rates even when HCQ dose was unchanged.

Results: In cohort 1 (N=398, 731.2 person-years), multivariable Cox analyses suggested that non-Caucasians (i.e., Asians, Blacks or First-Nations), patients with active SLE (SLEDAI-2K≥4) and those on prednisone at the time HCQ was tapered had a greater flare risk. Patients with ≥1 of these characteristics at the time of HCQ taper had a higher flare rate (4.2/1000 person-years, 95% CI 3.6, 4.9) than patients without any such characteristics (2.8, 95% CI 2.3, 3.4). In cohort 2 (N=395, 788.9 person-years), flare risk after HCQ discontinuation was greater for non-Caucasians and those with SLE onset at age ≤25 years. Patients belonging to one or both of these subgroups had an increased flare rate after HCQ discontinuation (4.2/1000 person-years, 95% CI 3.5, 5.0) versus those without these factors (2.2, 95% CI 1.8, 2.6). In patients remaining on HCQ (N=621), there was a trend towards higher flare rates in patients with risk factors (2.8/1000 person-years, 95% CI 2.5, 3.3) versus those without (1.9, 95% CI 1.4, 2.6), though 95% CIs overlapped.

Conclusions: Non-Caucasians, patients with SLE onset at age ≤25, those with more active SLE and/or using prednisone have more flares after HCQ tapering or discontinuation. Being aware of these factors may help physicians and patients in personalizing decisions regarding HCQ de-escalation or maintenance.

4408 | Data sources publicly available in Brazil for drug utilization research

Lisiane F. Leal[1], Claudia G.S. Osorio-de-Castro[2], Felipe Ferre[3], Ivan R. Zimmermann[4], Daniel M. Mota[5], Izabela Fulone[6], Marta Mde F. Fonteles[7], Andre O. Baldoni[8], Monique Elseviers[9] and Luciane C. Lopes[6]

[1]McGill University, Montréal, QC, Canada; [2]Oswaldo Cruz Foundation, Rio de Janeiro, Brazil; [3]Universidade Federal de Minas Gerais, Minas Gerais, Brazil; [4]Ministry of Health, Brasilia, Brazil; [5]Brazilian Health Regulatory Agency, Brasilia, Brazil; [6]University of Sorocaba, Sorocaba, Brazil; [7]Federal University of Ceara, Ceara, Brazil; [8]Federal University of Sao Joao Del-Rei, Sao Joao Del-Rei, Brazil; [9]Ghent University, Ghent, Belgium

Background: The use of large databases and its limitations for Drug Utilization Research (DUR) is not a new topic leading to discussions in several countries. In Brazil, studies to map the accessibility, feasibility and reliability of health databases to conduct DUR are still missing.

Objectives: To identify and catalogue publicly available data sources for DUR in Brazil. To characterize the type of data sources prone to be used for DUR.

Methods: The present study is part of the project entitled 'Publicly Available Data Sources for Drug Utilization Research in Latin American (LatAm) countries. In Brazil, a network of Brazilian health experts was defined. The process of searching, screening and selection of the data sources was made in three phases. Further, they were characterized according to their accessibility, geographic granularity, setting, type of data (aggregate or individual-level) and years of coverage. A general search for publications for each data source was conducted.

Results: A total of 55 data sources were identified. We excluded 17 (30.9%) data sources in which medication information was not available and 4 data sources were grouped into 2 different data sources, according to the type of data provided. Finally, 36 (65.4%) data sources were included for characterization. In the qualitative analysis, 10 (27.8%) were classified as Publicly and conveniently accessible online of which 9 (90.9%) the custodian was the Brazilian Ministry of Health through the Health Informatics Department of the Brazilian Ministry of Health (DATASUS). All data sources publicly available online provided national information, at least one year of coverage and presented both individual and aggregated-data levels. At least one scientific publication was found for each one, with exception of one data source which is an electronic system of purchases and contracts.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: In Brazil, DUR using publicly available data sources is feasible. National administrative health databases are provided through the DATASUS and give information regarding the population covered by the National Health System (SUS). Although available, data are not easily managed. Reliability for using Brazilian data for DUR will require further work.

4425 | Assessing the feasibility of evaluating tacrolimus use after solid organ transplantation in sentinel distributed database

Mingfeng Zhang[1], Sarah Dutcher[1], Monique Falconer[1], Nicole Haug[2], Zhong Wang[1], Lockwood Taylor[1], Andrew Petrone[2], Sheryl Kluberg[2] and Justin Bohn[2]

[1]U.S. Food and Drug Administration, Silver Spring, MD; [2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: Tacrolimus is an immunosuppressive drug for prophylaxis of organ rejection in patients receiving allogeneic kidney, liver or heart transplants. Concerns exist among healthcare providers about the therapeutic equivalence of brand and generic tacrolimus.

Objectives: To capture transplant patients and tacrolimus use in the Sentinel Distributed Database (SDD) to determine the feasibility of future studies on evaluating therapeutic equivalence of tacrolimus products.

Methods: We used data from August 10, 2009 to October 31, 2017 from 17 Data Partners in the SDD. Kidney, heart, and liver transplants were captured by inpatient CPT-4, ICD-9-CM and ICD-10-PCS codes. Transplant recipients were required to have continuous health plan enrollment for at least 12 months prior to inpatient admission and no multiple transplants, no prior transplant or tacrolimus dispensing during this time. We assessed the follow-up time in the SDD from hospital discharge until disenrollment, death, or the end of data availability. We estimated the gap in days between hospital discharge and first tacrolimus dispensing, identified using National Drug Codes (NDCs). For patients with first dispensing ≤30 days after discharge, we evaluated the duration of continuous tacrolimus use and length of gaps between episodes.

Results: We identified 3,655 liver transplants, 27,353 kidney transplants, and 1,586 heart transplants in the SDD, with median follow-up times of 557, 714 and 565 days, respectively. We captured dispensings of oral tacrolimus for 1,403 (38.4%) liver transplants, 4,904 (17.9%) kidney transplants and 477 (30.1%) heart transplants. When restricted to a non-Medicare population, we captured oral tacrolimus dispensings for 1,232 (72.5%) of 1,699 liver transplants, 3,360 (66.1%) of 5,083 kidney transplants, and 387 (64.9%) of 596 heart transplants. The median gap between discharge and first dispensing ranged 2-8 days for all transplant patients and 1-3 days for non-Medicare transplant patients. Among patients who had at least one gap between tacrolimus treatment episodes, the median gaps between the first and second episodes were 15, 20 and 14 days for liver, kidney and heart transplants, respectively.

Conclusions: We captured liver, kidney and heart transplant patients in the SDD, and the majority of them had less than 2 years of follow-up, which may impact the feasibility of evaluating long-term outcomes. We captured dispensings of individual oral tacrolimus products using NDC codes, although the fewer observed dispensings among the Medicare population requires further investigation.

4437 | The prevalence of polypharmacy in the elderly population: A multi-country database study in Europe

Paola Nasuti[1], Marion Bennie[2], Katja Taxis[3], Shruti Menon[1], Julien Trehony[4], Laurence Sophie Jouaville Abrouk[4], Monique Elseviers[5], Elisabetta Poluzzi[6], Catherina Sermet[7], Sean MacBride Stewart[8] and Ingrid Schubert[9]

[1]IQVIA Ltd, London, United Kingdom; [2]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom; [3]University of Groningen, PharmacoTherapy, Epidemiology and Economics, Groningen, Netherlands; [4]IQVIA Ltd, Paris, France; [5]University of Antwerp, Antwerp, Belgium; [6]University of Bologna, Bologna, Italy; [7]IRDES, Institut de Recherche en Economie de la Santé, Paris, France; [8]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [9]Faculty of Medicine and University Hospital of Cologne, Cologne, Germany

Background: The reported prevalence of polypharmacy in populations aged ≥65 years varies (38% - 65%) across Europe. This is attributable to differences in methodology and lack of consensus on the definition of polypharmacy in terms of number of medications. Most studies used a cut-off value of five. In older people polypharmacy increases the likelihood of potentially inappropriate medications (PIM). Antipsychotics and benzodiazepines (BDZ) are among the most frequently used PIMs. In addition, concerns have been recently raised about the potential overuse of proton pump inhibitors (PPIs) and opioids in this population. There is currently no recent cross-country literature on the prevalence of polypharmacy and use of these medications of special interest in the European elderly population.

Objectives: Estimate the prevalence of polypharmacy and explore the use of PIMs in older people across five European countries.

Methods: A descriptive retrospective study of elderly patients (≥65 years) with at least two GP visits in 2018 collected from nationally representative databases in Belgium (Longitudinal Patient Database [LPD]), France (LPD), Germany (LPD), Italy (LPD), and UK (IQVIA Medical Research Data). The index date was the last GP visit recorded during the study time period (1st January - 31st December 2018). Polypharmacy was defined as ≥5 distinct drug classes (ATC level 3) prescribed in 6 months before/at index date. Drugs known to be used short-term (e.g., antibiotics), irregularly (e.g., dermatologicals), prescribed by specialists (e.g., oncological medication), stoma and dressings were excluded from the analysis. Use of selected PIMs (e.g. BDZ), opioids and PPIs was also explored.

Results: Preliminary results covering France showed that the cohort consisted of 257,020 patients. 55.5% of these patients were female and 58.0% presented polypharmacy. Of the 149,089 patients with polypharmacy, 77.1% were prescribed 5-9 drugs and 22.9% ≥10

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

drugs. The most prescribed classes were analgesics and antipyretics N02B (65.4%), followed by drugs for treatment of peptic ulcer A02B (48.9%) and antithrombotic agents B01A (48.8%). A higher proportion of patients 65-74 yrs (48.9%) was observed vs. 75-84 yrs (35.7%) vs. >84 yrs (15.3%). Exploratory analyses showed that 32.9% of the study cohort was prescribed a PPI and/or a BDZ (14.1%).

Conclusions: The full study due to be completed by June 2020, will allow exploration of differences and similarities in polypharmacy across Europe. Exploratory analyses will potentially identify differences in local policies in regards to prescribing PIMs, PPIs and opioids.

4463 | Instruments to measure medication literacy: A scoping review

Lais L.N. Pantuzza, Elizabeth do Nascimento, Stephanie F. Botelho, Maria Auxiliadora P. Martins and Adriano M.M. Reis
Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Background: Considering that inadequate medication literacy can be associated with a greater risk of medication misuse and adverse drug events, there is a growing demand for valid/reliable tools to estimate its level. Although some tools have been developed, there is currently limited information on how medication literacy can be measured.

Objectives: To systematically review the literature on the instruments available to measure medication literacy.

Methods: The search was carried out in MEDLINE, LILACS, Cochrane, CINAHL, PsycINFO, Embase, Scopus, Web of science, ProQuest Dissertation & Theses Database, Ovid, Brazilian Digital Library of Theses and Dissertations and in the references of the selected studies. Search terms included *medication literacy* and its synonyms. Methodological studies for the development of instruments or observational/experimental studies that used an instrument to measure medication literacy published until December 2019 in English, Portuguese or Spanish were eligible for inclusion.

Results: Fourteen instruments were identified, but four of them were adapted/translated versions. Although the design of the instruments varied substantially, their items were generally based on real-life situations of medication use and on medications props (prescription bottles, auxiliary labels, products, patient medication information sheets or measuring devices). The number of items ranged from 6 to 37. There was great variability in terms of the target population of the instruments since it involved patients and even parents of pre-school children. Six instruments were developed to be administered as an interview, six for self-administration and two for both modes, with administration time ranging from 10 to 22 minutes. All instruments, except one, were evaluated as a single score and none had cut-off points for medication literacy levels. In general, they incorporated only functional literacy and numeracy, focusing on reading comprehension skills, word recognition or numerical abilities.

Conclusions: Although a relatively large number of instruments were identified to measure medication literacy, they generally did not analyze more advanced literacy skills, such as the ability to interpret, use and seek medication-related information and to communicate with healthcare professionals. In addition, the instruments were poorly analyzed in relation to their psychometric characteristics. These limitations prevent the effective identification of approaches to improve literacy skills and establish behavior changes for the proper use of medications.

4512 | Defining potential exposure periods from prescription medical records of nitrates taken on an as-needed basis

Anthony P. Nunes[1,2], Andrew Stewart[3], Alankar Gupta[3], Thomas McGraw[3], Jennifer Song[2] and John D. Seeger[2]
[1]*University of Massachusetts Medical School, Worcester, MA;* [2]*Optum Epidemiology, Boston, MA;* [3]*Sanofi, Boston, MA*

Background: Assessment of the risks and benefits of medications that are taken as needed is complicated in administrative data due to the uncertainty of exposure timing. Relative to pharmacy dispensing, prescription records in electronic health record (EHR) data have increased uncertainty because prescriptions may not be filled or refilled.

Objectives: To assess variability in inter-prescription intervals of as-needed nitrates and to seek to define nitrate possession based on prescription data.

Methods: Using Optum EHR data (2012 to 2016), we identified patients with any nitrate prescription. Inter-prescription interval duration was calculated as the difference between issue dates of consecutive within-patient nitrate prescriptions. Among patients with more than one nitrate prescription on unique days, we used linear regression models to assess the predictive ability of prescription elements to assess time to next prescription. Prescription elements (determinants) included number of refills on the prescription, along with the quantity and days. Models were run overall and within nitrate categories. Distributions of median, 90th percentile and 95th percentile of inter-prescription intervals were evaluated within categories of number of fills, quantity dispensed, days supplied, and total days supplied.

Results: Models explained very little of the variance, suggesting that the duration of exposure to nitrates from prescription data alone is uncertain. To address this uncertainty, we defined three exposure periods based on inter-prescription interval: likely possession (prescription date to the median), uncertain possession (from the median to the 95th percentile), and unlikely possession (beyond the 95th percentile). Generally, the uncertain period was notably longer than the likely possession period. For example, for oral nitrates, the uncertain duration was 164% of the likely duration. This difference was more pronounced for prescriptions with smaller days supplied and/or lower refills.

Conclusions: Pharmacoepidemiological assessments of medications taken on an as-needed basis, such as nitrates, must address uncertainty of exposure periods, and this is particularly important with prescription-based data sources. Creating intervals of likely, uncertain, and unlikely possession based on the inter-prescription intervals within stratum of combinations of refills, quantity dispensed, and days supplied offers an approach.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4521 | Switching of second generation antipsychotics in patients with severe mental disorders: A cohort study

Izabela Fulone, Marcus Tolentino Silva and Luciane Cruz Lopes
University of Sorocaba, Sorocaba, São Paulo, Brazil

Background: Switching antipsychotic therapy is a common clinical practice and can occur due to therapeutic failure and intolerable adverse reactions. Despite this, data on the frequency and types of exchanges are limited.

Objectives: To identify the factors associated with the switching of second generation of antipsychotic (SGA) in patients with severe mental disorders.

Methods: We conducted a retrospective cohort study of outpatients with severe mental disorders, which were taking SGA (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone) and were admitted to a pharmaceutical assistance program during 2008 to 2017 in Brazil. Data were obtained from national database (APAC/SIA). The outcome of interest was the switch of atypical antipsychotics. The association of predisposing factors for switching was analyzed using COX regression and the hazard ratios (HRs), 95% Confidence Interval (CI).

Results: Of the 759,654 patients identified, 50.5% were women, mean age 44 years and had as initial antipsychotic risperidone (33.1%), olanzapine (29.6%), quetiapine (27.7), ziprasidone (5.1%) and clozapine (4.5%). Over the ten years of the study period, 13.2% switched antipsychotics at least once. The main factors associated with the switches were: female sex (HR: 1.09, 95% CI 1.08 - 1.11), adults with age 19-64 years ($p < 0.001$) and initial use of ziprasidone (HR: 2.24, 95% CI 2.16 - 2.32). Ziprasidone had the highest frequency of switches (14/100 patients-year) and clozapine had the lowest frequency of switches (5/100 patient-year).

Conclusions: There are important differences between drugs of SGA which potentially determines the tendency for switching in real-world settings. The switch was seen more among women, adults and using ziprasidone. Clozapine use tended to show lower switches.

4542 | Mapping for pre-existing large-scale observational databases for acute coronary syndrome in China

Meng Su[1], Fuchun Li[2] and Shusen Liu[1]
[1]*Sanofi Medical, Beijing, China;* [2]*Sanofi R&D Trial Operation, Beijing, China*

Background: Ischemic heart disease (with acute coronary syndrome (ACS) as the main type) ranked second in cause of death in China. High quality pre-existing databases are the prerequisite of generating valid and reliable evidence for drug evaluation and health care quality improvement. Yet knowledge about mapping of ACS pre-existing database is scarce in China.

Objectives: We aim to describe the comprehensiveness of large-scale pre-existing databases for ACS in China.

Methods: Registries and cohorts targeting ACS with sample size larger than 1000 were enrolled by searching clinical trial registration websites, PubMed and Medline. Information on basic characteristics, representativeness, in-hospital (15 dimensions) and follow-up data were extracted from methodological articles, latest publications and registration files.

Results: Eighteen registries (72%) and 7 cohorts (28%) were enrolled with median sample size of 8000. Eight studies were classified as national representative (32%), four involved cross-province cooperation (16%) and the rest half (52%, 13/25) were single-center or localized studies. Overall, only 42% of studies (10/24, exclude one that not started) published protocol paper. For in-hospital information (4 studies excluded for no supporting documents available), good availability (at least 75%) was found in dimensions of demographics, clinical presentation, medical history and risk factors, revascularization, diagnostic procedures, lab results, medication use, in-hospital outcome and discharging information, while moderate availability was found in dimensions of imaging (52%, 11/21) and performance measurement (48%, 10/21) and poor in dimensions of bio-sample (19%, 4/21), costing (19%, 4/21), PROs (24%, 5/21), and hospital level information (28%, 6/21). Among the 21 studies had follow-up data, 17 studies (81%) were followed no longer than 12 months, the rest four followed 24 months. 3-point and 4-point MACE (all-cause death, nonfatal MI, ischemic stroke and revascularization) were the most common outcome (86%, 18/21). Moderate availability in outcomes of heart failure (33%, 7/21), readmission (48%, 10/21), bleeding (57%, 12/21) and medication use (43%, 9/21), while few studies collected information on cardiac shock/arrest (14%, 3/21) and costing (5%, 1/21).

Conclusions: Comprehensiveness for information of clinical treatment process was good in ACS registries and cohorts in China. Attention should be raised for information collected for research purposes on economic analysis, long-term follow-up assessment, patient perceptions evaluation and genetic studies.

4565 | Evaluating the performance of a novel urine-based point-of-care assay for assessing prep adherence for HIV prevention

Randy M. Stalter[1], Jared M. Baeten[1], Deborah Donnell[2], Matthew A. Spinelli[3], David V. Glidden[3], Warren C. Rodrigues[4], Guohong Wang[4], Michael Vincent[4], Nelly Mugo[5], Andrew Mujugira[6], Mark A. Marzinke[7], Craig Hendrix[7] and Monica Gandhi[3]
[1]*University of Washington, Seattle, WA;* [2]*Fred Hutchinson Cancer Research Center, Seattle, WA;* [3]*University of California, San Francisco, San Francisco, CA;* [4]*Abbott Rapid Diagnostics, Pomona, CA;* [5]*Kenya Medical Research Institute, Nairobi, Kenya;* [6]*Infectious Diseases Institute, Kampala, Uganda;* [7]*Johns Hopkins University, Baltimore, MD*

Background: Daily use of oral pre-exposure prophylaxis (PrEP) containing tenofovir (TFV) disoproxil fumarate/emtricitabine is highly efficacious for preventing HIV acquisition but adherence remains a challenge among many populations. We developed a first-of-its-kind, point-of-care lateral flow assay (LFA) with high selectivity for TFV in urine that could aid in counseling individuals on PrEP use in real-time.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: Evaluate the performance of the urine TFV LFA for assessing PrEP adherence and predicting HIV protection.

Methods: Data are from a randomly sampled cohort of HIV-negative men and women assigned to active PrEP use and HIV seroconverters in the Partners PrEP Study, a randomized, placebo-controlled PrEP efficacy trial that enrolled HIV serodiscordant couples in Kenya and Uganda. Urine samples collected at regular intervals were tested with the LFA for TFV concentrations ≥1500 ng/mL, the "threshold" associated with recent use in directly-observed-therapy studies. To provide an established daily TFV adherence standard, TFV concentrations were measured in date-matched plasma samples using a validated liquid chromatography-tandem mass spectrometry method. We calculated the LFA's sensitivity and specificity for detecting plasma TFV >40 ng/mL, which is consistent with daily PrEP use. To assess if urine TFV concentrations ≥1500 ng/mL were associated with HIV protection, we used a nested case-control analysis with incidence density sampling where HIV-negative controls were matched to seroconverter cases 35:1 on the month of case's HIV detection. Rate ratios (RR) were estimated using conditional logistic regression, adjusted for sex, baseline age and report of condomless sex at baseline.

Results: We included 241 cohort members and 17 cases, of which 38% and 47% were female, respectively. Of 391 cohort urine samples, 74% had TFV measurements ≥1500 ng/mL. Of 253 plasma samples with TFV >40 ng/mL, 219 had paired urine TFV concentrations ≥1500 ng/mL, for a sensitivity of 87% (95% CI: 82-91%). Of 138 individuals with plasma TFV ≤40 ng/mL, 68 had paired urine TFV <1500 ng/mL for a specificity of 49% (95% CI: 41-58%). In the case-control analysis, having a urine TFV concentration ≥1500 ng/mL per the LFA was associated with a 68% HIV risk reduction (RR: 0.32, 95%: 0.11-0.90).

Conclusions: A urine TFV LFA result above threshold has good sensitivity but limited specificity for daily PrEP adherence (using a plasma TFV benchmark). The LFA result is also associated with HIV protection. This novel point-of-care test has potential to be a valuable tool for supporting PrEP adherence interventions.

4704 | Acceptance of real world data use in evidence-based medicine or decision making by committee members affiliated with the Saudi food and drug authority

Fawaz Alharbi, Atheer Aldayel and Adel Alrwisan
Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: The role of real-world data (RWD) and real-world evidence (RWE) in health care and regulatory decisions is expanding.

Objectives: To explore the acceptance of RWD use in evidence-based medicine or decision making in clinical practice among members of committees involved in the regulatory decision-making at the Saudi Food and Drug authority (SFDA).

Methods:

Study design: a cross-sectional online survey comprising eight questions in English language. Study questions included demographics and acceptability of RWD in varying scenarios. Study population: external members of scientific committees (n=88) in Drug sector at SFDA were invited to participate in the survey on November 2019 through email, then followed by two reminders for non-respondents. Statistical analysis: a descriptive analysis (frequencies with percentages) of the study items.

Results: A total of 45 participants completed the survey (response rate 51%). The participants were mostly physicians (51%) and pharmacists (40%). The majority of respondents (73%) have some formal training in epidemiology. The vast majority of participants (82.2%) responded that they would use observational studies and to a lower extent (66.7%) published case report or case series, as sources of evidence for demonstrating post-marketing safety and adverse events of medications in clinical practice if a conventional randomized clinical trial were not available. On the other hand, 69% of participants stated that they would rely on observational studies to examine the effectiveness of medicines. Participants rated safety (91.1%) and effectiveness (88.9%) as the most relevant types of evidence generated from RWD. 82% of participants considered electronic health records and governmental data as a credible and useful source for RWD.

Conclusions: Our study shows that the physicians and pharmacists involved in the regulatory-decision making had a general acceptance of using RWD in evaluating outcomes of medication use.

4710 | Assessing the feasibility of leveraging healthcare databases to conduct cross-national comparisons of opioid utilisation

Teng-Chou Chen[1], Björn Wettermark[2], Douglas Steinke[1], Gillian Caughey[3], Mina Tadrous[4], Veronika Wirtz[5] and Li-Chia Chen[1]
[1]Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom; [2]Department of Pharmacy, Uppsala University, Uppsala, Sweden; [3]Registry of Senior Australians, South Australian Health and Medical Research Institute and Division of Health Sciences, University of South Australia, Adelaide, Australia; [4]Women's College Hospital, Toronto, ON, Canada; [5]School of Public Health, Boston University, Boston, MA

Background: The disproportional use of opioids globally is a public health problem as it not only resulted in suboptimal pain management but increased risk of harms and substance misuse. Globally, jurisdictions have tackled this issue differently and a cross-national comparison (CNC) study would allow important determinants to develop future policies. However, little is known about the accessibility and validity of information included in healthcare databases across regions.

Objectives: This study aimed to identify the feasibility of using healthcare databases to conduct a CNC study on opioid utilisation.

Methods: A cross-sectional survey was launched in March 2018 and included participants by purposeful and snowball sampling up to November 2018. Experts with interests in CNC studies comparing

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

opioid utilisation in the 2017 Drug Utilisation Research Special Interest Group (SIG) of the International Society of Pharmacoepidemiology were invited. A face validated electronic survey questionnaire was used to collect information related to database characteristics, medicine information and linkage information of each aggregate-level dataset (AD) and individual patient-level dataset (IPD). Descriptive statistics were applied to present the frequency of answers for each item in the survey questionnaire.

Results: Overall, participants from 22 geographical regions reported 20 ADs and 20 IPDs globally. The majority of ADs were established for claims/pharmacy dispensing purposes (n=15), and most of the 20 IPDs were electronic health records (n=7) or built for claims purposes (n=13). Most of the 20 ADs are publicly accessible without additional charge (n=14), but only 5 IPDs can be accessed without additional charge. Although 18 ADs include information from primary care settings, only 11 of the 18 ADs can obtain information from secondary care settings. Substance name, strength, formulation and the number of items dispensed are available from 18 ADs and 17 IPDs, but only 6 ADs can link observations to additional data sources. There were 15 IPDs that included patients' demographic characteristics and diagnosis records or could be retrieved from linkage databases.

Conclusions: The majority of ADs could be used to report opioid utilisation at a primary care setting, and IPDs with linkage databases should be applied to identify potential determinants and relative clinical outcomes associated with opioid use across geographic regions. Further studies would explore the differences which cannot be identified from the database such as prescribing policies between countries.

4798 | Non antibiotic medication use in children in Indonesia

Jarir At Thobari[1], Cahya Dewi Satria[1], Yohanes Ridora[1], Jullie Bines[2] and Yati Soenarto[1]

[1]Faculty of Medicine, Publich Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [2]Murdoch Children's Research Institute, University of Melbourne, Melbourne, Indonesia

Background: Rational medication use for treatment is mandatory, particularly in children as they are vulnerable to possible hazards of drugs. Understanding the medication use pattern is of importance to identify the problems of drug therapy and to improve the appropriate use of medication among this population.

Objectives: This study is to describe all non-antibiotic medications used in children between age 0-18 months in Indonesia

Methods: A post-hoc study of the RV3-BB Phase IIb trial which was conducted in Indonesia during January 2013 to July 2016. Any concomitant medication use and health events among 1621 trial participants during the 18 months of follow-up were documented. Information on medication use included the frequency, formulation, indication, duration of usage, number of regimens, medication types, and therapeutic classes.

Results: The majority of study participants (N=1333/1621; 82.2%) used at least one non-antibiotic medication for treatment during the 18-month observation period. A total of 7586 medication uses were recorded, mostly in the oral formulation (90.5%). Of all illnesses recorded, 24.7% were treated with a single drug regimen of non-antibiotic medication. The most common therapeutic classes used were analgesics/antipyretics (30.1%), antihistamines for systemic use (17.4%), cough and cold preparations (13.5%), vitamins (8.6%), and antidiarrheals (6.6%). The main medication types used were paracetamol (29.9%), chlorpheniramine (16.8%), guaifenesin (8.9%), zinc (4.6%), and ambroxol (4.1%). Respiratory system disorder was the most common reason for medication use (51.9%), followed by gastrointestinal disorders (19.2%), pyrexia (16.9%), and skin disorders (7.0%).

Conclusions: A large number of children were exposed to at least one medication during their early life, including those where evidence of efficacy and safety in a pediatric population is lacking. This supports the need for further research on pediatric drug therapy to improve the appropriate use of medication in this population.

4845 | Linking regional administrative data with an hospital pathology registry in Italy to describe first-line pharmacotherapy of non-resectable non-small cell lung cancer in 2009-2017

Andrea Spini[1], Giuseppe Roberto[2], Cristiana Bellan[3], Alessandra Pascucci[3], Pietro Rosellini[1], Adele Caldarella[4], Alessandro Barchielli[4], Sandra Donnini[5], Folco Furiesi[3], Lorenzo Leoncini[3], Silvano Giorgi[3], Claudia Bartolini[2], Marco Zappa[4], Marina Ziche[5], Francesco Salvo[1] and Rosa Gini[2]

[1]University of Bordeaux, Bordeaux, France; [2]Agenzia Regionale di Sanità della Toscana, Firenze, Italy; [3]Azienda Ospedaliera Universitaria Senese, Siena, Italy; [4]Istituto per lo Studio, la Prevenzione e la Rete Oncologica, Firenze, Italy; [5]Università di Siena, Siena, Italy

Background: During the last decade, treatment guidelines for advanced stage non-resectable *non-small cell lung cancer* (NSCLC) have rapidly changed mainly due to the introduction of new drugs, as target-therapies (TT) and immunotherapies (IT).

Objectives: To describe the first-line pharmacotherapy in non-resectable NSCLC patients between 2009 and 2017 at the University Hospital of Siena (UHS), a city in Tuscany (Italy).

Methods: Patients with a NSCLC diagnosis recorded in the pathology registry (PR) of UHS in 2009-2017 were identified through SNOMED codes and free text keywords and validated manually by two independent reviewers, based on PR free text. Patients were linked to administrative healthcare database (AHD) of Tuscany. The PR record date was considered as the index date (ID). Patients with a lung surgery recorded in AHD up to 6 months before or after ID were excluded. First-line pharmacotherapy was described using AHD: in particular, records of *Outpatient Drug Dispensings* (ODD) and *Hospital Discharge Records* (HDR) were used. While HDR recorded unspecified chemo- (uCT), monoclonal antibody-based therapy (uMAB) or radiotherapy (RT), ODD recorded drug ATC codes up to the fifth level. Using ODD and HDR, patients were classified according to the first-line treatment received during 6 months following ID: standard chemotherapy (CT), TT, IT, uCT, uMAB, RT, no drugs (ND), or death within six months with

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

no drug treatment (DnoT). Two study periods were considered based on patients' ID: 2009-2013 and 2014-2017.

Results: A total of 831 validated, advanced NSCLC cases were identified in the two study periods: 431 and 400, respectively. Overall, according to ODD and HDR, DnoT patients were about 20% while ND were about 10%. Around 45% of patients received CT or uCT. Patients that received a TT were 4.4% (n=19) in 2009-2013 and 9% (n=36) in 2014-2017. Among TT patients, those who performed an EGFR test increased from 58% in 2009-2013 to 92% in 2014-2017. During the whole study period, the most frequently used TT were gefitinib (n=22, 2.6% of the study cohort) and erlotinib (n=21, 2.5%). Three patients received IT in 2014-2017 (nivolumab n=2; pembrolizumab n=1).

Conclusions: At the UHS, in 2014-2017 use of innovative drugs for the first-line pharmacotherapy of patients with non-resectable NSCLC has increased when compared to 2009-2013. Selective EGFR tirosin-kinase inhibitors, such as gefitinib and erlotinib, were increasingly chosen based on tests for the molecular characterization of the tumor.

4849 | Drug utilization study of the medicinal combination product conjugated oestrogens/bazedoxifene in the European Union

Dorothea von Bredow[1], Margarita Shlaen[1], Vera Frajzyngier[2], Nikolaus Kolb[1], Barbara Thun[1], Leo Russo[3] and Jacco Keja[4]
[1]IQVIA, Munich, Germany; [2]Pfizer, New York City, NY; [3]Pfizer, Collegeville, PA; [4]IQVIA, Amsterdam, Netherlands

Background: Duavive® (conjugated estrogens with bazedoxifene) has been authorized in the EU since 2014 for the treatment of estrogen deficiency symptoms in postmenopausal women for whom treatment with progestin-containing therapy is not appropriate. This drug utilization study was designed to collect real-world data on use of Duavive and was a commitment to the European Medicines Agency.

Objectives: To describe 1) characteristics of EU patients initiating treatment with either Duavive or oestrogen + progestin hormone replacement therapy (E+P HRT) and 2) Duavive utilization patterns.

Methods: A non-interventional retrospective study was conducted using existing data sources in 6 EU countries (electronic medical records in France, Italy, Spain, UK; longitudinal prescription and cross-sectional databases in Belgium and the Netherlands) from March 2016 to March 2019. Age ≤45 was used as a proxy for premenopausal status in the analysis of potential off-label use.

Results: The numbers of Duavive initiators/ E+P HRT users in the longitudinal databases 3 years after Duavive launch were 11/ 29,799 in the UK, 22/ 29,047 in France, 73/ 2,573 in Spain, 177/ 76,550 in the Netherlands, 223/ 6,288 in Italy and 480/ 57,059 in Belgium. The majority of Duavive users were aged ≥50 years, ranging from 55% (UK) to 93% (Belgium); the range for E+P HRT users ≥50 years was 42% (Spain) to 91% (Belgium). Oestrogen deficiency symptoms were recorded in 49% (Spain) to 91% (Belgium) of Duavive users. Potential off-label use of Duavive ranged from 9% (France) to 29% (Spain) of patients and was primarily comprised of use in women ≤45 years of age. These women may have been postmenopausal and using Duavive in accordance with the label indication. Other evidence for potential off-label use included diagnostic codes for osteoporosis (0% in Belgium and France to 5% in Italy and Spain), hypersensitivity (1% in Italy and Spain), concomitant prescriptions of selective estrogen receptor modulators (SERMs; 2% and 7% in Belgium and the Netherlands), prescription of a non-approved dose (2% in Italy and the Netherlands), and malignancy related to oestrogens (<1% in Italy and 1% in Spain). In Belgium and in the Netherlands 4% and 5% of patients (respectively) were >75 years of age; 3% of patients in Belgium, 1% in the Netherlands and <1% in Italy were documented as male.

Conclusions: Overall, Duavive was prescribed to the indicated population and at the dosage recommended in the Summary of Product Characteristics.

4870 | Outpatient antibiotic use in Chinese pregnant women

Houyu Zhao[1], Jiaming Bian[2] and Siyan Zhan[1]
[1]Peking University, Beijing, China; [2]The 7th Medical Center of the Chinese PLA General Hospital, Beijing, China

Background: Antibiotic use in pregnant women is rarely described in China.

Objectives: To estimate the outpatient antibiotic prescription rates for pregnant women in China.

Methods: A data of 4912416 outpatient visits of pregnant women from 128 hospitals in 28 provinces of Mainland China from October 2014 to April 2018 were analyzed. Antibiotic prescription rates by hospital level, age group, and trimester of pregnancy were estimated and reported. The 95% confidence intervals (CIs) were estimated using the Clopper-Pearson Exact method.

Results: Among the 4912416 outpatient visits of pregnant women, 3.45% (95% CI, 3.43% - 3.46%) were prescribed at least one antibiotic. The percentages of antibiotic prescriptions for pregnant women were 8.39% (95% CI, 8.29% - 8.49%) and 3.11% (95% CI, 3.09% - 3.12%) in Chinese secondary and tertiary hospitals, respectively. Among pregnant women under 18 years old, 12.98% (95% CI, 12.32% - 13.66%) of outpatient visits were prescribed antibiotics, while only 2.42% (95% CI, 2.40% - 2.44%) of outpatient visits of pregnant women aged 26-30 years ended with antibiotics. In addition, antibiotic prescription rates varied much among different trimesters of pregnancy, which were 9.09% (95% CI, 9.04% - 9.14%) for the women of first trimester of pregnancy and 0.44% (95% CI, 0.43% - 0.46%) for the women of third trimester of pregnancy. However, among all visits with antibiotic prescriptions, 71.64% (95% CI, 71.33% - 71.95%) had no clear indication and thus might be inappropriate.

Conclusions: Approximately 3.5% of pregnant women received antibiotic prescriptions, while a large proportion of which might be inappropriate.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4896 | Characterizing concurrent use of gabapentin with opioid analgesics among Kentucky residents with long-term opioid prescriptions, 2018

GYeon Oh, Svetla Slavova and Patricia R. Freeman
University of Kentucky, Lexington, KY

Background: Gabapentin is commonly used for neuropathic pain. Although studies have shown limited effectiveness of gabapentin for other types of chronic pain, its use has increased over the past decade, due in part to the increased scrutiny of opioid analgesic (OA) prescribing and the need for non-opioid pain management strategies. Recent studies have documented increased opioid-related risk when gabapentin is used concurrently with OA, similar to that previously reported for use of OA and benzodiazepines (BDZ).

Objectives: The purpose of this study was to characterize the concurrent use of gabapentin, and gabapentin with BDZ, among long-term OA users in Kentucky

Methods: We used 2018 Kentucky All Schedule Prescription Electronic Reporting data for Kentucky residents. Long-term OA use was defined as 90+ consecutive days' supply of OA. Concurrent gabapentin-OA use and gabapentin-OA-BDZ use were defined as 90+ overlapping days and 7+ overlapping days, respectively. We estimated rates of use and concurrent use (per 100 long-term OA users), and reported rate ratios (RR) and 95% confidence intervals (CI) to compare demographic groups and geographical regions. Patents' average daily morphine milligram equivalent (MME) dose was calculated for the overlapping gabapentin-OA period and the period with OA only. Paired t-test was used to test the hypothesis that concurrent use of gabapentin reduces the average daily MME.

Results: The overall rate of concurrent use of gabapentin-OA was 33.5/100, with the highest rates among 45-54 years of age (40.2/100). Rates of concurrent use of gabapentin-OA were significantly higher in females vs. males [RR: 1.07; 95% CI: 1.06-1.09] and Appalachian Kentucky region vs. Central [1.35; 1.33-1.37] or Delta [1.41; 1.38-1.44] regions. One in ten long-term OA users used gabapentin-OA-BDZ concurrently for at least 7 days. The rate of concurrent use of gabapentin-OA-BDZ was highest in the 45-54 years of age (11.9/100). The estimated mean difference in the average daily MME dose among long-term OA users when they used gabapentin concurrently was statistically significant (1.06 MME, p<.0001) but no clinically meaningful reductions.

Conclusions: Given that concurrent use of OAs with gabapentin and gabapentin/BDZ is common, and that there are no clinically meaningful reductions in average daily MME when gabapentin and OAs are concurrently prescribed, a substantial number of individuals may be at heightened risk for opioid-related harm as a result of these drug combinations.

5012 | Persistence with teriparatide treatment in osteoporotic patients: A population-based study using Italian regional databases

Andrealuna Ucciero, Andrea Sarro, Alessandro Pecere and Francesco Barone-Adesi
University of Estern Piedmont, Novara, Italy

Background: Teriparatide (TPT) is an anabolic drug used in the secondary prevention of osteoporotic fragility fractures. It is administered as a daily subcutaneous injection and the treatment is recommended for a maximum of 24 months. The few real-world studies so far conducted suggest an alarming low persistence to TPT, even worse than in other osteoporosis treatments. As non-persistence is one of the most important predictors of treatment failure in osteoporosis, specific research on this topic is needed.

Objectives: Aim of our study was to estimate persistence to TPT in an Italian setting and to investigate possible determinants of non-persistence.

Methods: A retrospective analysis of administrative health databases was conducted in Piedmont, an Italian region with 4.3 million inhabitants. Relevant data were obtained from: i) inhabitant registry, ii) hospital discharge records, iii) drug registry, iv) exemption-from-co-payment registry. Patients who started TPT treatment during the period 2013-2016 were followed for 24 months and were considered as non-persistent if they had gaps in treatment longer than 90 days. Possible determinants of non-persistence were evaluated using non-parametric methods for survival analysis and Multivariable Cox regression models.

Results: During the study period, 2,615 TPT new-users were identified (87% women). Their mean age was 74 years. Average 24-month persistence was 68%. This value increased over time, from 57% in 2013 to 72% in 2016 (Adjusted Hazard Ratio [HR] of non-persistence 2016 vs. 2013: 0.67; 95%CI: 0.54-0.82). Patients aged at least 80 years (HR: 1.17; 95%CI: 1.01-1.36) and those with a Charlson Morbidity Index of 1 or more (HR: 1.35; 95%CI: 1.05-1.73) had a higher risk of non-persistence. Conversely, patients with a previous treatment of vitamin D (HR: 0.68; 95%CI: 0.57-0.81) and other anti-osteoporotic medications (HR: 0.78; 95%CI: 0.68-0.89) were less likely to be non-persistent.

Conclusions: Conclusions: Results from this Italian study suggest a reasonably high persistence to TPT, which steadily increased over time. This is probably due to a greater attention among doctors and patients to the correct use of this medication in recent years. Future research is needed to evaluate the role of early discontinuation of treatment on long term risk of fractures.

5028 | Real world use of opioids in COPD patients

Katia Verhamme[1], Marie Clyncke[2], Lies Lahousse[2], Esme Baan[1] and Guy Brusselle[2]
[1]EMC, Rotterdam, Netherlands; [2]Ghent University, Ghent, Belgium

Background: In COPD, opioids may be considered for relief of cough or pain, or for the palliative treatment of dyspnea.

Objectives: To investigate the real life use of opioids in COPD patients.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: A retrospective cohort study was designed to investigate opioid use in COPD patients and in a reference cohort of non-COPD patients using the Dutch Integrated Primary Care Information (IPCI) database. The study period was from 2000-2017. Opioid prescriptions were extracted through an automated search on the ATC code N02A (indication pain) and the ATC code R05DA (indication cough). Opioid use was expressed as the number of patients being prescribed an opioid divided by the follow-up time. Differences in prevalence rates were investigated using Poisson Regression analysis. Differences in patient characteristics between opioid vs. non-opioid treated COPD patients were explored using multivariable logistic regression analysis.

Results: The study population consisted of >1,3 million individuals, 40 years or older. Within this study population, we defined a COPD cohort of 67,990 patients (5,2%) and a reference cohort of non-COPD patients of >1,2 million subjects. The prevalence of opioid prescribing was significantly higher in COPD (206/1,000 person-years [PY]) than in control patients (78/1,000 PY) ($p<0.001$). Opioid use was higher in females and increased by age and calendar time in both cohorts. In both cohorts, use of codeine for pain increased with age, whereas use of codeine for cough decreased from the age of 70 onwards. In COPD patients, independent risk factors for opioid use were age, female sex, cancer (OR_{adj} 1.5; 95% CI 1.5-1.6), lungcancer (OR_{adj} 3.2; 95% CI 2.9-3.4), depression (OR_{adj} 1.6; 95% CI 1.5-1.7), and current smoking (OR_{adj} 1.5; 95% CI 1.4-1.5).

Conclusions: Opioid use was much higher in COPD patients than in non-COPD patients. Female sex, age, smoking and (lung)cancer were important risk factors for opioid use.

5037 | Quality of life in treatment-experienced multiple myeloma patients: A comparative analysis of therapeutic regimens

Jéssica S. Malta[1], Paula L.M. Drummond[1], Lívia P. Silveira[1], Naiane L. Costa[1], Taisa R.L. Machado[1], Roberta M.M. Santos[2], Adriano M.M. Reis[1] and Cristiane A.M. Pádua[1]

[1]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [2]Fundação Ezequiel Dias, Belo Horizonte, Brazil

Background: Multiple myeloma (MM) is a rare, incurable, but a treatment-sensitive hematological cancer, prevalent in elderly. Besides to other age-related factors, therapeutic regimens can promote several functional and Quality of Life (QoL) changes in individuals, such as the adverse effects promoted by thalidomide (Thal).

Objectives: To evaluate the QoL of patients with MM in use of Thal compared to other therapeutic regimens.

Methods: Cross-sectional study conducted with 182 MM patients (≥ 18 years old) attending public and private outpatient services in Belo Horizonte, Brazil from April to November 2019. All patients diagnosed with MM were invited to participate and signed an informed consent form. QoL was measured by interviews using the QoL Questionnaire for MM patients (QLQMY20, Brazilian Portuguese version) of the European Organization for Research and Treatment of Cancer. The score result ranges from 0 to 100. The higher the scores, the better the evaluation of the future perspective and body image domains. Higher scores for disease symptoms and side-effects of treatment represent worst outcomes. Socio-demographic and clinical variables were collected through interview and review of medical charts. Therapeutic regimens have been divided into two groups - Thal and other regimens for comparison. Mean, median standard deviation (SD) and absolute and relative frequencies were estimated and Student's t-test was used to describe continuous variables (level of significance of 5%).

Results: Half of participants was female, aged 66 years old. Most of them were retired (61%) and attended private health clinics (54%). At least one comorbidity and use other drugs than chemotherapeutics was found in 65% and 96% of patients, respectively. Therapeutic regimens comprised combinations of Thal, bortezomib, cyclophosphamide and dexamethasone; 41% patients were not on treated at the time of interview. Among patients who used Thal, 65% are participants who attended public health system. Mean QoL scores were found for patients on treatment with Thal (31%) vs. other therapeutic regimens (28%) - disease symptoms: 15.3 (SD=26.4) vs. 15.6 (SD=19.9); side-effects of treatment: 20.9 (SD=17.3) vs. 21.6 (SD=18.7), body image: 36.9 (SD=42.9) vs. 32 (SD=40.5) and future perspective: 55.4 (SD=29.2) vs. 53.8 (SD=29.5) (p-value >0.05).

Conclusions: Other therapeutic regimens did not show superiority over Thal in promoting QoL in MM patients. This is a positive issue in Brazilian context, since Thal is produced and available by public health system.

5050 | Adherence to immunomodulatory drugs in Brazilian patients with multiple myeloma

Lívia Pena Silveira, Paula Lana de Miranda Drummond, Jéssica Soares Malta, Naiane Lima Costa, Roberta Márcia Marques dos Santos, Taísa Roberta Lopes Machado, Adriano Max Moreira Reis and Cristiane Aparecida Menezes de Pádua

Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Background: Multiple myeloma (MM) is a hematological cancer which manifests mainly in older adults and has no cure. Oral Immunomodulatory drugs (IMID) are widely used in the treatment of MM patients. A primary challenge of oral antineoplastic treatment is ensuring patient adherence. To date, few data are available on IMID adherence in MM patients.

Objectives: To investigate IMID adherence in multiple myeloma patients in Brazilian public and private outpatient services.

Methods: A cross-sectional study was conducted with patients with multiple myeloma (> 18 years old), who have been receiving an IMID for at least 2 months and that consulted outpatient services between April to November 2019. The study was performed in two public and one private outpatient services in a metropolitan city in southeast of Brazil. Socio-demographic (sex, age, self-declared color skin, family income), clinical (disease staging, comorbidities and IMID) and related to health services (outpatient clinics) variables were obtained from interview and medical records. IMID adherence was measured by

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

interview using the Measuring of Treatment Adherence (MTA), developed in Portugal and validated to Brazilian Portuguese. Adherence was classified as adherent (Grade 5-6) or not adherent (Grade 1-4). Descriptive analysis was performed. The internal consistency of the MTA was measured by Cronbach's alpha coefficient. All analyses were performed using SPSS 26.0 software.

Results: A total of 61 patients were included in the study. Half patients were males and attended public outpatient service. Most of them reported to have white skin colored (42.6%), with family income until three minimum wages (54.1%). The mean age was 63.2 years old (SD 10.16). 68,9% had at least one comorbidity. Regarding staging, most patients had a more advanced stage of the MM (41% - DS IIIA and 31.1% ISS II). Thalidomide was the most frequent IMID prescribed in our study (80.3%), followed by lenalidomide and pomalidomide (18.0% and 1.6% respectively) and 83.6% made up to 2 lines of treatment. Regarding IMID adherence, a total of 97.2% were considered adherent according to the questionnaire (grade 5-6). The Cronbach's alpha coefficient was 0.403. Instruments with few items, such as MTA, an alpha value around 0.50 is acceptable.

Conclusions: MM patients attending outpatient services in southeast of Brazil are highly adherent to IMIDs. The development of adherence instruments with better internal consistency is a need to better measurement and understand the adherence of IMIDs in MM patients.

5071 | Effect of an educational program on the medication adherence in adult patients at transition of care

Jimmy Reyes, Carolina Bobadilla, Carlos Silva, Natalia Carrillo, Cristóbal Gutiérrez, Tamara Sandoval and Marcela Jirón
Universidad de Chile, Santiago, Chile

Background: After hospital discharge, patients commonly suffer potentially avoidable adverse outcomes due to poor medication adherence. Despite positive results of patient education to improve adherence, limited information on educational programs focused on the vulnerable transition period from hospital to home is available in developing countries.

Objectives: To assess the effect of an educational program (EP) conducted by pharmacists on medication adherence in adult patients at the transition of care from a teaching hospital to home.

Methods: A prospective pre/post quasi-experimental study was conducted during 5 months period in the Internal Medicine Service (IMS) at a teaching hospital in Santiago, Chile. Patients ≥ 18 years old with drug treatment at admission and signed inform consent form were included. An EP was conducted by 5 pharmacists during patient's hospitalization in the IMS and at discharge. The EP included daily patient and caregiver education on patient's diagnosis, drug therapy, risk of nonadherence, resolve questions and counseling focused on patient's specific needs and problems. At discharge, verbal education and written materials were provided to support patients overcome adherence barriers. Medication adherence and the knowledge of drug treatments were estimated using Morisky-Green scale and a questionnaire of drug therapy (acceptable, unacceptable), respectively, at admission and 30 days after hospitalization

Results: A total of 183 patients were included during the study period. The mean age was 61.3 ±18.8 years, 50.3% were men. A 33.3% of patients had ≥ 12 years of educational level. The main reason of hospital admission was pain (20.2%). Hypertension (49.2%) was the most frequent comorbidity. The mean number of comorbidities was 4.7 ± 1.9 drugs. The EP improved significantly medication adherence in 29.6% (from 46.3% to 75.9%; $p<0.01$). The knowledge of the drug treatments improved 42.3% (from 28.2% to 70.5%; $p<0.01$). Main changes on medication adherence were seen on women, patients with type 2 diabetes, ≥ 5 years of diagnose, and patients with ≥ 12 years of educational level.

Conclusions: A systematic EP based daily contacts with pharmacists during the hospitalization and at discharge could help adult patients to improve significantly adherence and knowledge of drug treatments during the transition of care from a teaching hospital to home. Future studies with a bigger sample and robust design should be conducted to determine the efficacy and safety of this EP.

5160 | Drug use during pregnancy according risk classification and associated factors

Caroline T. de Castro[1], Débora B. Costa[2] and Djanilson B. dos Santos[3]
[1]*Federal University of Bahia, Vitória da Conquista, Brazil;* [2]*Federal University of Ceará, Fortaleza, Brazil;* [3]*Federal University of Recôncavo da Bahia, Santo Antônio de Jesus, Brazil*

Background: The effect of the use of drugs in pregnancy is often unpredictable and can affect both the mother and the foetus.

Objectives: To investigate the factors associated with drug use in pregnancy by risk categories in pregnant women in Santo Antônio de Jesus, Bahia.

Methods: Cross-sectional cohort study with 1,091 pregnant women attended by UBS in the urban area of the municipality between 2012 and 2014. Drug use during pregnancy was classified according to the FDA risk classification system. Socioeconomic, demographic, maternal and health service utilization variables were analysed. Prevalence ratios (PR) and respective 95% confidence intervals (95% CI) were adjusted by Poisson regression with robust error variance.

Results: The prevalence of drug use was more pronounced in risk categories A, B, C, D and X, respectively. The use of safe medication was associated with education, number of prenatal consultations and health problems after data adjustment. The factors associated with the use of risk medication were age greater than 24 years, onset of prenatal care during the first trimester and having any health problems.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: The results of this study are similar to those described in the literature. Investments in continuing vocational education that promote rational antenatal drug use are needed.

Drug Utilization Research -> Quality use of medicines (including indicators and guidelines)

40 | A retrospective audit of the management of childhood acute asthma exacerbation in children: Adherence to global treatment guidelines

Kazeem Adeola Oshikoya[1], Ibrahim Abayomi Ogunyinka[2] and Shallom Ese Imuzie[2]
[1]*Lagos State University College of Medicine, Ikeja, Lagos, Nigeria;* [2]*Usmanu Danfodiyo University, Sokoto, Nigeria*

Background: Adequate management of childhood acute asthma exacerbation requires optimal non-pharmacotherapy and pharmacotherapy. Global asthma guidelines provide critical information and serves as a quick reference decision-support material for clinicians.
Objectives: To evaluate hospital management of childhood acute asthma exacerbation according to global treatment guidelines, and to identify factors that predict short or prolonged observation in the hospital.
Methods: This is a retrospective audit of the management of acute asthma exacerbation in children seen between 01 January 2017 and 31 December 2018 at Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Nigeria. Relevant data on demography, asthma triggers and severity, functional and clinical diagnoses, types of controller medications used before and after presentation, non-pharmacotherapy and pharmacotherapy instituted during presentation, duration of observation in the hospital, and treatment outcomes were extracted from the case file of each patient.
Results: All the 119 children presented with mild (88; 73.9%) or moderate (31; 26.1%) acute asthma exacerbation. Their median (interquartile range) age was 5 (2.4-8) years. More males (75; 63.0%) than females (44; 37.0%) presented with acute asthma exacerbation. Cold weather (39; 28.1%) and dust (21; 15.1%) were the predominant triggers. Seretide® (39/75; 52.0%) was the commonest controller medication used by the patients prior to presentation. Nebulized salbutamol (91; 76.5%), in addition to intravenous (44; 57.9%) or oral (32; 42.1%) corticosteroids, was used during hospital treatment. Patients were discharged mostly on short course of oral corticosteroid only (70; 58.8%). A total of 12 out of 14 recommendations were adhered to in over one-half of the patients. The odds of admission for <12 hours were nearly six times higher for patients on systemic corticosteroids.
Conclusions: Management of acute asthma exacerbation was considerably good in accordance with the GINA guidelines and adequate documentation of important details was common in at least one-half of the patients. Reinforcement of institutional guidelines, an adaptation from GINA document, for acute asthma management is suggested to further improve quality care of childhood acute asthma exacerbation.

119 | Potentially inappropriate psychotropic medications use among older adults with psychiatric disorders in the Jazan region, Saudi Arabia

Abdulkarim M. Meraya and Otilia J.F. Banji
College of Pharmacy, Jazan University, Jazan, Saudi Arabia

Background: Over 20% of older adults (>= 60 years) suffer from a mental or neurological disorder, globally. Beers criteria provide a list of psychotropic medications that should be avoided or used with caution in older adults due to the aging process and physiological changes. Evidence on following the criteria and not using potentially inappropriate psychotropic medications (PIPM) in Saudi Arabia, however, is limited.
Objectives: This study aimed at deciphering the pattern of drugs prescribed in older individuals in psychiatric settings, assessing the prevalence of PIPM based on the updated 2015 Beers criteria and discerning polypharmacy in older psychiatric patients.
Methods: This study was a retrospective cross-sectional review conducted on older adults who underwent treatment at the psychiatric hospital in the Jazan region, Saudi Arabia. Electronic medical records of older adults (>=60 years) were reviewed to extract data on clinical factors, demographics and medications used. The outcomes measured were pattern of drug use; in addition, the retrieved data was scrutinized based on Beer's criteria to identify PPIM. Also, the propensity of polypharmacy (prescription of >=2 psychotropic medications) among the elderly was assessed. Multivariable logistic regression was used to assess the relationship between the explanatory variables such as age, sex and psychiatric diagnoses with the use of PPIM.
Results: The final study sample consisted of 1,300 older adults with a psychiatric diagnosis. Of these, 68% were prescribed PIPM. Amitriptyline was the most commonly potentially inappropriate antidepressant followed by maprotiline. The most prescribed potentially inappropriate antipsychotics were chlorpromazine, trifluperazine and risperidone. PIPM use was associated with schizophrenia and anxiety. Furthermore, psychotropic polypharmacy was highly prevalent among the older adults (77.7%).
Conclusions: PIPM use was highly prevalent among older adults with psychiatric diagnoses in Jazan region, Saudi Arabia. Educational programs and interventions are required to increase the awareness about PIPM use among mental health care providers in the Jazan region to minimize risks of unwanted adverse drug reactions among older adults with mental disorders.

2367 | Disposal of leftover medicines: Prevalence and practices among the rural population of Kerala

Jose J. Kochuparambil[1], Akshay Nidha[1] and Aleena Issac[2]
[1]*St. Joseph's College of Pharmacy, Cherthala, Alappey, India;* [2]*Nirmala College of Pharmacy, Muvattupuzha, India*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Leftover medicines in the household is an evolving problem. There are no regulations from the government to safely dispose medicines kept as left over home. Along with this there is a greater number of people accessing medical care and the prescription of medicines also increased resulting in an increased per person consumption of medicines.

Objectives: To determine prevalence of households with leftover medicines and its disposal practices among the rural population of Kerala, India.

Methods: A cross-sectional study was conducted among the rural population of three districts of Kerala. The pre-tested data collection tool used for collecting information on medicine usage and medicine wastage. The houses numbered with multiples of 5 were selected for the study resulting in a total household of 181.

Results: Among the 181 houses surveyed, 93 (51%) households were reported to have left over medicines kept at home. The major reason for medicine left over was found to be symptom relief [42] (45%) and change of prescriber [18] (20%). Among the total families surveyed, 121 (67%) of the families responded that they are disposing their solid medicines along with household waste and in the case of liquid preparations, 98 (54%) were disposing their medicines along with household waste. Some of the responders disposed the medicines as fertilizers for plants.

Conclusions: There is no established system for safe medicine disposal in the community. Even though there are some good practices for collecting the unused medicines by non-profit organisations to re-use it among the needy, they are not standardized. The majority of respondents would support the implementation of a proper system for re-collecting the medicines. Hence, a regulated drug take-back program may result in a reduction in the household medicine wastage.

2398 | Trends in acid suppressant drug prescriptions in primary care in the United Kingdom

Devin Abrahami[1], Emily Gibson McDonald[2], Mireille Schnitzer[3] and Laurent Azoulay[1]

[1]McGill University, Montreal, QC, Canada; [2]McGill University Health Centre, Montreal, QC, Canada; [3]University of Montreal, Montreal, QC, Canada

Background: Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are among the most commonly prescribed drugs worldwide. However, there is some evidence that they are being used inappropriately, either in individuals without underlying disease, or for a longer duration than necessary. In light of emerging safety concerns, it has become increasingly important to understand how these drugs are being prescribed in clinical practice.

Objectives: To examine the prescribing patterns of PPIs and H2RAs over time by quantifying prevalence of use in the general population, intensity of use among drug users, and describing persistence patterns among new users.

Methods: Using the United Kingdom Clinical Practice Research Datalink, we defined a cohort of patients prescribed PPIs and H2RAs between January 1990 and December 2018. Annual prescription rates were estimated by dividing the number of patients with at least one prescription by the total population registered in the data. Yearly intensity of use was estimated by dividing the number of prescriptions by the person-years of follow-up, and change in intensity was calculated per decade using negative binomial regression. Finally, Kaplan-Meier curves were used to examine persistence to original treatment course among new users.

Results: PPIs were prescribed to 2,714,785 patients, while H2RAs were prescribed to 855,248 patients. Among new PPI and H2RA users, only 48.4 and 54.1%, respectively, had an approved indication for use. The prevalence of PPI use significantly increased from 1990 to 2018 (0.2 to 14.2%), while the prevalence of H2RA use remained low over the study period (2.5 to 1.9%). Prevalence of use was highest among females and the elderly (at least 60 years old). For every increase in year from 1990 to 1999, the yearly intensity of PPI use increased by 16% (IRR: 1.16, 95% CI: (1.16 to 1.16)), while the intensity of use remained constant from 2000 to 2009 and 2010 to 2018. In contrast, intensity of H2RA use decreased by 11% per year from 1990 to 1999 (IRR: 0.89, 95% CI: 0.89 to 0.90), decreased by 10% per year from 2000 to 2009 (IRR: 0.90, 95% CI: 0.90 to 0.90), and increased by 5% per year from 2010 to 2018 (IRR: 1.05, 95% CI: 1.05 to 1.05). Overall, 38% of PPI and 47% of H2RA users continued using these drugs beyond the one-year duration recommended in treatment guidelines.

Conclusions: This study demonstrates that use of PPIs has been steadily increasing over time, while use of H2RAs remains low. Given the high prevalence of patients who do not have an approved indication for use and the high persistence to treatment, programs which target medication overuse should be considered.

2402 | Utilization of hydroxyprogesterone during the 2nd or/and 3rd trimester among pregnancies with live birth deliveries in the sentinel distributed databases

Huei-Ting Tsai[1], Mayura Shinde[2], Austin Cosgrove[2], Jie Li[1], Christina Chang[1], Christine P. Nguyen[1], Corinne M. Woods[1], Joy Kolonoski[2], Tiffany Siu Woodworth[2] and David Moeny[1]

[1]Food and Drug Administration, Silver Spring, MD; [2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: Makena®, hydroxyprogesterone caproate (HPC) injection, is indicated for reducing the risk of preterm birth in women with a singleton pregnancy who had a prior singleton spontaneous preterm birth. The U.S. FDA approved Makena on February 3, 2011 under accelerated approval, contingent upon post-marketing confirmation of clinical benefit, such as improvement in neonatal mortality and morbidity. However, the confirmatory trial completed in 2018 (PROLONG trial), failed to confirm Makena's efficacy. An analysis of drug

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

utilization of HPC, including Makena, in pregnant women was undertaken to inform the landscape of HPC use for deliberations at the FDA's Advisory Committee meeting on Makena.

Objectives: To assess the utilization of HPC in pregnancy in the U.S.

Methods: We identified pregnant women aged 10-54 years, with a live birth from January 1, 2008 through April 30, 2018, and with continuous medical and drug insurance coverage for at least 301 days prior to a live birth delivery in the Sentinel Distributed Database (SDD). The exposures of interest included use of injectable HPC (Makena and its generics) and compounded HPC from bulk power during the 2nd or 3rd trimesters. We assessed three obstetrical conditions of interest as potential reasons for use: (1) history of preterm delivery, (2) preterm labor in the current pregnancy, and (3) cervical shortening in the current pregnancy. We evaluated the temporal trend of HPC use over the study period. Among pregnancies with injectable HPC use, we calculated the percentage of those with diagnoses for each related obstetrical condition; and the percentage of pregnancies with diagnoses for any of three related obstetrical conditions.

Results: We identified a total of 3,451,121 live-birth pregnancies (among 2,912,911 women) between 2008 and 2019 in the SDD. Of these pregnancies, 16,535 showed use of injectable HPC during the 2nd or 3rd trimesters. The yearly proportion of pregnancies with injectable HPC use increased over the study period from 0 in 2010 to 13 per 1,000 pregnancies in 2018; use of compounded HPC decreased from 4 to 0.25 per 1,000 pregnancies over the same time. Of 16,535 pregnancies with injectable HPC use, 6,443 (39%) had recorded history of preterm delivery and 12,060 (73%) had at least one related obstetrical condition.

Conclusions: We found modest use (about 1.3% in 2018) of HPC during the 2nd or 3rd trimesters of live-birth pregnancies in SDD. A high percentage (73%) of pregnancies with injectable HPC use had at least one obstetrical indication of interest.

2471 | The association between adherence to multiple chronic medications and healthcare utilisation in older community dwelling adults with multimorbidity

Caroline A. Walsh, Caitriona Cahir and Kathleen E. Bennett
Royal College of Surgeons in Ireland, Dublin, Ireland

Background: The evidence on measurement of adherence to multiple medications in older adults with multimorbidity is lacking.

Objectives: To (i) estimate medication adherence and identify patterns of suboptimal medication adherence in older people with multimorbidity and (ii) estimate the association between suboptimal adherence and healthcare utilisation.

Methods: This is a prospective cohort study using linked data from a national pharmacy claims database and Waves 1 and 2 of The Irish LongituDinal study on Ageing (TILDA). Morbidity was measured by the Rx-RiskV algorithm which classifies drug claims (ATC codes) into chronic disease classes. Participants with multi-morbidity and aged ≥70 years at wave 1 were identified by ≥2 RxRiskV conditions in the 6 months prior to wave 1 (baseline). Participants were included if they had ≥2 dispensings of the baseline RxRiskV medications in the 12 months after wave 1. Average adherence across RxRiskV conditions was estimated using continuous multiple-interval measure of medication availability (CMA7 function in AdhereR) over 12 months. Group-based trajectory models (GBTM) were used to group participants' adherence patterns. Negative binomial regression was used to estimate the association between adherence (average adherence and groups) and the number of self-reported primary care physician (GP) visits, Emergency department (ED) visits, outpatient visits and hospitalisations in the 12 months preceding wave 2. Adjusted IRR (aIRR) and 95% CIs are presented.

Results: In total 1050 participants were included. Average adherence among the population was 71% (SD 16%). GBTM identified 6 distinct adherence groups; (1) rapid decline, modest increase, (2) small decline, steep increase, (3) initial high adherence, rapid decline, (4) initial high adherence, delayed decline, (5) stable high adherence and (6) initial low adherence, rapid discontinuation. Higher average adherence was associated with a significant decrease in the number of GP visits (aIRR 0.70, CI 0.53, 0.94) and outpatient visits (aIRR 0.44, CI 0.23, 0.81). In comparison to group 5, group 1 membership (aIRR 1.72, CI 1.09, 2.73) and group 4 membership (aIRR 1.92, CI 1.19, 3.05) significantly increased the number of ED visits. Membership of group 6 significantly increased the number of outpatient visits in comparison to group 5 (aIRR 1.51, CI 1.08, 2.12).

Conclusions: Suboptimal medication adherence in older adults with multimorbidity increases healthcare utilisation. Interventions should target those with poor adherence patterns.

2490 | Comparison of a new three-item self-reported measure of adherence to medication with pharmacy claims data

Julie C. Lauffenburger[1], Constance P. Fontanet[1], Thomas Isaac[2], Chandrasekar Gopalakrishnan[1], Thomas D. Sequist[1], Joshua J. Gagne[1], Cynthia A. Jackevicius[3], Michael A. Fischer[1], Daniel H. Solomon[1] and Niteesh K. Choudhry[1]
[1]*Brigham and Women's Hospital, Harvard Medical School, Boston, MA;* [2]*Atrius Health, Newton, MA;* [3]*Western University of Health Sciences, Pomona, CA*

Background: Less than half of patients with cardiometabolic disease consistently take prescribed medications. While health insurers and some delivery organizations use insurer claims to measure adherence, most do not have rapid access to these data during routine interactions given administrative lag. Self-reported scales exist, but their practical utility is often limited by costs or length. By contrast, the accuracy of a new, free 3-item self-reported measure has been demonstrated in individuals with HIV but to our knowledge has not yet been compared with insurer claims or evaluated in other conditions.

Objectives: To evaluate the concordance between this self-reported tool and claims-based adherence measures in patients with cardiometabolic disease.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: We used a linked pharmacy claims and electronic health record (EHR) dataset from a recently-completed pragmatic trial of patients with cardiometabolic conditions. After 12 months of follow-up, intervention subjects were mailed a survey with the 3-item measure that queries about medication use in the prior 30 days. As in prior research, responses were linearly transformed and averaged. Adherence was also measured in pharmacy claims in Month 12 and Months 1-12 of the trial using proportion of days covered (PDC) metrics. We compared sensitivity, specificity, and likelihood ratios (LR) for non-adherence between self-report (average<0.80) and claims (PDC<0.80) as the referent and varied the survey cutpoint for "non-adherence" as a sensitivity analysis.

Results: Of 459 patients returning the survey (response rate: 43.5%), 50% were non- adherent in claims in Month 12, while 21% were non-adherent based on the survey. Compared with claims, the specificity of the 3-item metric was high (Month 12: 0.93), and sensitivity was relatively poor (Month 12: 0.25). Positive and negative LRs were 1.46 (95%CI: 1.01-2.09) and 0.91 (95%CI: 0.82-1.00), respectively. Survey measures were similarly accurate for longer (12 month) claims measurement windows (e.g., Sensitivity: 0.24 and Specificity: 0.87 in Months 1-12). Varying the cutpoint for non-adherence to <0.90 and <1.0 for the survey improved accuracy.

Conclusions: A new 3-item self-reported adherence measure has high specificity but poor sensitivity for non-adherence compared to pharmacy claims in cardiometabolic disease. This tool may be useful for clinicians or healthcare organizations to identify those needing adherence support in the absence of rapid access to claims data, as any admission of non-perfect adherence could potentially prove actionable.

2517 | Almost half of seniors initiating oral bisphosphonate therapy are exposed for 3 or more years - Understanding the benefits and harms of prolonged therapy is needed

Kaleen N. Hayes[1], Kevin Brown[1], Angela Cheung[1], David Juurlink[1], Nancy He[2] and Suzanne M. Cadarette[2]

[1]University of Toronto, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada

Background: Oral bisphosphonates (BP, alendronate and risedronate) are the primary drugs used to treat osteoporosis in Canada. Clinical guidelines recommend at least 3 years of BP therapy to reduce fracture risk. The benefits and harms of continued therapy is uncertain. Rare but serious adverse events are associated with BP use >5 years.

Objectives: To describe patterns of long-term (≥3 years) BP use.

Methods: The Ontario government covers prescription drugs listed on the public formulary for residents aged ≥65 years. This includes alendronate and risedronate since 2000/11 for women and 2003/07 for men. We identified first dispensation of BP drugs among adults aged ≥66 years from 2000/11 to 2016/12, and followed them forward until death or 2019/12 to identify patients with ≥3 years of BP use (proportion of days covered ≥80%, using 3-year rolling window approach after each BP dispensation). Patterns of long-term BP use were described based on length of time between first BP dispensation and the start of long-term therapy period, and compared between men and women.

Results: We identified 260,784 eligible seniors initiating BP therapy in Ontario, mean age=75.4 (SD 7.1) years, 77% women, 57% risedronate. Of these, 47% (n=121,786) met criteria for long-term therapy, mean age=75.0 (SD 6.7) years, 79% women, 55% risedronate. The mean length of BP therapy was 7.6 (SD 3.4, median 6.9, 99th percentile 16.6) years for women and 6.7 (SD 3.0, median 6.0, 99th percentile 15.1) years for men. Overall, 31% of patients (33% of women, 26% of men) were treated for ≥5 years. Eighty percent met criteria for long-term therapy after their first BP dispensation, 6% had a gap <12 months, and 14% had a gap of ≥12 months. Eleven percent of long-term therapy patients switched between alendronate and risedronate, and 35% switched between brand and generic formulations. The annual number of patients undergoing long-term BP therapy increased steadily from 2001 (n=3,079) until peaking in 2007 (n=15,649), then decreased annually thereafter, reaching n=5,783 in 2016.

Conclusions: Almost half of patients initiating oral BP are exposed to long-term therapy, with 80% meeting a minimum 3 years of therapy after their first BP dispensation and 31% continuing therapy for at least 5 years. The benefits and harms of continuing BP therapy beyond 3 years are needed to inform the true effects of long-term exposure. Better understanding of switching between alendronate and risedronate and brand and generic formulations will inform studies that consider the relative effects of prolonged BP therapy.

2520 | Anti-hypertensive drug prescribing pattern, adherence to guidelines and blood pressure control at a teaching hospital in Ghana

Mark A. Harrison[1], Kwame O. Buabeng[2], Afia FA Marfo[2], Florence A. Nkansah[3], Franklin Acheampong[3], Godwin Gulbi[1], Daniel K. Arhinful[4] and Daniel NA Ankrah[3]

[1]Korle Bu Teaching Hospital, Accra, Ghana; [2]Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [3]Korle Bu Teaching Hospital, Accra, Ghana; [4]Noguchi Memorial Institute for Medical Research, Accra, Ghana

Background: Blood pressure (BP) control is low in many low and middle income countries, despite various therapy options. Current guidelines can help achieve outcomes improvement. Therefore, guideline adherence needs to be studied.

Objectives: To evaluate the pattern of anti-hypertensive (anti-HPT) drug prescribing, its adherence to hypertension treatment guidelines by clinicians at the Korle Bu teaching hospital (KBTH) and association with blood pressure control.

Methods: Over a 3-month period, we carried out a cross-sectional study of hypertensive out-patients attending the KBTH polyclinic for treatment. After patients were selected, their medical notes were reviewed to collect data on: patient demographics and BP; the pattern

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of anti-hypertensive drug class and combination prescribing; level of generic and single pill combination (SPC) prescribing. Adherence to guidelines was measured as prescribing pattern conformity to recommendations by the 2018 European Society of cardiology (ESC) and the 2017 Ghana Standard Treatment Guidelines (STG).

Results: Out of 310 questionnaires 304 were completed, and 31.6% were diabetic. Monotherapy and dual therapy were 18.8% (n=57) and 52.6% (n=160) respectively. The 5 leading drugs, calcium channel blockers (CCB), diuretics, angiotensin receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACE-I), and beta blockers were given to 86.8% (n=264), 45.7% (n=139), 33.2% (n=101), 27% (n=82), and 11.8% (n=36) of patients respectively. Majority (71.4%; n=217) were on amlodipine. For 2 drugs, 50% (n=80) were CCB plus a renin-angiotensin system (RAS) blocker. The most common were CCB plus diuretic (37.1%), CCB plus ACE-I (23.8%) and CCB plus ARB (26.2%). SPC and generic prescriptions were 2.8% (n=7) and 84.5% (n=256) respectively. BP control was 41.8%. The 5 leading drugs agreed with 1st line recommendations of the 2017 Ghana STG. The 5 leading drugs and pattern of combination therapy agreed with 2018 guidelines of the ESC. The number of anti-HPT drugs was negatively associated with BP control with significance. (B= -0.402; p-value=0.015). Amlodipine, indapamide and hydrochlorothiazide were more likely to result in BP control (OR=1.53, 95% CI: 0.91 - 2.58; OR=1.7, 95% CI: 1.54 - 1.89; OR=1.7, 95% CI: 1.55 - 1.87).

Conclusions: Anti-hypertensive drug prescribing was based on the 5 major drug classes, and the majority of patients received 2 drugs (CCB and RAS blockers). Prescribing pattern agreed with the Ghana and ESC guidelines but SPC prescribing needs to be improved. CCB and diuretics are more likely to control BP in Ghanaians.

2532 | Impact of delays in initiation of adjuvant endocrine therapy on survival among patients with breast cancer

Kimberley Lee[1], Jodi Segal[2] and Lisa Jacobs[3]

[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [2]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [3]*Johns Hopkins School of Medicine, Baltimore, MD*

Background: Time to adjuvant endocrine therapy concerns patients and clinicians, but its impact on overall survival is not clear. There are no population level studies that address this question.

Objectives: To describe the relationship between time from diagnosis of breast cancer to start of adjuvant endocrine therapy (AET) and overall survival.

Methods: This is a population-based cohort study using population level data from the National Cancer Database (NCDB). The NCDB prospectively collects data on incident cancer cases from over 1500 Commission on Cancer-accredited facilities in the United States. The participants are women with Stage II and III estrogen or progesterone receptor positive (HR+), human epidermal receptor 2 negative, invasive breast cancer who underwent definitive surgical treatment. Multivariable Cox proportional hazards regression analyses were used to assess the impact of time to endocrine therapy on overall survival, after adjusting for patient, demographic, tumor-, and treatment-related factors.

Results: Of the 391,594 women in this study, 12,162 (3.1%) began treatment with adjuvant endocrine therapy more than 12 months after initial diagnosis of HR+ invasive breast cancer. Mean age at diagnosis was 59.7 years (SD 13.4). Predictors of delayed initiation of AET include Black race or Hispanic ethnicity (adjusted odds ratio [aOR] of Black vs White, 1.57; 95% CI, 1.48-1.66; P<.001, Hispanic vs White, aOR 1.22, 95% CI 1.13-1.32; P<.001), Insurance other than private insurance (Medicare vs Private, aOR 1.09, 95% CI 1.01-1.17; P=.007, Medicaid vs Private, aOR 1.36, 95% CI 1.28-1.45; P<.001), higher stage of disease at diagnosis (Stage III vs II, aOR 1.24, 95% CI 1.19-1.30; P<.001), and delayed surgery or chemotherapy (Delayed surgery vs On-time lumpectomy, aOR 2.76, 95% CI 2.60-2.93; P<.001 and Delayed chemotherapy vs no chemotherapy, aOR 11.5, 95%CI 10.6-12.5). With median follow-up of 63.2 months, 67,335 (17.2%) patients died by the end of follow-up. Delayed initiation of AET resulted in no change in the hazard of death (HR, 1.00; 95% CI, 0.95-1.05; P=.97) compared to initiation within 12 months of diagnosis after adjusting for age, race and ethnicity, insurance type, urban vs rural residence, neighborhood income and education, comorbidity, cancer grade, stage, and receipt of timely or delayed surgery, chemotherapy, and/or radiation therapy.

Conclusions: These results suggest that there may be no detriment to survival if initiation of adjuvant endocrine therapy occurs 12 to 24 months after initial diagnosis compared to within 12 months of diagnosis as currently recommended.

2543 | Community pharmacy practice evaluation in the United Arab Emirates using simulated patients with common cold

Subish Palaian[1], Muaed Al Omar[1], Nageeb Hassan[1], Dina Mourad[2], Waad Ahmed[2] and Arig Ewida[2]

[1]*College of Pharmacy and Health Sciences, Ajman University, Ajman, United Arab Emirates;* [2]*College of Pharmacy and Health Sciences, Ajman University, Ajman, United Arab Emirates*

Background: Patients seek medical advice from pharmacists regarding minor ailments. Pharmacists on the other hand are expected to counsel patients appropriately and dispense medications rationally. Simulated client method using 'Mystery patients' provides opportunity to investigate and explore actual dispensing practices (including client-provider interactions).

Objectives: To explore the dispensing and counseling practices of community pharmacists in United Arab Emirates.

Methods: A simulated client study was conducted among a conveniently selected 34 community pharmacies in Ajman, UAE in January 2020. Three simulated clients (third year pharmacy students) visited community pharmacies and exhibited symptoms of common cold (ICD-10 code J00). Uniformity was maintained while exhibiting symptoms across pharmacies and each of them exchanged their roles

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

routinely across encounters. Ethical approval was obtained for the research and pilot tested with three pharmacies. Filled checklists were analyzed and statistical analysis performed using Pearson correlation coefficient and independent t-test at α =0.05.

Results: The Simulated clients' interaction was with 9 female and 25 male pharmacists, five Arabs versus 29 non-Arabs. All pharmacists dispensed at least one medicine (average 3.08; n=105). Most common therapeutic category was antihistamines (21.90%; n= 23), followed by expectorants (16.19%; n=17). Commonly dispensed medicines were pseudoephedrine+Loratidine combination (n=8; 7.61%), followed by guaifenesin+pseudoephedrine+dextromethorphan+paracetamol in 6 (5.71%) cases. Only 12 pharmacists counseled on 'treatment duration' and none asked about 'medical history'. The labeling 'when to take' was mentioned by 20 (58.82%) pharmacists with the average dispensing time of 37.20± 25.97 seconds. Dosage regimen was appropriately chosen in 22 (64.70%) pharmacies. The average cost of medicines per patient was AED 55.32±36.93 (1 USD= 3.67 AED). Only one pharmacist counseled on medication allergy, 4(11.76%) on side effects, 2(5.88%) on contraindications, 3(8.82%) on drug-drug interactions and 31(91.17%) pharmacists provided appropriate instructions on medications usage. The average counseling time was 75.29 ± 74.62 seconds. Counseling duration had a positive correlation with cost (p=0.015), dispensing duration (p=0.000) and associated with race (p=0.003) but not gender (p= 0.8).

Conclusions: Pharmacists spent less time in understanding patients' condition and counseling. They were predominantly selling medicines with little or no information on safe and effective usage.

2585 | Longitudinal cumulative dose: A novel measure to evaluate multiple dimensions of chemotherapy adherence over time

Michael A. Webster-Clark[1], Alexander Keil[1], Hanna K. Sanoff[2], Til Stürmer[1], Daniel Westreich[1] and Jennifer L. Lund[1]

[1]*University of North Carolina, Chapel Hill, NC;* [2]*University of North Carolina, Chapel Hill, NC*

Background: Adjuvant chemotherapy regimens take months to complete, as do many other pharmacologic treatments. Despite this, clinical trials and observational studies often evaluate chemotherapy adherence via measures assessed at the end of treatment or end of an arbitrary time period (e.g. proportion of patients missing any dose, relative dose intensity [RDI], proportion of days covered). This approach may miss information patients and providers value that impacts outcomes, like timing of treatment delays.

Objectives: We sought to explore longitudinal cumulative dose (LCD) as a way to integrate the impact of dose reductions, missed doses, and dose delays at each visit on treatment received over time.

Methods: We obtained data from the 2,246 participants in the Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer (MOSAIC). We evaluated proportions of patients stopping treatment early, reducing a dose (based on the trial's protocol), missing a dose, or delaying a dose in each treatment arm for each chemotherapeutic agent at each visit. We obtained LCD, the fraction of the final standard dose a participant reached by a given day, for each participant and each chemotherapeutic agent. We compared LCD medians and interquartile ranges over time and at the end of the standard regimen (24 weeks) between and within treatment arms with respect to age and performance status. We also assessed agreement between LCD and RDI with Fleiss' kappa.

Results: Participants randomized to FOLFOX were more likely than those randomized to 5FU to stop treatment, reduce doses, miss doses, or delay visits; these differences increased over time. Median LCD for oxaliplatin in the FOLFOX arm at 24 weeks was 77%. Graphs of median LCD for 5FU showed a clear difference between arms (FOLFOX arm median LCD: 81%; 5FU arm median LCD, 96%). While 5FU LCD decreased with age in the FOLFOX arm (median LCD in those age <40: 85%; 40-64, 82%; 65-75, 76%), it was similar across ages in the 5FU arm (median LCD of 94%, 96%, and 96%, respectively), with smaller trends for performance status. There was only fair agreement between RDI and LCD (Fleiss' kappa of 0.34); 19% of those with RDI over 85% had LCD under 60%.

Conclusions: Visualizing the LCD highlighted the timing and scale of deviations from standard courses of therapy and illustrated major differences in 5FU treatment across arms. Next steps include evaluating how well LCD predicts clinical outcomes as an integrated measure of adherence as well as exploring deviation from the ideal LCD as a way to measure adherence to other types of interventions.

2603 | Antihypertensive polytherapy in Australia: Prevalence of inappropriate combinations, 2013-2018

Michael O. Falster[1], Nicholas A. Buckley[2], David Brieger[3] and Sallie-Anne Pearson[1]

[1]*University of New South Wales, Sydney, Australia;* [2]*University of Sydney, Sydney, Australia*[3]*Concord Hospital, Sydney, Australia*

Background: Antihypertensive polytherapy plays a significant role in treating hypertension and is endorsed increasingly in hypertension guidelines. There has been little population-based research to better understand how antihypertensive combinations, particularly inappropriate polytherapy, are used in routine clinical care.

Objectives: To estimate the prevalence of inappropriate antihypertensive polytherapy in Australia.

Methods: We conducted a retrospective cohort study using pharmaceutical claims data. We used a nationally representative 10% sample of Pharmaceutical Benefits Scheme (PBS) eligible Australians and their dispensing history to identify people aged 18+ years exposed to at least one PBS-listed antihypertensive, 2013-2018. We measured annual: prevalence of antihypertensive polypharmacy (≥40 days concomitant exposure), inappropriate antihypertensive combinations (against guideline recommendations; within-class polytherapy) and combinations to be used with caution.

Results: Almost half (47.5%) of people using antihypertensives in 2018 experienced polytherapy. Among these, 2.4% had an

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

inappropriate combination (1.5% against guidelines; 1.0% within-class polytherapy). Inappropriate combinations were more prevalent in people experiencing polytherapy with three (3.7%) or four (16.1%) antihypertensive medicines than people on dual therapy (0.7%). Inappropriate combinations occurred at a lower rate in people using fixed-dose rather than free-drug combinations for dual therapy (0% vs 0.7%; p<0.01) and in those using three antihypertensives (2.4% vs 7.3%; p<0.01); this was not the case for people using four or more antihypertensives (15.5% vs 16.1%; p=0.39). Between 2013-2018 the prevalence of antihypertensive polytherapy was relatively stable (49%-47%), however the prevalence of inappropriate combinations among these patients halved (from 5.1%-2.4%).

Conclusions: Antihypertensive polytherapy in Australia is common, but the prevalence of inappropriate combinations is low and is decreasing, suggesting strong awareness of Australian clinical guidelines. However, in 2018 approximately 49,000 Australian adults experience inappropriate polytherapy; prescribing of fixed-dose combinations in patients on dual or triple therapy may further reduce this inappropriate care, although increased vigilance treating patients with >3 antihypertensives is required.

2604 | Long-term trajectories of medicine use among older adults experiencing polypharmacy in Australia

Michael O Falster[1], Rayan Charrier[1,2], Sallie-Anne Pearson[1], Nicholas Buckley[3] and Benjamin Daniels[1]

[1]University of New South Wales, Sydney, Australia; [2]École Polytechnique, Paris, France[3]University of Sydney, Sydney, Australia

Background: Polypharmacy (the concurrent use of five or more medicines) is often considered a marker of potentially inappropriate care. Patients experiencing polypharmacy may follow a diverse range of clinical pathways, yet there is little understanding about how the number and nature of medicine use changes over time.

Objectives: To identify common pathways of medicine use over time among older patients experiencing polypharmacy.

Methods: We conducted a retrospective cohort study using administrative pharmaceutical claims data for a 10% sample of Australian Pharmaceutical Benefits Scheme (PBS) beneficiaries. We identified people aged 70 years and over who were exposed to five or more medicines on February 15, 2014. Using group-based trajectory modelling, we explored changes in the quarterly number and type of medicines people used over a five-year period (2014-2018).

Results: In our cohort of 98,539 older people, we identified two groups of people experiencing polypharmacy encompassing seven distinct trajectories: sustained polypharmacy (77% of people, 4 trajectories); and decreasing medicine use (23%, 3 trajectories). Patients in sustained polypharmacy trajectory groups with a lower mean number of medicines (e.g. 6 unique medicines) had relatively stable trajectories, while those with a higher mean number of medicines (e.g. 15 unique medicines) experienced greater seasonal variation in both the number and type of medicines used. Within the sustained polypharmacy trajectories, patients retained on average two-thirds of their medicines of exposure (chemical substance level) between adjacent quarters. For patients in decreasing medicine use trajectories, the most common trajectory was a slight drop in medicine exposure within the first three months. Overall, 21% of patients were no longer experiencing polypharmacy after one year.

Conclusions: Polypharmacy among older patients is largely a chronic phenomenon, reflecting the nature of multimorbidity within this population. However, there is an underlying volatility in the medicines involved, reflecting both changes in treatment and seasonal fluctuation in medicine dispensing. Care must be taken when measuring and interpreting polypharmacy, as a single measure may not reflect a patients' sustained medicine use over time.

3740 | Quality of buprenorphine care for opioid use disorder

Kelly E. Anderson[1], Julia Eckstein[1], Christine E. Chaisson[2], Sarah H. Scholle[3], Lauren Niles[1,3], Sydney M. Dy[1], Brendan Saloner[1] and G. Caleb Alexander[1]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [2]OptumLabs, Cambridge, MA; [3]National Committee for Quality Assurance, Washington, DC

Background: Buprenorphine has unique advantages to treat opioid use disorder (OUD) that facilitate its use in ambulatory settings. Buprenorphine does not require complete opioid abstinence before initiation, and is not restricted to specialized treatment programs; however, clinicians must undergo training and receive a waiver to prescribe it. High-quality, effective buprenorphine treatment includes continuous medication use and the absence of prescription fills for other opioids.

Objectives: To characterize quality of buprenorphine care for OUD by quantifying buprenorphine initiation, engagement, and maintenance for individuals in a large, diverse, real-world cohort in the United States.

Methods: Retrospective cohort analysis of 33,617 commercial and Medicare Advantage enrollees aged ≥18 years in the OptumLabs® Data Warehouse diagnosed with incident OUD between 1/1/16 and 12/31/17, with insurance coverage gaps ≤45 days in the year before and after diagnosis. We calculated 5 measures of buprenorphine treatment quality for individuals with OUD. We analyzed the association of clinical and sociodemographic characteristics with quality of buprenorphine treatment using ordered logistic regressions. Finally, we conducted a survival analysis to examine patterns in treatment duration.

Results: Of the 33,617 individuals included in the study, 1,962 individuals (5.8%) received buprenorphine at least once in the 365 days following diagnosis (Measure 1 - Any Buprenorphine), and 1,421 individuals (4.2%) received buprenorphine within 14 days of diagnosis (Measure 2 - Initiation). Of the 1,421 individuals who initiated buprenorphine, 812 (57.1%) had ≥2 claims for buprenorphine within

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

34 days of initiation (Measure 3 - Engagement). Only 1,161 individuals (3.5%) had 180 days or more of covered buprenorphine treatment in the 365 days following diagnosis (Measure 4 - Maintenance). Of the 1,962 individuals eligible, 730 (37.2%) filled an opioid prescription within the 180 days after receiving buprenorphine (Measure 5 - Concurrent Opioid Prescription). Compared to individuals who were white, individuals who were black had a 33.8% reduction in the odds of receiving higher quality buprenorphine treatment (OR = 0.66, 95% CI: 0.55-0.80) and individuals who were Hispanic had a 24.6% reduction in the odds of receiving higher quality buprenorphine treatment (OR = 0.75, 95% CI: 0.62-0.91).

Conclusions: While buprenorphine can reduce mortality for individuals with OUD, we found widespread and enduring gaps in its use that extended beyond treatment initiation, and that reflect disparities in quality of care based on the sociodemographic characteristics examined.

3763 | Patterns of direct-acting antivirals (DAAs) use for hepatitis c: A population-based cohort study in France

Anne Bénard-Laribière[1], Elodie Pambrun[1], Elisabeth Polard[2], Pernelle Noize[1] and Antoine Pariente[1]

[1]*Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Team PHARMACOEPIDEMIOLOGY, UMR 1219, Bordeaux, France;* [2]*Pharmacovigilance, Pharmacoepidemiology and Drug Information Centre, Department of Clinical Pharmacology, Rennes University Hospital, Rennes, France*

Background: DAAs have revolutionized the prospect of ending HCV epidemic over the coming years; but these were launched at very high prices in 2013, leading to a prioritization strategy for access to treatment based on fibrosis stage or high risk of transmission until May 2016 in France.

Objectives: To identify situations minimizing the likelihood of benefits for patients who initiated DAA treatment.

Methods: A population-based cohort study was performed using data from the French reimbursement healthcare system. New DAA users, who started treatment between September 2013 and June 2017, were followed until December 2017, date of death, or end of data availability. DAA exposure was estimated by using dates of successive DAA reimbursements, each reimbursement allowing 28 days of treatment. Discontinuation of DAA treatment episode was considered if no reimbursement was issued within 42 days after the last reimbursement. This study assessed patient characteristics, treatment duration, adherence to DDAs, retreatment of patients who failed after their first DAA regimen.

Results: The 2013-2017 cohort of new DAA users comprised 43,474 individuals. Median age was 55 years (IQR 50-64y); most were male (59.3%). Changes in patient characteristics were noticed after the announcement of the universal access to DAAs in 2016: women were prescribed DAAs more frequently, and access to DAAs for younger HCV infected patients with a non-advanced disease stage was enlarged. Nearly 92% of new DDA users (n=39,840) had a single treatment episode, during which 97% of drug regimens complied with the recommendations. Non-compliant regimens mostly consisted of monotherapy of DAAs that are indicated in combination with other DAAs or ribavirin (RIB), especially sofosbuvir (SOF). Single reimbursement of DAA was uncommon (5 to 9% of users according to the DAA). More than 75% of users of elbasvir/grazoprevir, ledipasvir/SOF, velpatasvir/SOF, and ombitasvir/paritaprevir/ritonavir (OPr) + dasabuvir had duration of use that complied with recommendations; it was between 60 and 70% for users of simeprevir/SOF, daclatasvir/SOF, and OPr + RIB. One third of users of SOF + RIB had adequate duration of use. Nearly 5% of new DAA users were considered as non-adherent. Retreatment of patients who failed after DAA regimen was estimated to be nearly 3%.

Conclusions: Results, obtained at a nationwide level, suggested optimal patterns of DAA use, allowing to expect benefits for patients: DDA use mostly complied with recommendations of treatment combination and duration of use, with low rates of non-adherence and of retreatment after DAA regimen failure.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3803 | Assessment of drug utilisation evaluation of anti-retroviral therapy and medication adherence behaviour of patients receiving medication at a district hospital in South India

Adepu Ramesh, Sonali Bendeskar, Akhila Gandikota and Divya Ramulakollu
Vikas College of Pharmaceutical Sciences, Suryapeta, Nalgonda, India

Background: Use of HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) has substantially reduced the death rate and made AIDS as manageable. a minimum of 95% adherence to medication is essential to keep the viral load under control. In India, National AIDS Control Organisation guidelines are followed to treat HIV patients. Thus it is essential to assess the prescription pattern of ART and its outcomes.
Objectives: To assess the drug utilization pattern of ART in HIV patients visiting a local ART center and also to study the medication adherence behavior among the study patients.
Methods: A prospective observational study was carried out. Details of demographic, clinical, laboratory and the treatment initiated were collected on a daily basis for new cases and the add on data was collected for old cases. Using standard National AIDS Control Organisations guidelines, staging and treatment pattern was assessed. Morisky Medication Adherence Scale-8 was applied for assessing the medication adherence behavior.
Results: During the study period, a total of 505 HIV patients were enrolled and analyzed. Among them, the majority of patients were women (61%), between the age group of 31-45(49.7%) and illiterate (52.6%). The major mode of transmission was intimate contact (74%) and the majority were in Stage I (49%). TLE regimen was prescribed in 69.9% of patients and for children, the prescribed regimen was ABC,3TC, EFV (5.1%). Nearly 220(43%) patients were found with medium adherence.
Conclusions: This study concludes that the most prescribed regimens constituted a combination of TLE [Tenofovir + Lamivudine + Efavirenz] and the majority of patients were found with medium adherence.

3849 | Medication errors: A perspective from four hospitals in rural Kenya

Perpetua Karanja
Kirinyaga County, Kerugoya, Kenya

Background: Medication errors contribute to patient morbidity and mortality and are a major concern in patient safety. Medication errors are common, preventable and can occur at any stage of medication use such as prescribing, dispensing and administration. Medication error reporting is important to ensure medication safety and identify areas of improvement in practice.
Objectives: To describe medication errors reported routinely in four rural hospitals in Kenya.
Methods: This was a descriptive study of medication error reports received from four hospitals in rural Kenya in 2019. Data were extracted using a standardized medication error reporting form from prescriptions presented at the pharmacy departments of the four hospitals. The study population was patients visiting the hospitals who received prescriptions for their treatment. The data was then coded and entered into REDCap™ and analyzed using STATA 13.
Results: There were 54 reported medication errors, with about 70% being captured in the outpatient department. The errors were more common among female patients and amongst adults (18-59 years olds). More than half (52%) were reported in the largest of the four facilities. Out of these, 78% occurred at the prescribing stage and 19% at the dispensing stage. 85% of the medication errors were recognized and corrected before reaching the patient and 7% of these had a capacity to cause an error due to look-alike packaging. Only 4 % of the errors that reached the patient caused temporary harm while 9% caused no harm and 2% was unknown. Antibacterials were the most affected class of drugs at 39 % followed by antihypertensives at 11%. The wrong drug was the most common type of error at 33% followed closely by improper doses at 25%. Continuous medical education was the most recommended action at 81%; others were distinct packaging of medicines and direct supervision of trainees.
Conclusions: Prescribing errors are the most prevalent errors mainly affecting antibacterial agents hence the need for antimicrobial stewardship. Pharmaceutical personnel play a great role in identifying and preventing medication errors. Medical education should be done continuously to keep health care workers abreast of updates in health practice.

3878 | The opioid epidemic in the Netherlands, causes and consequences

Ajda Bedene[1,2], Eveline L.A. van Dorp[2], Tariq Faquih[1], Suzanna C. Cannegieter[1,3], Dennis O. Mook-Kanamori[1,4], Marieke Niesters[2], Monique van Velzen[2], Maaike G.J. Gademan[1,5], Frits R. Rosendaal[1], Marcel L. Bouvy[6], Albert Dahan[2] and Willem M. Lijfering[1]
[1]Leiden University Medical Center, Leiden, Netherlands; [2]Leiden University Medical Center, Leiden, Netherlands; [3]Leiden University Medical Center, Leiden, Netherlands; [4]Leiden University Medical Center, Leiden, Netherlands; [5]Leiden University Medical Center, Leiden, Netherlands; [6]Utrecht Institute for Pharmaceutical Sciences, University Utrecht, Utrecht, Netherlands

Background: Opioid use has risen in the Netherlands.
Objectives: To determine potential causes and consequences of the increased opioid prescription in the Netherlands.
Methods: Design: Cohort study.
Setting: Dutch national statistics from 2013 to 2017 and annual national Health Surveys from 2014 to 2017. We included the total Dutch population, e.g., 17,081,507 residents in 2017 and around 38,000 respondents of the national Health Surveys.
Exposures or interventions: opioids, nonsteroidal anti-inflammatory drugs (NSAIDs)
Main outcome measure: analgesics prescriptions, opioids and NSAIDs, hospitalizations and deaths due to opioid poisoning, and severity and prevalence of pain.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Statistical analysis: We conducted descriptive statistics into national prescription, hospitalization and mortality registry. We presented findings as proportions of the total population per calendar year, and as risk ratios (aRR) with 95% confidence intervals (CI), adjusted for age and sex with direct standardization, comparing annual incidence with the incidence of the reference year, i.e., 2013. Similar analyses were performed in the 2014-2017 Health Surveys where we selected 2014 as a reference year.

Results: From 2013 to 2017 the proportion of Dutch residents receiving opioid prescription rose from 4.9% to 6.0%. During this period, the use of NSAIDs decreased (15.5% and 13.7% of Dutch residents in 2013 and 2017, respectively), while the total number of individuals receiving prescriptions for any analgesic was largely unchanged (n=2,998,925 in 2013 and n=2,887,389 in 2017). Self-reported pain prevalence and severity remained constant over the observation period (44.7% of 5119 reported no pain-impeded activities of daily living in 2014, aRR, 1.00; [95% CI, 0.95-1.06] in 2017 vs 2014).

Simultaneously, we observed an increase in hospitalization and death due to opioid poisoning related to opioid prescription (3.4 and 6.6 per 100,000 inhabitants in 2013 and 2017, respectively) and to either in-hospital or illicit opioid use (5.2 and 6.3 per 100,000 inhabitants in 2013 and 2017, respectively). Of those hospitalized for opioid poisoning 3.9% of 1,343 died in 2013 and 4.6% of 2,055 in 2017. Duration of opioid poisoning hospitalization was prolonged over the observation time, as 15.3% of 1,343 patients were subsequently transferred to another health facility in 2013 and 21.3% of 2,055 in 2017.

Conclusions: We demonstrated that NSAIDs prescription decreased and opioid prescription increased in the Netherlands since 2013, without an increase in prevalence and severity of pain. Incidence of severe outcomes related to opioids increased over the observation period.

3936 | Prescribed daily doses of anti-dementia drugs in South Africa: A database analysis

Ilse Truter

Nelson Mandela University, Port Elizabeth, South Africa

Background: Few drug utilisation studies have been published in South Africa on anti-dementia medication management, despite a growing population of people with dementia. Memantine (an N-methyl-D-aspartate (NMDA)-receptor antagonist) and the anticholinesterases (donepezil, galantamine and rivastigmine) are used for symptomatic treatment. There is especially a paucity of information on the dosages in which these medications are prescribed.

Objectives: The primary aim of the study was to analyse the prescribing patterns of anti-dementia drugs, focussing on the Prescribed Daily Doses (PDDs).

Methods: A retrospective drug utilisation study on a section of the private healthcare system in South Africa for 2018 was conducted. All products in Anatomical Therapeutic Chemical (ATC) subgroup N06D (anti-dementia drugs) were extracted and analysed. Only the products that were reimbursed by the different medical insurance schemes were included in the study. Descriptive statistics were calculated.

Results: A total of 42 patients received 211 products in ATC subgroup N06D during the year. The average age of the 42 patients was 67.00 (SD=19.14) years. Only memantine (N06DX01), donepezil (N06DA02) and ginkgo biloba (N06DX02, one prescription) were reimbursed. Memantine accounted for 56.40% of prescriptions. For both memantine and donepezil, the originator and four branded generics were prescribed. Eighty percent of prescriptions were dispensed by community pharmacies, and the rest in hospitals. The prescriptions dispensed in hospitals were for small quantities for short term use and were not included in the dosage analysis. The average PDD of memantine was 22.13 (SD=12.75) mg, which is slightly higher than the Defined Daily Dose (DDD) of 20 mg. Specific average PDDs were 10 mg, 20 mg and 40 mg (with one 60 mg). The average PDD for donepezil was 9.23 (SD=1.82) mg (range: 5 mg to 10 mg), which is also higher than the DDD of 7.5 mg. Only three patients received both memantine and donepezil during the year, confirming that combination therapy was not common.

Conclusions: Anti-dementia drugs constituted a small percentage of prescriptions in this private healthcare setting. For both memantine and donepezil, the average PDDs were higher than the DDDs and recommended maximum maintenance doses. This may be as a result of reports that higher dosages of these active ingredients may result in better therapeutic outcomes in selected patients. Further studies are recommended.

3941 | A descriptive study of the clinical experiences of healthcare providers with the use and quality of oxytocin injection across the six geo-political zones of Nigeria

Chioma S. Ejekam[1], Chimezie Anyakora[2], Florence Nyangara[2] and Jude Nwokike[2]

[1]Lagos University Teaching Hospital, Lagos, Surulere, Nigeria; [2]United States Pharmacoepia(USP), Rockville, MD

Background: Oxytocin is recommended as an affordable and effective drug in the prevention of postpartum hemorrhage (PPH)-one of the leading causes of maternal morbidity and mortality in low- and middle-income countries (LMICs), however there are concerns about its proper use and quality in LMICs.

Objectives: To assess the knowledge, practices and experiences of healthcare-providers around oxytocin injection in their clinical practices in Nigeria.

Methods: This was a descriptive cross-sectional study that surveyed 6,299 healthcare-providers who deliver babies, recruited from 1,894 health facilities in Public (52%), Private (47%) and Nonprofit (<1%) sectors that offer obstetrics and gynecological services across 12 states in the 6 geo-political zones of Nigeria. Data were collected using an electronic questionnaire, analyzed using SPSS, and presented in frequencies and percentages. Funding support was provided by MSD for Mothers USA.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Overall, about 46% of respondents (52.8% in private; 40.0% in public facilities) had proper knowledge on the correct storage of oxytocin at +2-8°C. Proper knowledge also varied by state with highest levels in Jigawa (84.9%) then Nasarawa (70%), professional cadre (doctors>nurses>CHWs) and by years of experience in practice (those with less than 10 years > those with more than 10 years), and by sector (private sector >public sector). Only 34% of the respondents (41%-private and 27.5%-public sector) reported that oxytocin is properly stored in the refrigerator at +2-8°C in their healthcare facility. About 77.9% of the respondents used oxytocin for prevention of PPH, 66.7% for augmentation of labor and 52.6% for induction of labor. Surprisingly, about 1/3rd of CHWs used oxytocin for augmentation (32.8%) and for induction (31.6%), indications that they are unauthorized in. High percentages of respondents who used oxytocin for prevention of PPH used above 10IU (WHO-recommended dose) for primiparous (43.1%) and multiparous (49%) women. Respondents perceived that most of the existing oxytocin brands were effective, while 21% reported experiencing oxytocin failure.

Conclusions: Poor knowledge of healthcare-providers on the proper storage of oxytocin may have contributed to poor storage practices. The widespread use of oxytocin above the WHO-recommended dose might be an indicator of healthcare-provider concerns about oxytocin's quality. Hence, clinical guidelines and trainings of healthcare-providers on the use of oxytocin for PPH prevention should be developed and applied to ensure oxytocin quality.

3954 | Anti-diabetic drug utilization knowledge and glycemic index control in patients with uncontrolled diabetes mellitus

Naima Ahmed Tamanna
Islamic University, Kushtia, Bangladesh

Background: Diabetes has become the seventh leading burden of diseases in South Asia. Roughly 1 in 13 achieves treatment targets to keep control of the glycaemic index, one of the reasons may be lack of diabetic drug utilization knowledge. However, there is not much research done on the impact of drug utilization knowledge to achieve glycaemic control in Bangladesh.

Objectives: We aimed to investigate the proper anti-diabetic drug use and glycemic control among uncontrolled diabetic patients.

Methods: A prospective intervention study carried out from September 2017 to August 2018 in BIRDEM General Hospital, Bangladesh. A structured diabetic education regarding the disease, medication adjustment (e.g. Metformin) and glucose monitoring including exercise management was provided to each patient separately and patients were followed in 3 months. Data were analyzed using a logistic regression through SPSS.

Results: Metformin was used for 47% patients and 59% of patients took Metformin plus Insulin. For the intervention group, the average HbA1c significantly ($p < 0.001$) changed from baseline (11.59±2.48) to end of the follow-up (7.55±0.58). Similarly, Systolic Blood Pressure and Diastolic Blood Pressure changed from (138.31±15.73) to (126.90±11.15) and from (83.33±6.50) to (80.24±4.12), respectively ($p < 0.001$). Higher educated patients were more likely to have improved on glycemic control than lower educated patients [OR=1.5, CI=0.24-9.30].

Conclusions: Proper knowledge on anti-diabetic drug utilization can help in glycemic control to include prevention of diabetes, improved quality of life and delaying of complications.

4046 | Titration: Where is the real-world evidence?

Aisling R Caffrey[1,2,3] and Eric P Borrelli[1]
[1]*College of Pharmacy, University of Rhode Island, Kingston, RI;* [2]*Providence Veterans Affairs Medical Center, Providence, RI;*[3]*School of Public Health, Brown University, Providence, RI*

Background: Drug titration is an individualized, patient-centered approach to dosing medications with a narrow therapeutic index in order to optimize therapeutic benefit while minimizing risk of adverse effects, and is commonly used with anticoagulants, anticonvulsants, antidepressants, antidiabetics, antipsychotics, opioids, stimulants, and certain antibiotics.

Objectives: To describe the complexities of drug titration and present examples which illustrate challenges in measuring titration schedules in clinical practice.

Methods: A literature review was conducted to identify various approaches to drug titration and challenges with drug titration, including real-world evidence supporting titration. Additionally, the de-identified Optum Clinformatics DataMart™ (2010-2015) and national Veterans Affairs (VA) data (2014-2018) were utilized to identify possible medication titration with anticonvulsants in clinical practice, based on days supply and quantity, or sig, respectively.

Results: Drug titration may occur as up-, down-, or cross-titration depending on whether the goal is to reach or maintain a therapeutic level, decrease the risk of adverse effects, and/or prevent withdrawal/discontinuation syndromes or recurrence of disease. In clinical practice, wide variations in titration schedules exist due to a lack of evidence and consensus on titration schedules that achieve an optimal benefit-harm profile. Further, drug titration is challenging for patients to follow and requires greater coordination of care amongst providers. Despite labelled titration schedules for initiation of anticonvulsants, which would represent near universal titration, possible titration was only observed in 4.3% of patients (n=93,601/2,179,601) in the Optum Clinformatics DataMart™ cohort. Possible titration was most common among patients receiving lamotrigine (9.1%), valproate (7.4%), topiramate (7.3%), and oxcarbazepine (6.4%). Even in the VA data (n=309,740), where sig was available, sigs indicating titration were uncommon, and when sig titrations were available, they varied widely, even for the same medication, and did not indicate labeled titration (i.e. oxcarbazepine up-titration every two days rather than weekly).

Conclusions: Current data systems do not accurately reflect medication titration in clinical practice. As a result, real-world evidence from comparative effectiveness and comparative safety research with

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

titrated medications is lacking. Therefore, data system improvements are needed in order to accurately capture medication titration, so that titration approaches and associated clinical outcomes can be studied.

4048 | Fracture rates in patients discontinuing alendronate treatment in real-life: A nationwide cohort study

Bianka Darvalics[1], Anne Sophie Sølling[2], Diana H. Christensen[1], Torben Harsløf[2], Reimar W. Thomsen[1] and Bente Langdahl[2]
[1]*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark;* [2]*Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark*

Background: Based on the FLEX trial, it has become clinical practice to discontinue the bisphosphonate alendronate (ALN) after 5 years of treatment for osteoporosis. However, information on the fracture risk after ALN discontinuation in a real-life setting is sparse.
Objectives: To examine ALN discontinuation patterns and to compare fracture rates in patients discontinuing ALN after 5.0-5.5 years of treatment to fracture rates in patients continuing ALN treatment for more than 5.5 years.
Methods: We conducted a population-based cohort study using Danish health registry data. The source population was patients living in Denmark who had redeemed at least two ALN prescriptions between January 1st 1995 and September 1st 2017 (n=186,219). ALN discontinuation was defined as no prescription redemption within the days' supply of a prescription + a grace period of 8 weeks (stock piling method). Using an on-treatment approach, we followed patients with PDC ≥ 80% who either discontinued ALN after 5.0-5.5 years or continued ALN beyond 5.5 years from 5.5 years after their first ALN prescription until fracture, change of ALN exposure status, death, emigration, 5 years of follow-up or study end. We used Cox proportional hazard regression analyses to adjust for potential confounding factors associated with both ALN use and risk of fractures.
Results: We found that 25% of ALN initiators used ALN for less than one year and only 43% continued treatment for more than 5 years. The incidence rate of any fracture was similar in those who discontinued ALN (55.3 events per 1000 person-years) compared to those who continued ALN (55.4 events per 1000 person-years). ALN discontinuation after 5 to 5.5 years of treatment was not associated with an increased risk of vertebral fractures (hazard ratios (HR) 0.59, 95% CI 0.33-1.06), hip fractures (HR 1.04, 95% CI 0.75-1.45) or major osteoporotic fractures (HR 1.05, 95% CI 0.88-1.25), when compared with ALN continuation. These results were robust in an additional intention-to-treat analysis. We found similar results with varying grace periods, with 6 month delayed start of follow-up, and in age-, sex-, and calendar year-stratified analyses.
Conclusions: Less than half of all ALN initiators in Denmark continue treatment beyond 5 years. Discontinuation of ALN treatment after 5.0-5.5 years was not associated with a subsequently increased fracture risk within the first 5 years after discontinuation, when compared with patients who continued ALN for more than 5.5 years.

4049 | Inappropriate empiric treatment with antibiotics in a tertiary hospital, in Kenya

Zaietuni A. Mulaa[1], Maureen Nerima[2] and Hilda K. Daywa[2]
[1]*University of Nairobi, Nairobi, Kenya;* [2]*Trans-Nzoia County, Kitale, Kenya*

Background: Many studies have linked irrational and misuse of antibiotics with development of antibiotic resistance. Increase in antibiotic use may produce resistance at the individual patient level and an even greater resistance in the population which we may be unable to recover from and increased costs of treatment.
Objectives: To evaluate the patterns of use of antibiotics in tertiary hospital in Kenya for setting appropriate guidelines to promote rational use of antibiotics.
Methods: A retrospective observational study was conducted to evaluate use of antibiotics in tertiary hospital in Kenya January 2020. Primary data was retrieved for a period of eight months between May 2019 to December 2019 from the Pharmacy, laboratory and records department from the facility was reviewed. The study included all out patient prescriptions for which an antimicrobial was prescribed and excluded the inpatient prescriptions. Demographic data such as age, gender and duration of treatment was also collected. Inferential data analysis was done
Results: During that study period 13, 192 patients were seen in the hospital out of these 10,561 (80.1%) prescriptions were written and had at least one antibiotic prescribed. The most commonly used drugs were the β-lactams (penicillin and cephalosporin) 6,310 (59.7%), followed by the Nitro-imidazole 3,203 (30.3%), quinolones 593 (5.6%), macrolides 321 (3.0%) aminoglycosides 135 (1.3%). These antibiotics were mostly used empirically with no culture and sensitivity tests done to inform treatment. According to the evaluation, the use of the antimicrobial therapy was found to be rational in 28% of patients. The average number of antibacterial agents which were prescribed per patient per course of treatment was found to be 3. The Medication related problems identified included: choice of antimicrobial agent, dosage calculation and duration of treatment.
Conclusions: Responsible prescribing guided by guidelines and policies is important to ensure rational use of antibiotics and other antimicrobial agents. In 2017 the Ministry of health in Kenya launched the "national policy on prevention and containment of antimicrobial resistance". This is a great start, all the hospitals in Kenya should form an antimicrobial stewardship team to come up with facility tailored guidelines on antimicrobial use.

4189 | Valproate prescribing practices before and after implementation of risk minimisation measures (RMMs) in 5 European Countries

Massoud Toussi[1], Florence Coste[2], Margarita Shlaen[3], Dimos Vasilis[4] and Sigal Kaplan[5]
[1]*IQVIA, Paris, France;* [2]*Sanofi, Paris, France;* [3]*IQVIA, Munich, Germany;* [4]*DEMO S.A, Attiki, Greece;* [5]*TEVA Pharmaceutical Industries, Netanya, Israel*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Following the Pharmacovigilance Risk Assessment Committee's final recommendations regarding valproate medicines and their use in women of childbearing age (WCBA) (aged 13 to 49 years), label restrictions and RMMs (Direct Healthcare Professional Communication and educational materials) were implemented starting in November 2014 in various European countries. A drug utilisation study was performed by the Marketing Authorization Holders of valproate in Europe to assess the effectiveness of the measures.

Objectives: To describe the prescribing practices before and after the implementation of RMMs

Methods: A multinational non-interventional cohort study was conducted in the outpatient setting using electronic medical records databases (France, Germany, Spain, UK) and national registers (Sweden) based on data recorded from 2012 to 2018. The main outcome was the proportion of valproate initiations preceded by other medications related to valproate indications (mainly epilepsy and bipolar disorder) in women during the main 21-month pre-implementation period and 30-month post-implementation period. Furthermore, the incidence of pregnancies exposed to valproate in WCBA during the entire 36-month pre-implementation period and 36-month post-implementation period of RMMs was investigated.

Results: The proportion of valproate initiations preceded by medications related to valproate indications increased after implementation of RMMs in incident female users in Sweden (from 81.1% to 84.5%) and in UK (from 66.4% to 72.4%), it remained the same in Germany and Spain and decreased in France from 48.7% to 40.6%. In total, 451 and 182 pregnancies exposed to valproate were identified in the entire pre- and post-implementation periods, respectively. In Sweden and UK, where pregnancy data were most interpretable, the incidence of pregnancies exposed to valproate decreased in the post-implementation period: from 9.5 to 8.0 per 1000 person-years in Sweden and from 16.9 to 10.9 in UK.

Conclusions: The effectiveness of RMMs, as measured by change in proportion of valproate initiations preceded by medications related to valproate indications, varied by country (most effective in Sweden and UK and least effective in France). Although the incidence of pregnancies exposed to valproate decreased substantially, the results suggest limited effectiveness of the RMMs. Additional RMMs were implemented in 2018 and an extension study is under way to further monitor the use of valproate in WCBA.

4247 | Use of medication among nursing home residents: A Danish drug utilization study

Carina Lundby[1], John Jensen[2], Søren P. Larsen[2], Helene Hoffmann[2], Anton Pottegård[1] and Mette Reilev[3]

[1]Odense University Hospital, Odense C, Denmark; [2]Type2dialog, Kongens Lyngby, Denmark[3]University of Southern Denmark, Odense C, Denmark

Background: Use of medication with questionable benefit is common among nursing home residents. To facilitate more appropriate medication use and reduce drug-related complications in this vulnerable population, more insight into trends in medication use in relation to nursing home admission is needed.

Objectives: To describe drug use patterns in Danish nursing home residents.

Methods: We established a database of 5,179 individuals (63% women; median age of 84 years) admitted into 94 nursing homes across 11 Danish municipalities during 2015-2017. Data on prescription drug use and other census data were obtained from the nationwide Danish health registries and linked to individual-level data on nursing home admission.

Results: The total number of drug classes filled increased from a median of 6 drugs (interquartile range [IQR] 3-9) at 18-24 months before nursing home admission to a median of 8 drugs (IQR 6-11) just after admission, with the most common drug classes comprising paracetamol (61%), platelet inhibitors (41%), proton pump inhibitors (34%), statins (33%), and potassium supplements (31%). The incidence rate of new drug treatments increased from 21 new treatments/100 residents/month at 12-24 months before admission to a peak of 71 new treatments/100 residents/month in the month prior to admission, while it leveled off to about 34 new treatments/100 residents/month at 6-9 months after admission. The drug classes primarily responsible for this peak were laxatives, antibiotics, and analgesics. The largest absolute increases were seen for laxatives (53%), paracetamol (43%), and antidepressants (36%), all showing a marked increase up to and following admission. A high proportion of residents remained on therapy in the 3-year period following admission, with users of antidepressants and antidementia drugs being most persistent (76-85% still using these drugs after 3 years), followed by users of statins and bisphosphonates (66-70%) and opioids and benzodiazepines (49-58%), respectively.

Conclusions: We found that nursing home admission is associated with an increase in use of both preventive and non-preventive drug classes and that it remains on a level slightly higher than before admission. Although some drug classes may be of questionable benefit in individuals reaching the last years of life, a relatively high persistence to such treatment is common among nursing home residents.

4285 | Adherence and Persistence to Methylphenidate in Children in the Netherlands

Chii Chyi Cheung

Erasmus Medical Center, Rotterdam, Netherlands

Background: Several studies have examined factors that may contribute to adherence or persistence to methylphenidate, but these were mainly conducted in adults and not in children. In children, determinants of adherence and persistence likely differ as information about the family and child characteristics in relation to adherence and persistence to methylphenidate treatment is often limited.

Objectives: To study determinants of adherence and persistence to methylphenidate in children.

Methods: The study was conducted within the Generation R Study, a large population-based cohort study investigating children's health

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

from fetal life onwards in Rotterdam, the Netherlands. The study population included 307 children who all had at least one dispensing record of methylphenidate. Adherence was defined as a medication possession ratio (MPR) of 0.80 or higher and persistence as use until the onset of a continuous discontinuation period of 6 months or longer. Family and child characteristics were tested as determinants of adherence with multivariable logistic regression analysis. Persistence was evaluated using the Kaplan Meier curve.

Results: Children of nulliparous mothers (adjusted OR: 2.31, 95%CI: 1.17-4.54) or mothers with an average household income compared to high income were more likely to be adherent (adjusted OR: 3.45, 95%CI: 1.43-8.31). Girls were more often non-persistent than boys (adjusted HR: 1.44, 95%CI:1.07-1.95) and children who started treatment at age 12-16 were more often non-persistent than younger children (adjusted HR: 3.55, 95%CI:2.54-4.98).

Conclusions: In conclusion, the results of our study showed that not only children but also family characteristics may play a role in treatment adherence. Considering these findings, it is important for healthcare professionals to take these into account when initiating methylphenidate treatment.

4299 | The effect of a pharmacist intervention on guideline adherence for double and triple antithrombotic therapy in a clinical setting

Renate CAE Uden, van
Pharmacy Foundation of Haarlem Hospitals, Haarlem, Netherlands

Background: The use of antithrombotic therapy is a delicate balance between the risk of haemorrhage and thrombotic events. Guidelines on double and triple antithrombotic therapy advise to use this therapy for a limited period of time. A too long continuation exposes a patient to an unnecessary high bleeding risk.

Objectives: To determine the rate of double and triple antithrombotic therapy that is prescribed according to the guidelines in hospitalized patients, and to assess this rate after intervention from a pharmacist.

Methods: Design We performed a prospective intervention study in admitted patients using double or triple antithrombotic therapy. Patients were identified by an algorithm that was implemented in the hospital information system EPIC. Setting The study was performed in three general teaching hospitals in the Netherlands (two cardiovascular intervention centres and a non-intervention centre). The source population were admitted patients that were 18 years or older who used two or more antithrombotic agents, including at least an anticoagulant. Intervention All patients who used double or triple therapy were evaluated on a daily basis whether they had a guideline based indication for the therapy. If not, the pharmacist called the physician and discussed the therapy. Main outcome measures The primary endpoint was the proportion adherence to guidelines prior to intervention. Secondary endpoints were the proportion of patients who had a guideline based indication after intervention and the proportion where the physician intentionally deviated from the guidelines. Statistical analysis Descriptive statistics were used to determine the frequency of double and triple therapy in line with the guidelines. The effect of the intervention was analyzed using a McNemar test.

Results: Of the included 988 patients, 538 patients (54.5%) had a guideline based indication for the prescribed therapy. For 40 patients (4.96%) there was an intentional deviation from the guidelines. For the other patients the pharmacist made an intervention and advised to adjust the therapy. After intervention 922 patients (93.3%) were treated according to the guidelines. The difference in guideline based treatment before and after intervention was significant ($p < 0.0001$).

Conclusions: A considerable proportion of patients treated with double or triple antithrombotic therapy is not treated according to the guidelines. Evaluation of antithrombotic therapy and intervention by a pharmacist is a valuable addition for medication surveillance and may prevent bleeding events.

4304 | Treatment patterns and medication adherence among newly diagnosed migraine patients: A drug utilization study

Sara Mucherino[1], Valentina Orlando[1], Valeria M. Monetti[1], Ugo Trama[2] and Enrica Menditto[1]
[1]*Centre of Pharmacoeconomics, University of Naples Federico II, Naples, Italy, Italy;* [2]*Regional Pharmaceutical Unit, Campania Region, Naples, Italy, Italy*

Background: Guidelines for pharmacological treatment of migraine enlist acute or prophylactic approaches. A few studies are available describing utilization patterns of migraine drugs and adherence to prophylactic treatment.

Objectives: Study aims are: to describe the utilization patterns of migraine drugs at baseline; to evaluate adherence to prophylactic medications; to asses drug-related costs.

Methods: Retrospective population-based study in Primary care setting of Campania Region, Southern Italy. 12,894 subjects with any diagnosis of migraine as primary or secondary hospital discharge or at least 2 medical dispensations of migraine specific acute or prophylactic medication (triptans or pizotifen), were selected from 1 January 2016 to 31 October 2017. Those identified were classified into 4 treatment cohorts (no treatment, acute, prophylactic, both) based on type of migraine medication received, and were analysed (1 year follow-up). Utilization patterns of migraine drugs at baseline and annual drug costs per patient were analysed. Adherence to prophylactic treatment was the main outcome. Differences between patient characteristics were compared using chi-square test for categorical variables or unpaired t test for numerical variables, as appropriate. P value <0.05 was considered significant. Persistence rates were estimated using the Kaplan-Meier method and statistical differences between curves were assessed using Log-rank test.

Results: 81.1% of subjects received acute treatment as their initial therapy, 10.7% prophylactic and 8.2% both. Among those with acute treatment, 53% received triptans, 31.4% NSAIDs. Among those with prophylactic treatment, 31.7% received anticonvulsants. 599 were

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients treated with prophylactic medications. 26.2% were persistent to the initial treatment, while 73.8% interrupted it. Among these, 46.4% fully discontinued the treatment within 103 days (IQR 89.0), 31% restarted it after 46 days (IQR 60.0) from the interruption and 22.6% switched within 98 days (IQR 57.5) (p<0.001). Annual median drug cost was: €103 per patient treated with acute medications, €75 with prophylactic, €163 with both.

Conclusions: In Italian clinical practice migraine treatment with acute medications is still prevalent. A few patients started with prophylactic treatment and persistence was poor. Most of non-persistent patients tended to quit prophylactic therapy within three months from the beginning. These findings reflect an unmet need for improved prophylactic therapies for a better migraine management.

4323 | Adherence and risk factors for stopping treatment in a cohort of Quebec patients newly initiated on statins (OBSTAT cohort)

Sarasa MA Johnson[1,2], Manon Choinière[2,3], Michele Bally[2], Marie-Pierre Dubé[3,2], Jean-Claude Tardif[4], Daniel Gaudet[3], Jean Bergeron[5], Hélène Lanctôt[2] and Jacques Lelorier[1,2,3]

[1]CNODES (Canadian Network of Drug Effect Studies), Montreal, QC, Canada; [2]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal, QC, Canada; [3]Université de Montréal, Montreal, QC, Canada; [4]Centre de Recherche de l'Institut de Cardiologie de Montréal, Montreal, QC, Canada; [5]Centre de Recherche du CHU de Québec Université Laval, Quebec, QC, Canada

Background: Despite the demonstrated effectiveness of statins in reducing risk of cardiovascular events in high risk patients, adherence to treatment remains a barrier.

Objectives: To describe adherence of patients newly initiated on a statin, and identify potential risk factors for stopping treatment.

Methods: Patients newly initiating statin therapy in Montreal, Chicoutimi or Quebec City were invited to participate in this prospective cohort study. At baseline, eligible participants completed questionnaires detailing their personal and familial medical histories, context for statin initiation, lifestyle habits, and biological parameters. Patients were followed at 1, 3, 6, 9, 12, 18, and 24 months where treatment continuation status and potential side effects were recorded. Adherence was defined as taking statins during at least 80% of follow-up. Multivariate cox regression with forward selection was used to identify potential risk factors for stopping treatment.

Results: 1631 new statin-users were enrolled (mean age 57.4 yrs, 47.6% women, mean follow-up time 706.8 days). 33.6% of patients stopped treatment at least once during follow-up. 74.3% of patients were considered adherent. History of pain (HR=1.43), switching statins (HR=1.84) and mention of potential adverse effects by their physician (HR=1.22) increased the likelihood of stopping treatment. Family history of cardiovascular risk (HR=0.64), male gender (HR=0.73), perceiving controlling cholesterol as important (HR=0.49), and living outside Montreal (HR_{Quebec}=0.49, $HR_{Chicoutimi}$=0.81) were considered protective.

Conclusions: Almost three quarters of patients were adherent to treatment. Those who switched statins, had been made aware of potential adverse effects, or who had a history of pain were more likely to stop treatment.

4325 | Trends in fluoroquinolone use in the inpatient and outpatient settings in Nairobi, Kenya: A drug utilisation study

Sylvia A. Opanga, Yvonne L. Isaidi, Antony B. Kodiwo and Joy N. Waithaka

School of Pharmacy, University of Nairobi, Nairobi, Kenya

Background: Fluoroquinolones are used in management of various bacterial infections. Recent pharmacoepidemiological studies have linked them with adverse effects like blood sugar disturbances, aortic dissections, neuropsychiatric effects and tendon disorders, with global regulatory bodies recommending restriction of use.

Objectives: To describe fluoroquinolone prescribing and dispensing patterns in the inpatient and outpatient settings in Nairobi, Kenya.

Methods: A cross sectional study was conducted in the medical and paediatric wards of a leading referral hospital as well as four community pharmacies in Nairobi, Kenya, between April and July 2019. Data was collected through patient interviews and review of medical records and analysed descriptively using SPSS v26. Ethical approval was sought from the University of Nairobi/Kenyatta National Hospital Research and Ethics Committee.

Results: A total of 356 patients were enrolled in the community pharmacies, 115 in the medical wards and 122 in the paediatric wards. In the community pharmacy, the prevalence of fluoroquinolone dispensing was 15%, with ciprofloxacin being the most commonly dispensed. The indications for fluoroquinolone use in the outpatient setting were uncomplicated urinary tract infections (36.4%) and gastrointestinal infections (22.7%). Fluoroquinolones were dispensed over the counter without a prescription in 27% of the cases. In the medical ward, the prevalence of fluoroquinolone use was 13% (n=10), with the most common indication being intra-abdominal infections. In the paediatric ward, 3.8% of the patients were on fluoroquinolones, with the indications being conjunctivitis (75%) and otitis media (25%). In the medical wards and the outpatients, fluoroquinolones were prescribed in the presence of known risks factors of fluoroquinolone adverse effects while in the paediatrics, patients were evaluated for risk factors before prescribing.

Conclusions: Although fluoroquinolone use has dropped after regulatory restrictions, patients in the medical wards and outpatient settings were not screened for risk factors of developing fluoroquinolone adverse effects. Some outpatients received the drugs without a prescription. Regulation of community pharmacies is required to ensure adherence to fluoroquinolone dispensing policies. Assessment of patients for risk of adverse effects from fluoroquinolones should be done.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4375 | Adverse events related to overtreatment for hypertension in type 2 diabetes patients: impact of age and polypharmacy

Martina Ambrož[1], Sieta T. de Vries[1], Klaas Hoogenberg[2] and Petra Denig[1]

[1]*University of Groningen, University Medical Center Groningen, Groningen, Netherlands;* [2]*Martini Hospital, Groningen, Netherlands*

Background: Overtreatment for hypertension can lead to unwanted outcomes in people with type 2 diabetes (T2D). Too strict systolic blood pressure (SBP) targets may increase the risk of adverse events (AEs), particularly in older patients or patients with polypharmacy.

Objectives: To assess whether age and polypharmacy have an impact on the occurrence of AEs related to low SBP levels in T2D patients treated with antihypertensives.

Methods: We conducted a cross-sectional study using data from the Groningen Initiative to Analyze Type 2 diabetes Treatment (GIANTT) database, which includes primary care T2D patients from the north of the Netherlands. Included patients received chronic treatment with antihypertensive medication in 2012, were >18 years and had at least 1 SBP measurement in this year. The outcome was the occurrence of hypotension-related AEs. Determinants were low SBP level (<130 mmHg), older age (≥80 years), polypharmacy (5-9 or ≥10 drugs), and the interactions between age or polypharmacy and SBP. We conducted logistic regression analyses adjusted for confounders, such as sex, diabetes duration, diastolic blood pressure, and other risk factor levels, and present Odds Ratios (OR) with 95% Confidence Intervals (CI) for the effect of age or polypharmacy on AEs, and for their interaction with a low SBP level.

Results: We included 16,219 patients, 52% of which were females. In total, 16% were aged 80 years or older, 56% used 5-9 drugs and 30% used ≥10 drugs. The average SBP was 143 mmHg (SD 16), with a median number of antihypertensives of 2 (IQR 1-3). AEs were seen for 5.8% of patients with an SBP<130 mmHg and 5.0% of patients with an SPB≥130 mmHg. In older patients with an SBP<130 mmHg this was 8.3%; for polypharmacy (5-9 or ≥10 drugs) this was 4.7% or 9.2%, respectively. Both older age (OR 1.60, 95%CI 1.35-1.89) and polypharmacy (5-9 drugs: OR 2.13, 95%CI 1.56-2.92; ≥10 drugs OR 4.75, 95%CI 3.48-6.48) showed a significant association with the occurrence of AEs. The interactions were not statistically significant (p=0.61 for interaction with age; p=0.17 and p=0.27 for interactions with polypharmacy).

Conclusions: Prevention of overtreatment for hypertension needs attention in T2D patients who are older or have polypharmacy, since both are potential risk factors for hypotension-related AEs in T2D patients treated with antihypertensives. We found no evidence, however, that these factors enhance the risk of low SBP levels on hypotension-related AEs.

4455 | The comparison of drug use in children and adults with allergy in primary care

Volkan Aydin[1], N Ipek Kirmizi[2], Omer Atac[2], Narin Akici[3] and Ahmet Akici[1]

[1]*Marmara University, Istanbul, Turkey;* [2]*Istanbul Medipol University, Istanbul, Turkey;* [3]*Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey*

Background: As a common condition encountered in primary care, allergy is managed with a variety of different medications depending on wide spectrum of its clinical picture.

Objectives: We aimed to compare drug use of allergic children and adults in primary care.

Methods: We reviewed prescriptions of pediatric (<18-year-old) and adult (≥18-year-old) patients with single"allergy, unspecified (ICD Code: T78.4)" diagnosis in primary care centers of Istanbul province in 2016 (n=37,042). The details of drug utilization were compared in these groups.

Results: Over half of the prescriptions (55.9%) belonged to adult population. We identified the mean age of the children and adults as 6.7 ±4.5 and 47.3±17.8 years, respectively. The percentage of female patients were lower in children (47.6%) than that in adults (67.7%), (p<0.0001). "R-Respiratory system" drugs constituted the most commonly used drugs in children (61.2%) and adults (51.8%). Among all drugs, desloratadine was the most frequently prescribed drug, followed by cetirizine both in children (21.2% and 16.2%, respectively) and adults (10.3% and 7.7%, respectively). Children had higher percentage of prescriptions with topical medication (51.7% vs 42.7%, p<0.0001) whereas adults had higher percentage of prescriptions with systemic antihistamines (85.3% vs. 83.4, p<0.0001) and systemic corticosteroids (5.4% vs. 1.6%, p<0.0001) compared to their counterparts. The percentages of prescriptions with systemic anti-infectives were similar in children (6.4%) and adults (6.7%), (p>0.05).

Conclusions: This study shows an antihistamine-based pharmacotherapy in primary care management of allergy both in children and adults. While main drug classes preferred in this indication seem similar, their utilization rates exhibit differences between children and adults.

4518 | Qualitative assessment of special instructions or warnings provided to patients prescribed a nitrate with a concurrent contraindicated medication

Anthony P. Nunes[1,2], Andrew Stewart[3], Alankar Gupta[3], Thomas McGraw[3], Jennifer Song[2] and John D. Seeger[2]

[1]*University of Massachusetts Medical School, Boston, MA;*[2]*Optum Epidemiology, Boston, MA;*[3]*Sanofi, Boston, MA*

Background: Clinical notes complement the prescription record by documenting anticipated dosing frequency and instructions or warnings regarding use. This added information is enhances assessment of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

potentially inappropriate exposure, such as concurrent contraindicated medications.

Objectives: To assess and describe EHR documentation of special instructions and/or warnings provided to patients who were prescribed a nitrate with a current contraindicated medication.

Methods: Within the Optum electronic health record (EHR) data (2012 to 2016), we identified patients with any nitrate prescription and also those with a concurrent contraindicated prescription. We used natural language processing (NLP) to identify patients with at least one note mentioning nitrates or the contraindicated drug. We reviewed a sample of 250 patient profiles (chronological listings of EHR data), and deidentified source clinical notes. The patient profiles were reviewed and categorized according to whether there was evidence of special instructions or warnings. Major themes were identified and summarized.

Results: Overall, 131 (52%) of the 252 of the reviewed patient profiles contained documentation that patients had discussions with their physician during their co-possession period. Just over half contained a direct warning against using both medications together or advice to discontinue one of the medications. Upon review of the deidentified source clinical note, the following themes were identified (1) nitrate prescribed with a warning and guidance to defer use until contraindicated drug is discontinued (2) nitrate prescribed concurrent with contraindicated medication due to infrequent nitrate use, and (3) nitrate prescribed without EHR documentation of any warning or special instructions. Examples of observed warnings include: "We discussed drug interactions, particularly with nitrates. He was warned not to take nitroglycerin with his medication", and "He does carry nitroglycerin but has not used it in the past 10 years… he was warned about possible interaction with nitroglycerin." Additional examples will be provided.

Conclusions: We observed that clinicians were often aware of nitrate contraindications, and documented awareness, circumstances, patient characteristics, anticipated use, and ability to manage the contraindication. By adding NLP and free text note review as a supplement to structured data elements from the prescription record, we may better understand the potential for contraindicated exposures.

4611 | Assessment of World Health Organisation core drug use indicators in tertiary care hospital of Kathmandu, Nepal: A cross-sectional study

Rakesh Ghimire[1], Bijay Bhandari[1], Nirmal Poudel[2], Sandesh Pradhan[2] and Shristi Kharel[3]

[1]Institute of Medicine, kathmandu, Nepal; [2]Institute of Medicine, kathmandu, Nepal; [3]Himal Hospital, kathmandu, Nepal

Background: Inappropriate drug use has serious health and economic influences for the success of national health care system. Promoting the rational use of drug can provide better health and medical care to patients and to the community as a whole. A number of indicators have been developed, standardized and evaluated by the World Health Organization (WHO) to assess the rational use of the drug. The three core drug indicators are prescribing indicators, patient care indicators and facility indicators.

Objectives: The aim of the present study was to assess WHO core drug use indicators at Tribhuvan University Teaching Hospital (TUTH), a tertiary care hospital of Kathmandu, Nepal

Methods: A prospective cross-sectional study on WHO core drug use indicators was done at one of the biggest referral centres of Nepal. Data were collected using standard prescribing, patient care and facility-specific indicator forms. Reliability of the data was ensured by following the WHO guidelines and methods. A total of 300 encounters were investigated and simple descriptive analysis was done.

Results: The average number of drugs per prescription was 8.59 and 16.87% of the medicines were prescribed by generic name. Prescriptions containing antibiotics and that of injectable were 22.3% and 1.6% respectively. The percentage of the drugs prescribed on the essential drug list was 16.43. The average consultation was found to be 13.30 minutes and dispensing time was 192.05 seconds. Furthermore, 69.35% of the prescribed drugs were actually dispensed. None of the prescriptions was adequately labelled and 85% of patients know about the dosage of the prescription. The hospital has a copy of the national list of essential medicines-Nepal. However, the hospital doesn't have a list of key drugs.

Conclusions: The study concluded that polypharmacy and the number of drugs prescribed by brand names were common. The doctors spending time to a patient was found to be higher than the WHO standard. The study warrants the need for hospital's standard treatment guidelines and availability of key drugs.

4675 | Inappropriate drug therapy prescription in older outpatients in Italy

Federica Galimberti[1], Manuela Casula[1,2], Elena Olmastroni[1], Veronica Russo[3], Enrica Menditto[3], Alberico L. Catapano[1,2] and Elena Tragni[1]

[1]University of Milan, Department of Pharmacological and Biomolecular Sciences, Epidemiology and Preventive Pharmacology Service (SEFAP), Milan, Italy; [2]IRCCS MultiMedica, Sesto S. Giovanni (MI), Italy; [3]CIRFF - Department of Pharmacy, University of Naples Federico II, Naples, Italy

Background: Pharmacological intervention is an essential step in health promotion. However, the process of setting a diagnosis and choosing appropriate drug treatment is complex and lots of drugs are often prescribed and used in inappropriate ways, especially in older patients.

Objectives: The aim of this study was to retrospectively evaluate prevalence of potential inappropriate prescribing in community-dwelling elderly population in Italy.

Methods: This analysis was based on baseline data from the EDU.RE.DRUG (*Effectiveness of informative and educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients*) project, that was funded by the Italian Medicines Agency and included all GPs and their adult patients (≥40 years)

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

from 8 local health units (LHUs) in Campania and Lombardy regions. We defined a set of explicit indicators for potential inappropriate prescription, including polypharmacy, potential drug-drug interactions (pDDIs) and drugs to be avoided in the elderly according to the ERD list [EDU.RE.DRUG list], which is based on validated Beers, STOPP and EU(7)PIM criteria, and adapted to the Italian drug formulary. Using administrative healthcare databases from the involved LHUs, we retrospectively assessed the annual prevalence rates of the selected indicators during the period 2014-2016 among subjects aged ≥65 years.

Results: We observed high rates of polypharmacy in both the regions. About one out of three older patients in Lombardy LHUs received 5 to 9 drugs compared one in two in Campania LHUs; hyper-polypharmacy (≥10 drugs) ranged from 5 to 9% and from 18 to 25%, respectively. Around 25-35% in Lombardy and 50-65% in Campania were prescribed at least one inappropriate drug included in the ERD-list; among them proton pump inhibitors (used for more than 8 weeks) and NSAIDs (i.e. ketoprofen and diclofenac) represented the most frequently occurred ERD-list criteria. Furthermore, 18-27% of older patients in Lombardy were exposed to at least one pDDI, while in Campania this percentage was even higher (35-43%). The most frequent pDDIs were hydrochlorothiazide-ibuprofen and pantoprazole-levothyroxine in Lombardy, and hydrochlorothiazide-diclofenac in Campania for the 3 years considered.

Conclusions: Despite some remarkable geographical differences, these results highlight a widespread need for intervention to improve the quality of prescribing in primary care setting in Italy. Moreover, the tools provided to identify patients at higher risk of medicine-related problems based on Italian drug-utilization patterns will be also adaptable to other national contexts.

4689 | Differential missingness of antibiotic indications in claims data

Paula D Strassle, Rachael K Ross, Ashley H Marx, Zachary I Willis, Claire E Farel and Alan K Kinlaw
University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Indication is critical in identifying opportunities for antibiotic stewardship and to control confounding in health outcomes analyses. Studies in claims data regularly use outpatient service records to identify indications for dispensed prescriptions; however, little is known about how identifying indications vary across antibiotic classes or individual characteristics.

Objectives: To estimate prevalence of unknown indication in antibiotic fills and examine variability of missingness across antibiotic class, patient subgroups, and insurance plan types.

Methods: We identified all oral, systemic antibiotic prescription fills from individuals age <65 years in IBM Watson Health MarketScan data (2017-2018). 60 days of pre-fill and 7 days post-fill insurance coverage was required. Indications were classified based on need for antibiotic treatment: "almost always", "sometimes", and "not indicated" using classification scheme developed by Fleming-Dutra et al. (doi 10.1001/jama.2016.4151) using outpatient claims 7 days prior through 7 days after the fill. We grouped antibiotics by Anatomical Therapeutic Chemical codes. Multivariable binomial regression was used to estimate prevalence differences (PD) for unknown indication data by demographic characteristics, prior antibiotic use, prior inpatient admission, antibiotic class, and season. Repeated observations were handled with generalized estimating equations with compound symmetric correlation structure. All 95% confidence limits were within 0.01 of PD estimates and thus not presented.

Results: Overall, 30,306,593 antibiotic fills (12,642,528 unique individuals) were included. Penicillins (36%), macrolides (19%), and tetracyclines (11%) were most common. 49% of antibiotic fills only had "not indicated" diagnoses (28%) or no healthcare claims (21%) during the measurement window. Unknown indication was more prevalent in adults than children (PD 0.21). Compared to penicillins, unknown indication was more common for lincosamides (PD 0.13), macrolides (PD 0.10), 1st generation cephalosporins (PD 0.09) and tetracyclines (PD 0.07), and less common for oxazolidinones (PD -0.14), 2nd/3rd generation cephalosporins (PD -0.09), and sulfonamides/trimethoprim (PD -0.05). Gender, prior antibiotic use, and prior hospitalization had minimal impact.

Conclusions: In this privately insured population, half of antibiotic fills lacked supporting claims data on relevant indication for antibiotics; moreover, unknown indication differed by antibiotic class and age. Future claims-based studies of antibiotics should regularly address missing data on indication.

4712 | Utilization of rotigotine transdermal patch in Germany: results from a claims database study

Lars Joeres[1], Stephan Luca[2], Guilhem Pietri[3] and Lisa Zimmermann[4]
[1]*UCB Biosciences GmbH, Monheim, Germany;* [2]*UCB Pharma GmbH, Monheim, Germany;* [3]*Data Pyxis Ltd, Stevenage, United Kingdom;* [4]*Gesundheitsforen Leipzig GmbH, Leipzig, Germany*

Background: Rotigotine (RTG), a dopamine agonist, is authorized in EU as a transdermal patch for the treatment of Parkinson's disease (PD) and restless legs syndrome (RLS) with a recommended dose ranging from 4 to 16mg/24h for PD and 1-3mg/24h for RLS. Data on real-life usage of RTG in Germany are not available.

Objectives: To assess utilization and persistence (overall and dose-dependent) of RTG for RLS and PD in real-world practice in Germany.

Methods: Utilization and persistence of RTG among prevalent PD and RLS patients were assessed between 2013 and 2017 using the Deutsche Analysedatenbank, a collection of claims data from German sick funds, according to ICD-10 and ATC codes. Annual prevalence rates were calculated for PD and RLS and extrapolated to the German social health insured (SHI) population. RTG utilization in prevalent PD and RLS patients was assessed as number of treated patients, mean and median dosage per indication; persistence was assessed as mean

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

treatment duration (in days) overall and per dosage. Summary descriptive statistics were calculated.

Results: Approx. 2 million insured persons could be evaluated. Among those, 9,876 (PD) and 16,617 (RLS) patients could be identified using G20.0, G20.1, G20.2, G20.9 ICD-10 codes for PD and G25.80, G25.81 and G25.88 for RLS (extrapolated to 291,026 PD and 489,669 RLS patients in the SHI population). Of those, 543 PD patients and 699 RLS patients claimed at least one prescription of RTG (ATC code N04BC09; extrapolated to 16,001 PD and 20,598 RLS patients). A mean dose of 4.88mg/24h in PD and 2.58mg/24h in RLS was calculated. Dosages of 2, 4, 6, and 8mg/24h in PD and 1, 2, 3mg/24h in RLS were mainly used (29.7%, 33.7%, 23.6%, and 23.6% of PD patients were treated with RTG 2mg, 4mg, 6mg, and 8mg, respectively; 34.8%, 42.6% and 28.5% of RLS patients were treated with RTG 1mg, 2mg and 3mg, respectively), reflecting the commercially available patch sizes. Persistence overall was calculated as 218.3 days in PD and 391.1 days in RLS. The persistence in PD for stable doses of 4 - 6mg/24h ranged from 136.1 to 122.2 days; the highest persistence was observed in PD at 8mg/24h with 322.5 days. In RLS, persistence ranged from 522.0 to 343.1 days within approved dose range of 1-3mg/24h.

Conclusions: The analysis suggests that RTG is prescribed according to prescribing recommendations but using a lower recommended dose range for PD. Mean dose for RTG in PD was in a lower dose range. Persistence is higher for RLS and equally distributed among approved dosages but for PD persistence appears to be dose-dependent, with highest persistence at 8mg/24h. Further research needs to be conducted to corroborate the findings.

4779 | Real-world therapeutic management of stroke survivors with atrial fibrillation, predictors, and clinical outcomes

A Population-based Cohort

Clara Liliana Rodríguez-Bernal, Daniel Bejarano-Quisoboni, Isabel Hurtado, Anibal Garcia-Sempere, Salvador Peiró and Gabriel Sanfelix-Gimeno FISABIO, Valencia, Spain

Background: In stroke survivors with atrial fibrillation (AF), physicians have to weigh the risk-benefit of preventing recurrence of stroke while avoiding hemorrhagic events, working with guidelines that are based on consensus (instead of empirical evidence).

Objectives: To assess patterns of therapeutic management of stroke survivors with atrial fibrillation, predictors of treatment at discharge and clinical outcomes using data from routine practice.

Methods: Population-based retrospective cohort study. All patients with a previous diagnosis of AF, discharged alive after hospitalization for an acute ischemic stroke or TIA in the Valencia region from Jan 2010 to Dec 2015. Data were obtained from the Valencia Health System (VHS) Integrated Databases (VID), covering 97% of the population of the Region (5 million inhabitants, ≈12% of the Spanish population). Treatment strategies at discharge (no antithrombotic treatment, antiplatelets- APT, oral anticoagulants-OAC or OAC+APT) and their predictors are described as well as incidence rates of clinical outcomes (gastrointestinal bleeding, stroke/TIA, acute coronary syndrome-ACS- and death) according to treatment decisions.

Results: Of the 8084 patients with AF, discharged alive after a stroke, 847 (10.5%) did not receive antithrombotic treatment within 1month, 2323 (28.7%) were prescribed APT, 3496 (43.3%) OAC and 1418 (17.5%) OAC+APT. Regarding predictors of treatment strategy, overall, being older, female, having chronic heart failure, dementia, malignancy and previous GI and intracranial bleeding were associated to being untreated or treated with APT only. History of coronary heart disease was one of the strongest predictors of being treated with APT, alone or in combination. Overall, previous treatment with the different strategies was a strong predictor of post-discharge treatment decisions. Regarding clinical outcomes, patients treated with APT only had the highest incidence of GI bleeding (18.6 per 1000 person-years) and recurrent stroke/TIA (91.8 per 1000 p-y) while those untreated had the highest incidence of death (523.1 per 1000 p-y). Patients treated with OAC+APT showed the highest incidence of ACS (13.7 per 1000 p-y).

Conclusions: In this large population-based cohort of patients with AF who suffered a stroke, we found that although the most common treatment strategy at discharge was OAC therapy, almost one third were treated with APT only. Untreated patients and patients treated with APT only had an increased risk of adverse clinical outcomes, probably due to their clinical profile.

4785 | Appropriateness of outpatient antibiotic prescribing in china: nationwide cross-sectional study

Houyu Zhao[1], Jiaming Bian[2] and Siyan Zhan[1]

[1]*Peking University, Beijing, China;* [2]*The 7th Medical Center of the Chinese PLA General Hospital, Beijing, China*

Background: Little is known about the appropriateness of outpatient antibiotic prescribing at the national level in China, where antibiotic consumption is very high.

Objectives: To estimate the antibiotic prescription rates for common diagnosis categories and to assess the appropriateness of outpatient antibiotic prescriptions for all conditions and all ages in China.

Methods: A data of 172.7 million outpatient and emergency department visits from 139 secondary- and tertiary-level hospitals in 28 provinces of Mainland China from October 2014 to April 2018 were analyzed. Prescription diagnoses were classified as being appropriate, potentially appropriate, inappropriate, or not linked to any diagnosis for antibiotic use by following a published classification scheme. Antibiotic prescription rates for various diagnosis categories and proportions of inappropriate antibiotic prescribing for different subgroups were estimated. Antibiotic prescribing pattern and proportions of individual antibiotics prescribing for different diagnosis categories were analyzed and reported.

Results: Among the 172704117 outpatient visits, 18848864 (10.9%) were prescribed at least one antibiotic. For conditions that antibiotic

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

use is almost always appropriate, potentially appropriate, and almost always inappropriate, 42.2%, 30.6%, and 7.6% visits ended with antibiotic prescriptions. Among all 18848864 antibiotic prescriptions, 9 689 937 (51.4%) were inappropriate, 5354224 (28.4%) were potentially appropriate, 2893102 (15.3%) were appropriate, and 911601 (4.8%) could not be linked to any diagnosis. Among these 18848864 antibiotic prescriptions, a total of 23266533 individual antibiotics were prescribed, the top three most prescribed antibiotics were cefdinir (2121584, 9.1%), followed by levofloxacin (2027757, 8.7%), and azithromycin (2010669, 8.6%).

Conclusions: In Chinese secondary- and tertiary-level hospitals, over half of antibiotic prescriptions were inappropriate, suggesting an urgent need of outpatient antibiotic stewardship aiming at reducing inappropriate antibiotic prescribing to achieve the goals set in the Global Action Plan and National Action Plan.

4805 | Use of adjusted sequence symmetry analysis to quantify the impact of a new diagnosis on off-label prescribing: A case example with NAFLD and pioglitazone

Anthony P. Nunes, Danni Zhao and Matthew J. Alcusky
University of Massachusetts Medical School, Worcester, MA

Background: Sequence symmetry analysis (SSA) has historically been used to identify adverse event signals. This approach relies on the temporal relationship between two incident events to quantify the association between an exposure and outcome. SSA may be an efficient means of identifying clinical responses to new diagnoses, including off-label prescribing of medications.

Objectives: We employ an adjusted SSA to quantify the extent to which a new diagnosis may increase off-label prescribing of a drug, using pioglitazone and NAFLD as the applied example.

Methods: We identified patients with a new diagnosis of NAFLD and an initiation of pioglitazone (from dispensing claims) from 2012 to 2019 in the MarketScan® Explorys® Claims- EMR Data Set. We defined 3, 6, and 12-month windows preceding and following the NAFLD date and created indicators of presence or absence of pioglitazone initiation within these windows. Analyses were limited to patients with a pioglitazone initiation in either the preceding or following window. A control was created by generating a random date representing a pseudo-pioglitazone initiation and categorizing the pseudo initiation date as described for the actual initiation date. The final adjusted effect estimate was obtained via conditional logistic regression modeling, with the independent variable being the exposure indicator (actual or pseudo pioglitazone initiation vs no initiation) and the dependent variables being the analysis indicator (actual vs pseudo pioglitazone initiation) and the interaction between the analysis indicator and NAFLD indicator (NAFLD=1 if exposure observed in follow-up window or 0 if observed in preceding window). The parameter estimate for the interaction term served as our estimate of the increased odds of initiating pioglitazone due to a new NAFLD diagnosis.

Results: We identified 350 eligible patients. Of these, 110 were included in the analysis of the 3-month window, 183 for the 6-month window, and 350 for the 12-month window. Crude odds ratios and 95% confidence intervals were 1.00 (1.69-1.45), 1.18 (0.88-1.58), and 1.59 (1.28-1.98) for 3, 6, and 12-month analyses respectively. Adjusted odds ratios were attenuated to 0.96 (0.80-1.15), 1.14 (0.99-1.32), and 1.42 (1.27-1.59) for corresponding analyses.

Conclusions: SSA is an efficient means of estimating the effect of a new diagnosis on subsequent off-label drug initiation. In our case example, there was no evidence of an immediate response, though there may be a shift towards initiating pioglitazone as we expand the observation window beyond 6-months.

4819 | Antipsychotics used to treat patients with severe mental disorder in outpatient follow-up at a psychiatric hospital

Ronaldo Portela[1], Cristina M. Ruas[1], Helian N. Oliveira[2] and Mariana D. Lula[1]
[1]*Federal University of Minas Gerais, Belo Horizonte, Brazil;* [2]*Federal University of Minas Gerais, Belo Horizonte, Brazil*

Background: Although antipsychotics are frequently used by patients diagnosed with severe mental disorder, few studies have been conducted to characterize outpatient treatment in psychiatric hospitals.

Objectives: To evaluate the use of antipsychotropic drugs divided into three groups (typical, atypical and long-acting injectables).

Methods: It is an observational cohort review study of 625 patients' medical records. The study included patients diagnosed with severe and persistent mental disorder who received their first hospital discharge from January to December 2012 and continued maintenance treatment at the hospital until December 2017. Descriptive statistical analyzes were performed to evaluate sociodemographic and clinical characteristics. In the descriptive analysis of categorical variables, absolute and relative frequencies were used and for quantitative variables, measures of position, central tendency and dispersion were used.

Results: Most patients are male (51.5%) with an average age of 37 (± 11) years. Patients have an average of 1.7 (± 1.5) children. The age of the first psychotic break was at 23 (± 8.3) years. The percentage of suicide attempt was 11.0% (± 1.4), with the majority being 60.9% female. Most patients (82.9%) did not use associated antipsychotics. The majority (65.8%) adhered to the treatment and 13.9% reported that they interrupted it due to the lack of the drug in public pharmacies. There was a need to change the antipsychotic due to the lack of therapeutic response for 11.2% of the patients and for 5.3% due to the adverse reaction to the antipsychotic used. The group of typical antipsychotics was the most used (62.9%), with haloperidol (54.3%) being the most prescribed.

Conclusions: Contrary to other studies, the percentage of male patients with severe mental disorders is not significantly higher than that of females. It is observed in the study that the association of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

antipsychotics in out-of-hospital treatment is low. The study confirms that non-adherence to treatment, difficulty in accessing the medication, as well as its profile of therapeutic response and adverse reactions are determining factors in the assessment of outpatient treatment. In contrast to other studies that demonstrate a growing option for the use of atypical antipsychotics and long-acting injectables, it is observed in the present study that typical antipsychotics, especially haloperidol, are still the most used.

4827 | Prevalence and characteristics of adverse drug reaction-related hospital admissions in older Patients

Caitriona Cahir[1], Carmel Curran[2], Caroline Walsh[1], David J Williams[2] and Kathleen Bennett[1]
[1]*Royal College of Surgeons in Ireland, Dublin, Ireland;* [2]*Beaumont Hospital, Dublin, Ireland*

Background: Older people experience greater morbidity with a corresponding increase in medication use resulting in a potentially higher risk of adverse drug reactions (ADRs).
Objectives: The aim of this study was to determine the prevalence and characteristics of ADR-related hospital admissions among older patients (≥ 65 years).
Methods: A cross-sectional study of ADR prevalence in patients aged ≥ 65 years admitted acutely to a large tertiary referral hospital in Ireland over a 7 month period (November 2016- June 2017). A multifaceted review of each hospital admission was undertaken to assess the likelihood of an ADR being a reason for admission (cause of admission or contributing to admission) in the context of the patient's medication, clinical condition, medical history, comorbidities and investigations. A number of decision aids were applied by two independent reviewers to assess ADR causality (Naranjo criteria, WHO criteria, Liverpool Algorithm). The avoidability (Hallas criteria) and severity (Hartwig severity assessment scale) of the ADR were also assessed. Differences in causality, preventability and severity were reviewed by a third reviewer.
Results: In total, 3760 hospital admission episodes (in 3091 patients) were screened and 377 admissions were ADR-related (10.0 %, 95% CI 9.1%, 11.0%); 43 admissions were due to ≥2 ADRs (N= 424 ADRs). 360 (11.6% 95% CI 10.5%, 12.8%) patients had at least one ADR with 50 (16.2%) patients experiencing ≥ 1 ADR-related admission. In summary, 219 (58.1%) admissions were caused by an ADR, while ADRs contributed to 158 (41.9%) admissions. For the majority of admissions (N= 216, 57.6%) there was no other known acute medical issue that may have acted in synergy with the medication resulting in the ADR. Of the 377 ADR-related admissions, 43 (11.4%) were deemed definitely avoidable and 225 (59.7%) possibly avoidable and 350 (92.8%) were classified as moderate severity.
Conclusions: One in ten hospital admissions were ADR-related, with approximately 70% potentially avoidable. Interventions are needed to reduce ADRs and improve medication management in older populations.

4834 | Pharmacological treatment of insomnia in general practice

Mette H Bakker[1], Nina A Oldejans[1], Henriëtte E van der Horst[1], Jacqueline G Hugtenburg[2] and Pauline Slottje[1]
[1]*Amsterdam UMC, location VUmc, Amsterdam, Netherlands;* [2]*Amsterdam UMC, location VUmc, Amsterdam, Netherlands*

Background: According to the Dutch general practitioners guideline for insomnia, insomnia should initially be treated with non-pharmacological treatment. Only in an acute crisis or if non-drug treatment not leads to improvement, short-acting benzodiazepines or Z drugs may be used to a limited extent. Adherence to this guideline has not been studied as yet.
Objectives: The aim of this study was to gain insight into the current pharmacological treatment of insomnia in Dutch general practice.
Methods: Anonymized electronic medical records from 20 Dutch general practices covering the period between 01/01/2013 and 01/01/2018 were derived from a pseudonymized general practice database. The study comprised 1,125 adults with insomnia diagnosed after the publishing date of the current guideline (01/07/2014) who could be prospectively followed for two years after diagnosis. Free text documentation was reviewed by three instructed researchers using a scoring protocol and combined with structured data for descriptive analysis.
Results: Preliminary results show that 82% of patients were prescribed sleep medication the first two years after diagnosis. Nearly a quarter of these patients were found to have used up to 6 agents. Less than 10% of the patients appeared to have received non-pharmacological treatment prior to the prescription of sleep medication. For about 50% of patients pharmacological treatment consisted of a short-acting benzodiazepine, whereas about 15% were treated with another benzodiazepine and almost 25% with other (off-label) agents.
Conclusions: Sleep medication was often prescribed in the first two years after the diagnosis of insomnia. Only in a small part of patients non-drug treatment preceded the prescribing of sleep medication. Off-label sleep medication and benzodiazepine other than recommended by the guideline are regularly prescribed. Moreover, different agents were used in a large number of patients.

4840 | Prevalence and predictors of potential drug-drug interactions in an older community-based population

John Hughes[1], Kathleen Bennett[1], Veronica Russo[2], Caroline Walsh[1], Enrica Menditto[3] and Caitriona Cahir[1]
[1]*Royal College of Surgeons in Ireland, Dublin, Ireland;* [2]*University of Naples Federico II, Naples, Italy;* [3]*University of Naples Federico II, Naples, Italy*

Background: Multimorbidity, commonly defined as the co-existence of two or more chronic conditions, affects almost three-quarters of adults aged ≥ 65 years. Older people are often prescribed multiple

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

medications to manage their chronic conditions which increase an individual's risk of experiencing a drug-drug interaction (DDI).

Objectives: The aim of this study was to: (1) determine the prevalence of potentially severe cardiovascular and central nervous system (CNS) DDIs and; (2) examine potential predictors of any DDIs in a cohort of community-dwelling older adults.

Methods: A prospective cohort study (aged ≥ 70 years), using linked data from a national pharmacy claims database and Waves 1 & 2 of The Irish LongituDinal study on Ageing (TILDA). 'Severe' cardiovascular and CNS DDIs were first identified using the BNF 77. These were then cross-referenced using Stockley's Drug Interactions and drug combinations identified as being contraindicated or requiring close monitoring were included. Prevalence was calculated as the presence of any DDI out of all eligible participants. A chronic DDI was defined as ≥ 3 consecutive months of dispensed medication with the same DDI. Logistic regression was used to examine participant-level risk factors associated with the risk of a DDI between Waves 1 & 2 and included age, gender, marital status, education, smoking status, number of chronic conditions, poor delayed recall, depression, frailty and polypharmacy. Adjusted odds ratios (OR) and 95% CIs are presented.

Results: In total, 1,466 patients were included (mean age=78 SD=5.5; Female N=795, 54.2%). The overall prevalence of DDIs was 29.6% (N=434); 210 (48%) of these patients had a chronic DDI. The prevalence of DDIs per claim was 14.4% (N=33,548 claims). Aspirin and warfarin were the most frequently prescribed DDI per prescription claim (N=217, 4.5%), followed by ramipril and allopurinol (N=214, 4.4%). Polypharmacy (≥ 10 drugs) (OR=29.2; 95% CI 9.1, 93.5), frailty (OR=1.7; 95% CI 1.1, 2.7), smoking history (OR=1.3; 95% CI 1.0, 1.8) and depression (OR=1.7; 95% CI 1.1, 2.6) were significantly associated with experiencing a DDI.

Conclusions: DDIs are highly prevalent in older people and frail patients with polypharmacy require regular medication reviews and prescribing optimisation

4851 | Agreement between self-reported morbidity and pharmacy claims data for prescribed medications in a community based population

Clionadh Mannion[1], John Hughes[2], Frank Moriarty[2], Kathleen Bennett[2] and Caitriona Cahir[2]

[1]Trinity College Dublin, Dublin, Ireland; [2]Royal College of Surgeons in Ireland, Dublin, Ireland

Background: Studies have indicated variability around prevalence estimates of multimorbidity due to poor consensus regarding its definition and measurement. Medication-based measures of morbidity may be valuable resources in the community-care setting where access to medical data can be limited.

Objectives: To compare the agreement between patient self-reported and medication-based morbidity and examine potential patient-level predictors of discordance between these two measures of morbidity in a community-based population.

Methods: A retrospective cohort study (aged ≥ 50 years) using national pharmacy claims data linked to The Irish LongituDinal study on Ageing (TILDA). Morbidity was measured by patient self-report (TILDA) and two medication-based measures, the Rx-Risk (< 65 years) and Rx-Risk-V (≥ 65 years), which classify drug claims into chronic disease classes. The kappa(κ) statistic measured agreement between patient self-reported and medication-based morbidity at the individual level. Multivariate logistic regression was used to examine patient-level characteristics associated with discordance between measures of morbidity with odds ratios (OR) and 95% CI presented.

Results: In total 2,925 patients were included (<65 years: N=1,095, 37.4%; and ≥ 65 years: N=1,830 62.6%). Hypertension and high cholesterol were the most prevalent self-reported morbidities in both age cohorts. Agreement was good or very good (κ=0.61-0.81) for diabetes, osteoporosis and glaucoma; and moderate for high cholesterol, asthma, Parkinson's and angina (κ=0.44-0.56). All other conditions had fair or poor agreement. Age, gender, marital status, education, poor-delayed recall, depression and polypharmacy were significantly associated with discordance between morbidity measures (p<0.05).

Conclusions: Most conditions achieved only moderate or fair agreement between self-reported and medication-based morbidity. The current Rx-Risk and Rx-Risk-V require updating to assess their true reliability and validity as medication-based measures of morbidity.

4922 | Bacterial isolates and their patterns of antibiotic resistance in the critical care unit of a national referral hospital in Kenya

Emmah B. Obegi[1], Margaret N. Oluka[2], Sylvia A. Opanga[3] and Faith A. Okalebo[2]

[1]University of Nairobi, Nairobi, Kenya; [2]University of Nairobi, Nairobi, Kenya; [3]University of Nairobi, Nairobi, Kenya

Background: Critically ill patients have a high risk of developing life-threatening infections. The extensive and indiscriminate use of antimicrobials in the critical care unit leads to selective pressure for resistant bacteria.

Objectives: To determine the commonest micro-organisms isolated from patients admitted in the Critical Care Unit and their susceptibility patterns.

Methods: A retrospective longitudinal study was conducted at the selected Critical Care Units of KNH. The study involved the extraction of data from medical records of patients aged 13 years and above admitted to the Critical Care Units for 12 months. Data were abstracted using a pre-designed standardized data collection tool. The study variables were the five commonest isolated micro-organisms and the susceptibility patterns of the bacteria to the commonly used antibiotics. The prescribing patterns of the various antibiotics were also assessed.

Results: This study included 309 patients. The median age was 37 years [IQR 13, 83] There were more males (n=158, 51.1%). The most commonly isolated microorganisms were *Klebsiella pneumonia*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(23.9 %), *Acinetobacter baumanii* (16.4%) and *Escherichia coli* (10.5%). 11(67%) *K. pneumonia* isolates were sensitive to meropenem. *A. baumanii* isolates (82%, n=9) were sensitive to amikacin, 55% (n=6) to meropenem, 27% (n=3) were sensitive to ceftazidime and cefepime. All the *A. baumanii* isolates were resistant to tigecycline, linezolid, and teicoplanin. Most of the *E. coli* isolated were sensitive to meropenem (86%, n=6), amikacin (71%, n=5) and 43% (n=3) to gentamycin. The antimicrobial agents commonly prescribed were Ceftriaxone (36.8%), Metronidazole (16.9%) and Meropenem (12.4%).

Conclusions: Klebsiella pneumonia, Acinetobacter baumanii, and Escherichia coli were the principal pathogens isolated. They showed susceptibility to meropenem and amikacin. Ceftriaxone was the most common antibiotic prescribed despite most isolates showing resistance. The study observed that the culture and sensitivity results seldom informed antibiotic prescribing

5015 | Influence of Dementia on Medication-related Quality of Care in Long-term Aged Care

Gillian E Caughey[1,2], Catherine Lang[1], Janet Sluggett[1], Steve Wesselingh[1] and Maria C Inacio[1]

[1]*South Australian Health and Medical Research Institute, Adelaide, Australia*; [2]*University of South Australia, Adelaide, Australia*

Background: Dementia is one of the biggest global challenges for health and social care and is highly prevalent in older people living in long-term aged care. People with dementia are particularly susceptible to medication-related adverse events and harms, and poor quality of life due to their physical and psychological frailty and presence of multimorbidity and polypharmacy. Clinical indicators of medication-related quality of care can be used to monitor, evaluate and improve medication use and resident outcomes.

Objectives: To examine the influence of dementia on medication-related quality of care in older people residing in long-term aged care.

Methods: A retrospective cohort study of all older people residing in long-term care facilities in Australia between 1 Jan and 31 Dec 2016 was conducted using national data from the Registry of Senior Australians (ROSA), a national cohort of over 2.8 million older Australians receiving aged care services and linked to multiple databases, including pharmacy claims. Medication-related quality of care indicators examined included antipsychotic use without a diagnosis of psychosis, high sedative load (score >=3), and chronic opioid use. Logistic regression was used to determine indicator prevalence rates and 95% CI, adjusted for age, sex and number of comorbid conditions and stratified by the presence of dementia.

Results: A total of 212,405 long-term residents, including 108,489 (51.1%) with dementia, in 2690 facilities throughout Australia were included in the study cohort. The median age was 84 years (IQR 79-89), 62% were female and the median number of comorbid conditions was 5 (IQR 3-7). Polypharmacy was common; 77.5% were dispensed > 5 medications with 47.4% receiving > 10 medications. The prevalence of antipsychotic use in residents with dementia was 31.7% (95% CI 31.5-32.0), and in residents without dementia 13.1% (95% CI 12.9-13.2). Little difference in the prevalence of high sedative load between those with dementia (45.3% 95% CI 45.0-48.0) and without dementia (50.8% 95% CI 50.5-51.2) or chronic opioid use (dementia 24.3% 95% CI 24.1-24.6 and no dementia 26.7% 95% CI 26.5-26.9) was observed.

Conclusions: Little differences in medication-related quality of care was observed between residents with and without dementia apart from the use of antipsychotics. However, given the high prevalence of utilisation of these medications, together with the potential for significant risk of harms, monitoring their use is important to facilitate the identification of those in need of medication review, to assess appropriateness, continued use or potentially deprescribe.

5016 | Prevalence of and factors associated with chronic opioid utilization among commercially insured us adults with co-morbid chronic pain and mental health disorders

Abisola Olopoenia and Linda Simoni-Wastila

University of Maryland, Baltimore, MD

Background: Little is known about factors associated with chronic use of opioids among youth and adults with co-morbid chronic non-cancer pain (CNCP) and mental health disorders (MHD)

Objectives: Our goal was to examine the prevalence of, and potential risk factors associated with, chronic use of prescription opioids among commercially insured youth and adults aged 14 through 64 with co-morbid CNCP and MHD

Methods: We conducted a retrospective cohort study utilizing the IQVIA™ Health Plan Claims Data from January 1, 2006 to December 31, 2015. CNCP was defined as any diagnosis of back, head, neck, arthritis, or chronic pain (index date). MHD was assessed in the 6-months prior to the index date and included mood disorders, anxiety, depression, personality disorders, adjustment disorders, and attention deficit disorders. Demographic and clinical factors included age, sex, non-chronic non-cancer pain (NCNCP), sedatives, muscle relaxants, number of chronic co-morbidities, antidepressants, and substance use disorders (SUD.) These factors were assessed in the 6-months prior to the index pain diagnosis. Based on days supplied (none, acute [<90 days] and chronic[≥90days]), we constructed a 3-categorical level dependent measure of opioid use. We estimated the prevalence of chronic opioid receipt among youths and adults with concurrent CNCP and MHD, and used multinomial logistic regression (AOR; 95 CI) to estimate the associations of these clinical and demographic factors with chronic opioid receipt

Results: Among 143,923 adults with CNCP and MHD, 32,621 (3.71%) and 10,592 (1.20%) had acute and chronic use of opioids, respectively. When compared to acute opioid use, chronic prescription opioid use was higher among middle-aged adults (46-64) and those with diagnoses of SUD, NCNCP, and ≥3 chronic co-morbidities (p<0.01) After adjusting for demographic and clinical factors, muscle relaxants (3.98;3.80-4.17), ≥3 chronic co-morbidities (3.14;2.89-3.41), opioid-

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

related SUD (2.99;2.67-3.36), non-opioid related SUD (1.94;1.73-2.18), neuropathic pain (1.75;1.64-1.86), and antidepressants (1.78;1.69-1.87) were the strongest predictors of chronic opioid use

Conclusions: A considerable proportion of individuals with co-morbid CNCP and MHD chronically utilize opioids. Within this population, individuals with diagnoses of substance use disorders, multiple co-morbidities, and those who use muscle relaxants are at even higher risk of chronic opioid use. This population is potentially highly susceptible to opioid-related adverse outcomes

5034 | Linaclotide utilization and potential for off-label use or misuse in three European countries

Javier Cid Ruzafa[1], Anna Schultze[2], Mai Duong[3], Yi Lu[3], Robert Donaldson[3], Darren Weissman[4] and Ahunna Ukah[5]
[1]*Evidera, Barcelona, Spain;* [2]*London School of Hygiene and Tropical Medicine, London, United Kingdom;* [3]*Evidera, London, United Kingdom;* [4]*Allergan, Madison, NJ;* [5]*Allergan, Irvine, CA*

Background: Linaclotide is used to treat moderate-to-severe irritable bowel syndrome (IBS) with constipation (IBS-C) in adults. Real-world treatment patterns of linaclotide use are largely unknown. Two subgroups with potential for off-label use are patients with obesity/eating disorders (ED), considered at risk of use for weight loss or as a laxative, and those with prior mechanical bowel obstruction (MBO) or inflammatory bowel disease (IBD).

Objectives: To describe real-world use of linaclotide in groups of patients with potential for off-label use.

Methods: This was a post-authorisation safety study requested by European health authorities, conducted in 3 databases: the UK Clinical Practice Research Datalink, the Information System for Research in Primary Care platform in Spain and the linked Patient, Prescription and Causes of Death Registries in Sweden. Patients prescribed linaclotide between its launch date (UK, Sweden 2013; Spain 2014) and end of 2017 were included. The date of the first linaclotide prescription or dispensation was index date. IBS was identified with diagnostic (Read codes in the UK and International Classification of Diseases 10th revision diagnostic codes in Spain and Sweden) and treatment codes using an algorithm. Obesity, ED, MBO and IBD were assessed through codes, body mass index, and medical history.

Results: There were 1,319, 1,981 and 5,081 linaclotide users from the UK, Spain and Sweden with a median age of 45, 57 and 51 years, respectively, mostly females. The most common concomitant medications were laxatives in the UK and Sweden (72%) and proton pump inhibitors in Spain (41%). In the UK, Spain and Sweden, respectively: 41%, 40% and 69% of linaclotide users did not have an IBS diagnosis and among IBS patients, 69%, 62% and 93% were classified as having IBS-C; 17%, 30% and 2% of users were considered at risk of use of linaclotide for weight loss or as a laxative because of obesity or ED and 0.6%, 2.5% and 1.2% of all users had a history of ED in the year prior to index date; 3.5%, 4.6% and 5.7% of linaclotide users had history of MBO in the year prior to index date or IBD at any time up to index date, with MBO accounting for 0.3%, 2.4%, and 1.1% of all users. The median time between the last MBO and the index date was 6 months.

Conclusions: Linaclotide use by patients with no code of IBS diagnosis was common. Potential linaclotide misuse was limited, as evidenced by the small subgroup sizes, except for those with a possible risk of use for weight loss or as laxative. Linaclotide prescription should occur in accordance with the approved label and use by patients in which its use is contraindicated should be avoided.

5059 | The Use of antibiotics without prescription and the emergence of multidrug-resistant bacteria

Jose J. Hernandez[1,2]
[1]*University of Puerto Rico School of Pharmacy, San Juan, PR;* [2]*Texas A&M College of Pharmacy, College Station, TX*

Background: The irrational use of antibiotics is primarily responsible for the global spread of antibiotic resistance. The use of antibiotics without prescription has been associated with shorter courses and suboptimal drug and dose choices. It has been estimated that more than 50% of the antibiotics worldwide are sold without a medical prescription even though dispensing without a prescription is illegal in most countries.

Objectives: 1) Determine the prevalence of obtaining antibiotics without a prescription in the Commonwealth of Puerto Rico; 2) Describe the patterns of dispensing antibiotics without a valid prescription; 3) Establish if the development of Community-Acquired Multidrug-Resistant (CA-MDR) infections requiring hospitalization is associated with the practice of obtaining antibiotics without a prescription, and describe the pattern of dispensing antibiotics without prescription in Puerto Rico.

Methods: This study followed a case-control study design. Patients hospitalized in a secondary hospital in the northern part of Puerto Rico between August 1, 2018, and April 30, 2019, were considered for potential inclusion. The case group consisted of hospitalized patients with CA-MDR infections as defined by the Magiorakos criteria. The control group consisted of hospitalized patients with community-acquired infections that were non-resistant. Infections occurring ≤ 2 days after the hospitalization were considered community-acquired infections, and those manifesting at a later point, were considered nosocomial infections.

Results: 126 patients were included in the study. Mean (SD) age 68.8 (±15.8) years and 66 (52%) were female. 72 (57%) met the criteria for CA-MDR infections and 48 (38%) reported obtaining antibiotics without prescription. Among those who obtained antibiotics without a prescription, 38 (79%) acquired them from a pharmacy, while 30 (63%) reported their reason for the illegal acquisition was poor accessibility to physicians. The multivariate analysis showed that patients who used antibiotics without prescription were 1.24 times more likely to had a CA-MDR infection than those who did not use

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

them [OR 1.24, CI = 0.60-2.58, p = 0.56]. Despite the apparent association, the result was not statistically significant.

Conclusions: This study provides an up-to-date estimate of CA-MDR infections in hospitalized patients that may have resulted from the use of antibiotics without a prescription in Puerto Rico. Also, the findings suggest that antibiotics are frequently supplied without prescription in Puerto Rico, even though this is an illegal practice.

5061 | Adherence to oral anticoagulant and antiplatelet therapies after an acute ischemic stroke or TIA in atrial fibrillation patients

Judit Riera-Arnau[1,2], Gabriel Sanfélix-Gimeno[3], Clara Liliana Rodriguez-Bernal[3], Daniel Bejarano-Quisoboni[3], Isabel Hurtado[3], Aníbal García-Sempere[3] and Salvador Peiró[3]

[1]Vall d'Hebron University Hospital, Barcelona, Spain; [2]Autonomous University of Barcelona, Bellaterra, Spain; [3]Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO), Valencia, Spain

Background: Antiplatelet therapies (APT) are often given as antithrombotic treatment (ATT) for secondary prevention in atrial fibrillation (AF) although they should be only an alternative when oral anticoagulants (OAC) are contraindicated.

Objectives: To assess adherence to different ATT options after discharge for an acute ischemic stroke (AIS) or TIA in patients with AF.

Methods: This is a population-based retrospective study using electronic health records from the Valencia Region, Spain. We included all the patients diagnosed with AF that were prescribed an ATT after discharge for an AIS or TIA, from Jan 2010 to Dec 2015. We classified them as treated with OAC or APT alone, or OAC+APT, based on the prescriptions within the first month after the first one. We calculated the proportion of days covered (PDC) for a fixed time-window of 12 months after discharge. We used prescription and dispensation data, and thus we are actually estimating the adherence of the patients to the prescribed medications issued by physicians. We defined adherence as PDC>=80%. Discontinuation was also estimated for the 1st year after discharge using a permissible gap of 30 days.

Results: We included 8084 with AF and discharged after an AIS or TIA, of which 7,237 (89,5%) were prescribed an ATT. The 32,1% (n=2,323) of those treated received an APT, a 48,3% (n=3,496) an OAC, and a 19,6% (n=1,418) OAC+APT. The lag time to initiate ATT after discharge, took a mean of 15.6 days in the APT group, 15.7 in the OAC group and 15.2 in the OAC+APT group, all of them with a median of 4 days [IQR:0-17]. 96/2505 patients that in the first month were prescribed APT never filled a dispensation, compared with 82/3751 and 12/1244 in the OAC and OAC+APT groups. Patients in the APT, OAC and APT +OAC groups had a PDC during the first year after discharge of 87.6%, 93.8% and 92.9%, respectively. The percentage of adherent patients was 82.6%, 91.4% and 89.5%. The discontinuation rate at 1 year was significantly higher in the APT group (35.4%), as compared with OAC (27.4%) and OAC+APT (23.6%) groups.

Conclusions: In this study, patients with AF and AIS or TIA who started OAC or OAC+APT after discharge, showed a higher adherence than APT, despite among all of them it was high. The majority of patients had a PDC>80%. One third of the patients in the APT group discontinued the treatment within the first year, compared with a quarter in the others. Further research is needed to assess other factors related to this adherence results, and their clinical implications for this population.

5075 | Concurrent Use of Multiple Antipsychotics Plus Excessive Polypharmacy: Cross-sectional Study of a Vulnerable Population

Maíra R Alves, Rejane CF Mayer, Fabiane R Motter and Luciane C Lopes

University of Sorocaba, Sorocaba, Brazil

Background: The deinstitutionalized patients with mental illness using public Assisted Living Services (ALS) are a vulnerable population. The use of multiple concurrent antipsychotics plus excessive polypharmacy could bring serious adverse events and consequences for functional status of this vulnerable population.

Objectives: To examine the prevalence and the associated factors with concurrent use of multiple antipsychotic and excessive polypharmacy.

Methods: Cross-sectional study conducted with users with mental illness from 40 ALS of a city of São Paulo State, Brazil. We collected data from three sources of information: 1. Medical records; 2. Pharmacy records; 3. Interview with patients using validated tools. The information about drug utilization was crosschecked using the medical and pharmacy records. Sociodemographic data (sex and age) and functional were obtained using the interview with WHODAS tool. Clinical variables (diagnostic, comorbidities, time in hospital, timing of deinstitutionalization) were extracted from the medical records. Poisson regression was performed to identify factors associated with concurrent use of multiple antipsychotics plus excessive polypharmacy.

Results: Of 245 users interviewed, 132 individuals (53.8%, CI 39.8; 52,.4) were men, and the median age was 50.9 (SD±11.7) years. Overall, 63.1% (CI 95% 57.0%; 69.2%) of the participants had concurrent use of multiple antipsychotics and 23.4% (CI 18.1%; 28.7%) of the participants had excessive polypharmacy. Haloperidol (62.9%), Chlorpromazine (46.1%) and Risperidone (30.6%) were the most frequently prescribed. The functional status index found with the WHODAS tool was 10,4 (SD±7,6). After adjusted analysis, only excessive polypharmacy was associated with age < 60 years (PR= 2.93, CI 95%1.03; 8.34, p= 0.027) and time in hospital < 10 years (PR= 2.74, CI 95% 1.16; p= 0.021) and timing of deinstitutionalization < 4 years (PR= 2.54, CI 95%1.29; 5.01, p= 0.007).

Conclusions: We found high prevalence of concurrent use of multiple antipsychotics plus excessive polypharmacy. This represents that the prescription practices are failing the guidelines recommendations and that old prescription practices used before deinstitutionalization are still being held, what can be affecting the process

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of social rehabilitation and the functional status of this vulnerable population. The results suggest the need for interventions by health authorities.

5078 | The role of the patient-provider relationship in racial/ethnic disparities in nonadherence to antihypertensive medications

Macarius Donneyong[1], Teng-Jen Chang[1], Autumn Carey[2] and John Bridges[3]

[1]Ohio State University, Columbus, OH; [2]Ohio State University, Columbus, OH; [3]Ohio State University, Columbus, OH

Background: Nonadherence (NA) to antihypertensive medications (AHM) treatment is higher among Blacks compared to non-Hispanic Whites (NHW).

Objectives: To quantify race/ethnic disparities in AHM NA and to assess whether constructs of patient-provider relationships (PPRs) modify this association.

Methods: AHM users were identified from the Medical Expenditure Panel Survey (MEPS) data, 2010-2017. MEPS is a national panel survey on health care expenditures, verified self-reported prescribed medication use, several self-reported healthcare access measures, etc. Three domains of PPRs (communication, trust and shared-decision making) were defined from participant responses to surveys about their experiences with healthcare services received. Measures of annual medication refill adherence (MRA) were calculated separately for each therapeutic class (TC) as the total days' supply divided by 365 days. Overall MRA was obtained as the average of MRAs for participants was using more than one AHM. Patients were considered to be nonadherent if their overall MRA was <80%. Data collected in year 1 was used to define patient-provider factors and all covariates; year's 2 data used to define AHM NA. Multivariable-adjusted Generalized Linear Models (GLM), weighted by survey weights, were used to measure the odds ratios (ORs) between race/ethnicity and AHM NA. Separate GLMs were also used to assess the associations between each PPR construct and AHM NA, adjusted for by patient demographics and provider's race/ethnicity, gender, specialty and location. Relative excess risk due to interactions (RERIs) between race/ethnicity (each minority group vs. NHW) and each binary construct of PPR were calculated to test for potential effect modification.

Results: The results reported are based on a weighted sample of 17,796,539 (50% NHW; 25% Blacks; 18% Hispanics; and 7% Others) participants. Compared to NHW, AHM NA was higher among Blacks (OR=1.44, 95%CI: 1.28, 1.63), Hispanics (OR=1.30, 95%CI:1.10, 1.52) and others (OR=1.30, 95%CI:1.09, 1.55) in multivariable-adjusted models. Patient involvement in shared decision making was significantly associated with lower risk of AHM NA in unadjusted but not in multivariable-adjusted models; other PPR constructs were not significant in both models. Positive additive interactions were observed between race/ethnicity and high trust and shared decision making.

Conclusions: NA to AHM was significantly higher among racial/ethnic minorities, compared to NHW. This relationship was modified by trust and patient involvement in shared decision making.

5096 | Prevalence of exposure to high-priority drug-drug interactions among community-dwelling non-elderly adults in Quebec, Canada

Araceli Gonzalez Reyes[1], Pierre Pluye[2], Denis Roy[3] and Tibor Schuster[1]

[1]McGill University, Montreal, QC, Canada; [2]McGill University, Montreal, QC, Canada; [3]Institut National d'Excellence en Santé et en Services Sociaux, Montreal, QC, Canada

Background: Drug-drug interactions (DDI) are a recognized risk for specific patient populations, such as hospitalized patients and those living with a condition requiring complex pharmacotherapy; their prevalence among the general population of non-elderly community-dwelling adults is unknown.

Objectives: 1) To measure the prevalence of exposure to high-priority DDI among community-dwelling adults in Quebec; 2) To identify the demographic and health system variables that may help predict the risk of exposure to high-priority DDI.

Methods: We conducted a retrospective cohort study using provincial medical administrative databases on a random sample of 5% of all community-dwelling adults aged 18-64 years on April 1, 2015 with continuous coverage by the public drug insurance between April 1, 2014 and March 31, 2017. Drug reimbursement claims were used to identify periods of temporally overlapping exposure to ≥2 active ingredients (AI) between April 1, 2015 and March 31, 2016. DDI were identified within periods of temporally overlapping exposure to ≥2 drugs using the list of high-priority DDI developed by the U.S. Office of the National Coordinator for health information, in combination with the AZCERT lists of clinically important DDI and QT-prolonging drugs. Incident DDI cases were identified as having no prior exposure to any high-priority DDI in the 12 months preceding the study. Demographic characteristics, health service use, continuity of care, and index of multimorbidity were evaluated as predictors of exposure to DDI; analyses are ongoing.

Results: Our cohort included 63,834 individuals aged 18-64 (mean age 44.9 [95% CI: 44.8-45], 51.6% female); among these, 41,380 (65.3%) claimed ≥1 active ingredient (AI) during the study year, and 34,553 (54.1%) claimed ≥2 AI during the study year. A total of 33,273 individuals (52.1% of full cohort, 96.3% of those with≥2 AI) had ≥1 day of overlapping exposure to ≥2 drugs. A total of 7,498 individuals were exposed to ≥1 DDI over 12 months (11.7% of full cohort, 22.5% of those with ≥1 day of overlapping exposure to ≥2 drugs); exposed individuals had a median of 1 DDI (IQR 2, range 1-28). The DDI with highest prevalence involved QT-prolonging drugs (19 of the 26 most prevalent DDI). Atypical antipsychotics and SSRI antidepressants were involved in 14 of the 26 most prevalent DDI among this population.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Exposure to high-priority DDI is common among community-dwelling non-elderly adults in Quebec. The clinical consequences of this exposure are unknown.

5132 | Factors Driving Self-medication with Antimicrobials in Karaikal, India

Devashree Moktan[1] and Syed Ilyas Shehnaz[2]
[1]*Jawaharlal institute of postgraduate medical education & research (JIPMER), India, Pondicherry, India;* [2]*Saveetha Medical College and Hospital, Chennai, India*

Background: The habitual use of antimicrobials is linked to the rise of bacterial resistance, narrowing the effective range of the available drugs. A leading cause of bacterial resistance is the overall volume of antimicrobial consumption, especially the self-medication with antimicrobials (SMA). Inquiring the general public directly and recognizing the reasons and rationale of individuals for SMA enables formation of effectual strategies tackling the key predictors. However to the best of our knowledge no studies have been done in Karaikal to find out the extent of this problem.

Objectives: To determine the factors driving individuals to self-medicate with antimicrobials and to ascertain the prevalence and practice of consumption of non-prescribed antimicrobials in Karaikal, Puducherry, India.

Methods: Our hospital based cross-sectional study was conducted between June 2018 and September 2018 in the various Out-Patient Departments (OPD) of the Government General Hospital of Karaikal, India. After Institutional Ethics Committee clearance was obtained, a structured validated questionnaire was used to collect data from 504 patients and their relatives. Data analysis was done using SPSS version 25. Descriptive statistics were used and Pearson's Chi-square test was used to determine the associations between different variables. Variables found significantly associated with SMA ($p<0.05$) in the bivariate analysis were included in the multiple logistic regression model and the odds ratio (OR) and corresponding 95% confidence intervals were generated.

Results: One-third of the participants (33.9%) reported SMA in the past six months with the prevalence significantly affected by male gender(adjusted OR=1.83; 95% C.I.:1.2-2.79), a preference for SMA during minor illnesses (adjusted OR=3.05; 95%C.I.:1.77-5.25)and a history of SMA among family members(adjusted OR=3.43; 95%C.I.:2.16-5.43). The most commonly self-prescribed drug was Amoxicillin (55.2%) and the antimicrobials were mostly obtained from pharmacies (91.8%). Self-prescribed antimicrobials were commonly used to treat cold, cough and fever. Our participants self-medicated with antimicrobials because they found it easier to do so (32.2%) and as it saved them time (35.7%) and money (32.2%).

Conclusions: Our study revealed that the prevalence of SMA was high in Karaikal, Puducherry, India The high prevalence of self-prescribed antimicrobials can be lowered by approaching societal-cultural practices through community education, the supply-demand chain through stricter regulations of pharmacies and enforcing health policies for rational use of antimicrobials.

5133 | Are patients less likely to adhere to antidepressant treatment if they are not satisfied with their provider?

Macarius Donneyong[1], Teng-Jen Chang[1], John Bridges[2] and Olivia Okereke[3]
[1]*Ohio State University, Columbus, OH;* [2]*Ohio State University, Columbus, OH;* [3]*Massachusetts General Hospital and Harvard Medical School, Boston, MA*

Background: There is inadequate data on how patient satisfaction with their provider might impact racial/ethnic disparities in non-adherence (NA) to antidepressant (AD).

Objectives: To quantify racial/ethnic disparities in AD nonadherence and to assess whether disparities in patient satisfaction with their provider modifies the race/ethnicity-AD NA relationship.

Methods: AD users were identified from the Medical Expenditure Panel Survey (MEPS) data, 2010-2017. MEPS is a national panel survey on health care expenditures, verified self-reported prescribed medication use, access to and satisfaction with provider, etc. Satisfaction with provider was defined from patient responses to five major questions including whether the provider asks about medications and other treatments received elsewhere. Measures of annual medication refill adherence (MRA) were calculated separately for each therapeutic class (TC) as the total days' supply divided by 365 days. Overall MRA was obtained as the average of MRAs for participants using more than one AD. Patients were considered to be nonadherent if their overall MRA was <80%. Data collected in year 1 was used to define satisfaction levels and all covariates; year's 2 data was used to define AD NA. Multivariable-adjusted Generalized Linear Models (GLM), weighted by survey weights, were used to measure the odds ratios (ORs) between race/ethnicity and AD NA. Separate GLMs were also used to assess the associations between satisfaction levels (high, medium, low) and AD NA, adjusted for by patient demographics and provider's race/ethnicity, gender and specialty. Statistical interaction and stratified analysis were performed to assess for effect modification.

Results: Of the 58,021,381 weighted sample of AD users, majority (84%) were non-Hispanic Whites (NHW) compared to 6% Blacks; 7% Hispanics; and 3% Others. Compared to NHW, AD NA was significantly higher among Blacks (OR=1.51, 95%CI: 1.20, 1.89), Hispanics (OR=1.63, 95%CI:1.30, 2.04) and others (OR=1.15, 95%CI:0.81, 1.63) in multivariable-adjusted models. High satisfaction with provider, compared to low, was significantly associated with lower risk of AD NA (OR=0.63, 95%CI:0.48, 0.83) in multivariable-adjusted models. Racial/ethnic minorities were less satisfied with their providers compared to NHW ($P<0.05$); this further exaggerated the magnitudes of racial/ethnic disparities.

Conclusions: Racial/ethnic minorities were less satisfied with their providers and more likely to be nonadherent to AD. Disparities in satisfaction with providers further expanded racial/ethnic disparities in AD NA.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5146 | Utilization of Antihypertensive Medication in Ghana

Macarius Donneyong[1], Teng-Jen Chang[1], Anton Pottegård[2] and Jesper Hallas[2]

[1]*Ohio State University, Columbus, OH;*[2]*University of Southern Denmark, Odense, Denmark*

Background: Hypertension is now the second leading cause of outpatient morbidity in Ghana. However, there is little data on the access to and quality of antihypertensive medication (AHM) treatment in Ghana.

Objectives: To identify the predictors of use and quality of AHM treatment.

Methods: We analyzed the 205 Ghana National Health Insurance Scheme (NHIS) electronic claims data. Hypertension diagnosis was defined using the ICD-10 codes. We restricted our analysis to patients aged 12 years or older. Three AHM use and quality of treatment outcomes were measured: 1) prevalence of AHM use; 2) clinical guideline-concordant AHM use; and 3) the daily defined dose of AHM used. Patient-related (age, sex, comorbidities, use of other medications) and provider-related (region of healthcare provider, specialty type of healthcare provider) factors. Logistic regression models were used to model all outcomes except dose of antihypertensive treatment which was a continuous variable. A separate multiple linear regression model was used to identify potential predictors of dose (DDD) of antihypertensive medications dispensed per patient.

Results: Of the 11,215 hypertension patients identified, 92.6% of them were using at least one AHM agent. AHM used was associated with older age, female sex, outpatient hospital visits, use of other cardiovascular and antidiabetic agents. However, those with comorbid diabetes (OR=0.49, 95%CI:0.35, 0.68) and peripheral artery disease (PAD) (OR=0.16, 95%CI:0.05, 0.55) were less likely to use AHM. Only nearly a third (36.6%) of patients were treated according to clinical guidelines; the major predictors of which included older age, comorbid diabetes (OR=4.21, 95%CI:2.90, 6.10) and renal disease (OR=36.5; 95%CI:28.28, 47.15). All but male sex, metformin use, anticoagulant use and PAD were associated with increasing AHM DDDs.

Conclusions: Although AHM use was nearly impressive, only a about a third of hypertension patients were treated according to clinical guidelines. Several patient demographic, comorbidity and medication use factors were significant predictors of AHM access and quality of treatment.

Drug Utilization Research -> Trends and comparisons

49 | Characteristics of New Users of Newer Antidiabetic Drugs in Canada and the United Kingdom

Vanessa C Brunetti[1,2], Audray St-Jean[2], Sophie Dell'Aniello[2], Anat Fisher[3], Oriana HY Yu[2,4], Shawn C Budgen[5,6], Jean-Marc Daigle[7], Nianping Hu[8], Silvia Alessi-Severini[5,9], Baiju R Shah[10,11], Paul E. Ronksley[12], Lisa M. Lix[13], Pierre Ernst[2,14], Kristian B Filion[1,2,14] and the CNODES Investigators[15]

[1]*McGill University, Montreal, QC, Canada*[2]*Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada*[3]*University of British Columbia, Vancouver, BC, Canada*[4]*Jewish General Hospital, Montreal, QC, Canada*[5]*University of Manitoba, Winnipeg, MB, Canada*[6]*Memorial University of Newfoundland, St John's, NL, Canada*[7]*Institut National d'Excellence en Santé et en Services Sociaux (INESSS), Quebec, QC, Canada*[8]*The Health Quality Council, Saskatoon, SK, Canada*[9]*University of Manitoba, Winnipeg, MB, Canada*[10]*Institute for Clinical Evaluative Sciences (I.C.E.S.), Toronto, ON, Canada*[11]*Sunnybrook Health Sciences Centre, Toronto, ON, Canada*[12]*University of Calgary, Calgary, AB, Canada*[13]*University of Manitoba, Winnipeg, AB, Canada*[14]*McGill University, Montreal, QC, Canada*[15]*Canadian Network for Observational Drug Effect Studies (CNODES) Investigators, Montreal, QC, Canada*

Background: The characteristics of patients using newer antidiabetic drugs (sodium-glucose co-transporter 2 inhibitors [SGLT-2i], dipeptidyl peptidase 4 inhibitors [DPP-4i], and glucagon-like peptide 1 [GLP-1] receptor agonists) in a real-world setting are poorly understood.

Objectives: To describe the characteristics of new users of SGLT-2i, DPP-4i, and GLP-1 receptor agonists in Canada and the United Kingdom (UK).

Methods: The Canadian Network for Observational Drug Effect Studies (CNODES) conducted a multi-center cohort study using administrative health databases from 7 Canadian provinces and the UK Clinical Practice Research Datalink. We assembled a base cohort of new users of antidiabetic drugs between 2006 and 2018. From this base cohort, we constructed 3 separate cohorts of new users of SGLT-2i, DPP-4i, or GLP-1 receptor agonists between 2016 and 2018. Descriptive statistics were used to characterize the cohorts.

Results: Our base cohort of 2,175,815 new users of antidiabetic drugs included 166,722, 194,070 and 27,719 new users of SGLT-2i, DPP-4i and GLP-1 receptor agonists respectively, across jurisdictions. New users of GLP-1 receptor agonists were more likely to be female (54%) than new users of SGLT-2i (41%) or DPP-4i (44%), while new users of DPP-4i were more likely to be older (mean ± SD: 67.8 ± 12.3 yrs) than new users of SGLT-2i (64.4 ± 11.1 yrs) and GLP-1 receptor agonists (56.7 ± 12.2 yrs). The prevalence of cerebrovascular disease (SGLT-2i: 4%, DPP-4i: 7%, GLP-1 receptor agonists: 2%) and coronary artery disease (SGLT-2i: 20%, DPP-4i: 22%, GLP-1 receptor agonists: 16%) was similar among groups. In the UK, prevalence of obesity (body mass index ≥30kg/m^2; SGLT-2i: 71%, DPP-4i: 52%, GLP-1i: 88%) and impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73m^2; SGLT-2i: 6%, DPP-4i: 25%, GLP-1 receptor agonists: 15%) differed greatly between groups. New use of SGLT-2i or GLP-1 receptor agonists, but not DPP-4i, was commonly preceded by insulin use in Canada (SGLT-2i: 26%, GLP-1 receptor agonists: 33%) and the UK (SGLT-2i: 17%, GLP-1 receptor agonists: 29%).

Conclusions: Although all 3 classes are recommended as 2nd or 3rd line therapy, important differences in patient characteristics of new users of newer antidiabetic drugs exist. GLP-1 receptor agonists appear to have been prescribed off-label for weight loss, and SGLT-2i are less frequently used among patients with renal insufficiency. Although large trials have demonstrated benefits with SGLT2i and GLP-1 receptor agonists, these drugs do not appear to be preferentially prescribed to patients at elevated cardiovascular risk.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

113 | Spatial Distribution of Deprivation Driven Inequalities in Opioid Prescribing in English Primary Care: A Cross-sectional Analysis

Magdalena Nowakowska, Salwa Zghebi, Rosa Parisi, Li-Chia Chen, Darren M Ashcroft and Evangelos Kontopantelis
University of Manchester, Manchester, United Kingdom

Background: In 2018/19, over 23 million opioid prescriptions were issued in English primary care. Levels of prescribing are not distributed equally across regions and populations. A greater understanding of the geographical differences and social drivers of opioid prescribing is needed to guide policy responses and interventions.

Objectives: To explore regional variations in opioid prescribing in England and the role of socio-economic deprivation in driving inequalities in opioid prescribing.

Methods: National cross-sectional study of opioid prescriptions in year 2018/2019 in England. Using national general practice prescription data, the total volume of opioids prescribed in a practice was calculated and translated into Defined Daily Doses (DDD). The prescription data was attributed to 32,844 Lower Layer Super Output Areas (LSOAs), geographical units with an average of 1,500 people. Linear regression was used to model the association of socio-economic deprivation, measured using the Index of Multiple Deprivation (IMD) 2019 data, with levels of prescribing. The model accounted for population demographics and prevalence of selected health conditions. To examine the deprivation driven inequalities in opioid prescribing, we estimated the predicted average value of prescribing at each IMD level and compared prescribing in most and least deprived areas in each Clinical Commissioning Group (CCG).

Results: In total, 5,350,151,699 DDDs of opioids were prescribed. Prescribing of opioids, measured by DDD/1000 populations/day, was not distributed randomly between LSOAs across England and varied between 4 to 1,905 DDD/1000 population/day. On average, 93.77 (SD: 1.90, p-value < 0.001) more DDD/1000 population/day were prescribed in the most deprived areas compared to the least deprived areas. There were 10 CCGs where average prescribing in the most deprived areas was over 100% higher than in the least deprived areas. CCGs with on average higher levels of prescribing and higher average levels of deprivation also had higher levels within prescribing variation.

Conclusions: Even after adjusting for differences in population structure, practices differ significantly across the country in opioid prescribing. Socio-economic deprivation is a significant predictor of prescribing. The difference between prescribing in most and least deprived areas was more substantial in some CCGs compared to others. Future policies and interventions should focus on areas with elevated levels of prescribing and tackling the deprivation driven inequalities in areas where they are most prevalent.

130 | Temporal trends and changes in indication for opioid use in Catalonia, 2007-2017: A population-based study of 6 million individuals

Junqing Xie[1], Aleksandra Turkiewicz[2], Gary Collins[1], Martin Englund[2], Victoria Y. Strauss[1] and D. Prieto-Alhambra[1]
[1]*University of Oxford, Oxfordshire, United Kingdom;* [2]*Lund University, Lund, Sweden*

Background: North America is currently suffering from an opioid epidemic, and recent data suggesting an increase in opioid use is also seen in northern and central Europe, but little data have been reported for the situation in southern Europe.

Objectives: To evaluate secular trends of opioid and their subtypes use in primary care and changes in indication associated with opioid initiation from 2007 to 2017 in Catalonia, Spain.

Methods: Data were obtained from the SIDIAP (The System for the Development of Research in Primary Care) database, which contains electronic medical records and dispensation data for ~ 6 million people (>80% of the Catalan population). The incidence proportion of opioid use (codeine, tramadol, fentanyl, and morphine, with the latter three classified as strong opioids) in each calendar year was calculated. The denominators were registered individuals meeting following criteria at the first day of each calendar year: 1) ≥18 years old, 2) ≥1 year of valid data, 3) no registered use of the same opioid in previous one year. The numerators were all new opioid users during each calendar year. Age-sex standardization was performed using the population at the year of 2007 as the reference. Indications were obtained based on the related diagnosis closet prior to therapy initiation from a prespecified list including musculoskeletal pains, bone fracture/s, post-surgery, and cancer.

Results: Between 2007 and 2017, the incidence proportion of total opioid use decreased firstly and then increased, with the lowest rate in 2013 (2.0%) and the highest rate in 2017 (3.3%). Specifically, the use codeine followed a similar trend with total opioid, but tramadol, fentanyl and morphine increased continuously from 0.61% to 1.71%, 0.03% to 0.12%, and 0.01% to 0.05% respectively. In the same period, musculoskeletal pains (back pain, neck/shoulder pain, and osteoarthritis pain) consistently dominated the indications for total opioid, codeine, tramadol treatment, with an attributable 90% of total use over years. But the proportion of strong opioid/s use related to musculoskeletal pain increased from 75% to 80% for fentanyl and 40% to 72% for morphine, which is companied by cancer-related opioid use decreasing from 17% to 8% and 55% to 13% respectively.

Conclusions: Use of strong opioids in primary care has increased substantially during the study period (2007-2017) in Catalonia, replacing the use of weaker opioids (codeine). Musculoskeletal pain has gradually become the most common indication for strong opioid prescriptions, which is an unexpected sign of chronic pain management.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

133 | Prescription drug use in testicular cancer patients: A Danish nationwide registry study

Anne Katrine Duun-Henriksen[1], Michael Kreiberg[2], Jakob Lauritsen[2], Mikkel Bandak[2], Thomas Wagner[2], Josephine Rosenvilde[2], Irene Petersen[3], Klaus K. Andersen[1], Christian Dehlendorff[1] and Gedske Daugaard[2]

[1]*Danish Cancer Society Research Centre, Copenhagen, Denmark;* [2]*Rigshospitalet, Copenhagen, Denmark;* [3]*University College London, London, United Kingdom*

Background: In developed countries testicular cancer is the most common solid tumour in men between 14 and 44 years of age. Testicular cancer is a highly curable disease with a 5-year survival rate around 95%, which gives rise to a growing population of long-term survivors.

Objectives: To describe the use of prescription drugs in testicular cancer survivors compared to a cohort matched on age.

Methods: From the Danish nationwide registries, we identified males diagnosed with incident testicular cancer during 2000-2015 and a randomly selected male comparison cohort matched on age at date of diagnosis. Eligible comparisons had to be cancer free and alive on the date of diagnosis (index date). Prescription history was obtained from the Danish National Prescription Registry. The men were followed from time of diagnosis/index date until date of death, date of second (testicular cancer patients)/incident cancer (comparisons) or end of study (31.12.2016) whichever occurred first. Drug use was assessed for 0-5, 5-10 and 10-15 years post diagnosis by estimating prescription rates with 95% confidence intervals (CI) for each time interval.

Results: In total, 5,043 patients and 22,197 individuals in a comparison cohort were included in the study with a mean age at time of diagnosis/index date of 38 years. Median follow up from diagnosis was 8.8 years (interquartile range: 4.9-13.6 years). Testicular cancer patients had a higher prescription rate in all three intervals compared to the comparison cohort. Within the first 5 years after diagnosis/index date the rates among cancer patients and comparisons were 5.80 (95% CI: 5.76-5.83) prescriptions/person-year and 4.81 (95% CI: 4.80-4.83) prescriptions/person-year, respectively. Further, 5-10 years after diagnosis/index date, the rate among cancer patients and comparisons were 6.99 (95% CI: 6.95-7.03) prescriptions/person-year and 6.00 (95% CI: 5.99-6.02) prescriptions/person-year. The rates among cancer patients and comparisons 10-15 years after diagnosis/index date were 8.23 (95% CI: 8.16-8.29) prescriptions/person-year and 7.11 (95% CI: 7.09-7.14) prescriptions/person-year, respectively. We will assess and present which drug classes that contributed to this elevated prescription rate in testicular cancer survivors.

Conclusions: We confirmed a larger prescription drug burden in testicular cancer survivors during the first 15 years after diagnosis compared to a comparison cohort.

2354 | Over - the - counter drugs: A pharmacoepidemiological study in Greece

Georgios Poulentzas[1], Panagiotis Nikolaos Lalagkas[1], Theodora Tatsiou[1], Eleftherios Berberoglou[2], Dimitra Hadjipavlou - Litina[1], Christos Kontogiorgis[2] and Theodoros Constantinides[2]

[1]*Aristotle University of Thessaloniki, Thessaloniki, Greece;* [2]*Democritus University of Thrace, Alexandroupolis, Greece*

Background: Some medicines are available over the counter (OTC) in Greece without a prescription from physicians. There is a limited understanding of patients' knowledge level regarding OTC medicines, how they get informed about their proper use and whether there are any associated potential health issues.

Objectives: The goal of this study is to determine the knowledge level, habits, sources of information and selection criteria of Greek residents regarding OTC medicines, as well as their opinion about the dispensing of these medicines in non-pharmacy settings.

Methods: During 5 months of 2017, 920 people aged over 17, who were approached in community pharmacies and gathering points, were interviewed anonymously. 782 of those individuals participated (85% response rate) by answering a predesigned, cross-sectional questionnaire consisting of 12 multiple choice questions. Statistical analysis was performed with IBM SPSS Statistics v.15.0 program using descriptive statistics and chi-square while crude odds ratios were calculated with logistic regression.

Results: 507 respondents (64.8%) exhibited good knowledge about which medicines are categorized as OTC and which are not. Healthcare professionals (such as pharmacists and physicians) are the main source of information about the proper use, dosage and adverse effects of OTC medications for 648 (84%) of the respondents. When asked about the selection criteria regarding the purchase of OTC medication, physicians play the most critical role for 510 respondents (65.6%), followed by pharmacists for 468 (60.2%) and friends and family for 173 (22.3%). Product price is a more important factor for the selection of OTC medicines when it comes to elderly people (OR 1.73, 95% CI 1.10-2.72) Furthermore, 61.2% of the respondents stated that they are reluctant to buy OTC medicines from a non-pharmacy setting, while 69.6% believes that retail of OTC medicines in super markets will increase their abuse and misuse. However, younger people seem to be more positive about purchasing them elsewhere than pharmacies than older people (OR 2.20, 95% CI 1.37-3.54).

Conclusions: Healthcare professionals play a crucial role in people's information about OTC use and they have the biggest impact in the final selection. Finally, Greek society presents reluctance to accept OTC disposal elsewhere than community pharmacies.

2415 | Decreasing adherence to antiretroviral therapy over 4 years of follow-up in a commercially-insured US population of patients with HIV

Julie Priest[1], Rachel Bhak[2], Maral DerSarkissian[2], Cindy Garris[1], Alan Oglesby[1], Colin Kunzweiler[2], Ellie Fuqua[2], Suna Park[2] and Mei S Duh[2]

[1]*ViiV Healthcare, Durham, NC;* [2]*Analysis Group, Boston, MA*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Research has shown single-tablet regimens (STRs) of antiretrovirals (ARVs) lead to better medication adherence and viral suppression than multi-tablet regimens (MTRs); however literature in the commercially-insured US population is limited.

Objectives: This study compared yearly and longer-term ARV adherence among HIV patients overall and by STRs vs. MTRs.

Methods: A retrospective study using Optum Clinformatics US-based commercial claims data was conducted. Patients with an HIV-1 diagnosis during 2011-2017, age ≥ 18 years at index (date of first complete ARV regimen during the study period), and continuous enrollment for ≥ 3 months before index (baseline) and ≥ 12 months after index (observation) were included. MTRs were required to be comprised of 3 or more agents across at least 2 classes. Adherence was measured as the proportion of days covered (PDC) and compared using a Chi-square test. PDC was examined in the 1-year observation period for the overall analysis, and each year following index among patients with at least 4 years of continuous data. A subgroup analysis was conducted among patients with index during 2014-2016 to evaluate modern ARV adherence.

Results: Among the 15,153 included patients, median age was 45 years, the majority were male (88%), and 53% were in the Southern region of the US. At index, 58% (n = 8,715) were receiving an STR and 43% (n = 6,438) an MTR. During year 1, the proportion of patients with PDC ≥ 0.90 was 63% overall, and greater for STR than MTR (67% vs. 58%, $P < .001$). Among patients with at least 4 years of observation (STR: n = 1,961, MTR: n = 1,857), PDC ≥ 0.90 decreased over time, from 67% in year 1 to 53% in year 4, and was consistently significantly higher for STR than MTR ($P < .001$). In the subgroup of patients with index during 2014-2016 (STR: n = 3,646, MTR: n = 1,668), similar but slightly worse trends were observed, with PDC ≥ 0.90 for 57% of patients overall (STR: 62% vs. MTR: 48%, $P < .001$). Among patients with at least 3 years of observation (STR: n = 489, MTR: n = 322), PDC ≥ 0.90 also decreased over time (59% in year 1 to 42% in year 3), and was consistently significantly higher for STR than MTR ($P < .001$).

Conclusions: Adherence in this population of patients with HIV showed room for improvement in the first year of observation overall and in the modern ARV era, with those receiving STRs having higher adherence compared to those receiving MTRs. For the patients with 4 years of follow-up, adherence tended to decrease year on year. Maintaining high rates of ARV adherence is a critically important aspect of therapy for patients with HIV.

2427 | Frequency of opioid dispensing after surgical abortion in the United States

Liza R Gibbs[1], Julia A Pisc[1], Kari P Braaten[2], Brian T Bateman[3] and Elizabeth M Garry[1]

[1]*Aetion, Inc, Boston, MA;* [2]*Brigham and Women's Hospital, Boston, MA;* [3]*Brigham and Women's Hospital, Boston, MA*

Background: Over 800,000 induced abortions occur annually in the US, of which two thirds are surgical. NSAIDs, not opioids, are recommended for pain management after surgical abortion.

Objectives: Characterization of opioid dispensing among US commercially insured women after surgical abortion.

Methods: Women aged 15-50 years with an outpatient claim for dilation and curettage or evacuation surgical abortion (D&C/D&E) were identified in the IBM MarketScan database from Jan 2015 - Sep 2018, excluding those with >1 opioid fill in the prior 90d, evidence of opioid dependence or abuse in the prior 180d (baseline), or spontaneous abortion or mifespristone use in the 7d prior. The frequency of an oral opioid dispensing within 7d after abortion, refill in 6w after initial fill, chronic use (≥6 fills) in 1y after abortion or initial fill, and median morphine milligram equivalent (MME) total dose of the initial fill and refill were described. Multivariable logistic regression was used to evaluate predictors of opioid fill.

Results: Among the 28,304 women who underwent induced surgical abortion, 41.0% had D&E, 35.5% had anesthesia (not inclusive of moderate sedation), 9.4% had moderate sedation, and 8.3% had an opioid fill within 7d. The strongest predictors of an opioid fill were non-Northeast region [aOR (95% CI) West: 8.25 (7.23-9.42); South: 7.74 (6.75-8.87); Midwest: 5.12 (4.37-5.98)], moderate sedation for the procedure [1.57 (1.36-1.80)], and baseline depression or antidepressant use [1.41 (1.24-1.61)]. The median (IQR) MME dose was 75 (50-113), similar for D&C and D&E, and increased for women with an abortion complication [90 (75-150)] and from the Northeast [90.0 (54.0-150.0)] and South [90.0 (54.0-120.0)]. Of those with an opioid fill and 6w follow-up (N=2,257), 10.0% had a refill. Complication was the strongest predictor of refill [2.98 (1.59-5.59)]. Refill dose was 112.5 (75.0-225.0), increased relative to dose of the initial fill. Among women with 1y follow-up, chronic use was identified among 2.2% of women with an initial fill (N=1,396), versus 0.3% among those without (N=13,942). All analyses were conducted using the Aetion Evidence Platform v3.19.

Conclusions: The frequency of an opioid fill after surgical abortion among commercially insured women was high given recommendations that NSAIDs be used for clinical analgesia. Opioid prescribing contrary to recommendations may increase the potential for misuse or abuse.

2450 | Prescription patterns of outpatients and the potential of multiplexed pharmacogenomic testing

Sze Ling Chan[1], Hariz ZW Liew[1], Francis Nguyen[1], Julian Thumboo[2], Wan Cheng Chow[3] and Cynthia Sung[4]

[1]*SingHealth, Singapore, Singapore;* [2]*Singapore General Hospital, Singapore, Singapore;* [3]*Singapore General Hospital, Singapore, Singapore;* [4]*Duke-NUS Medical School, Singapore, Singapore*

Background: Pre-emptive pharmacogenomic (PGx) testing is potentially an efficient approach to improve safety and efficacy of drug treatment. However, it is unclear who and when to test in initial implementation efforts.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: The aim of this study was to describe the prescription pattern of PGx drugs among medical outpatients at a large tertiary-care hospital in Singapore to ascertain the potential of multiplexed PGx testing.

Methods: This is a retrospective cohort study of adult medical outpatients. The 5-year cumulative incidence (CI) for receiving new PGx drugs was estimated from dispensing records using competing risks analysis. We considered 3 groups of drugs in our analysis: (i) all PGx drugs (defined as Clinical Pharmacogenetics Implementation Consortium (CPIC) level A or B), (ii) PGx drugs with a CPIC or Dutch Pharmacogenetics Working Group (DPWG) guideline and (iii) PGx drugs with a clinical effect of class D-F based on DPWG guidelines (termed 'high risk' drug). Comparisons of CIs were also done by demographic and clinical characteristics using Gray's test.

Results: The 5-year CIs of receiving any new PGx drug, PGx drug with guidelines, and a 'high risk' drug were 42.6%, 37.3% and 13.7%, respectively. The most common newly prescribed PGx drugs were omeprazole, codeine, simvastatin, dextromethorphan and clopidogrel (5-year CIs: 17.4%, 8.8%, 8.1%, 4.9% and 3.7%, respectively). The 5-year CI of receiving at least 1 PGx drug was higher for patients >40 years old at index visit (43.6% vs. ≤40 years old 36.0%, $p < 2.2 \times 10^{-22}$), Malays and Indians (50.3% and 49.8% vs. Chinese 31.1%, $p < 2.2 \times 10^{-22}$) and those who attended one of the following 4 specialties at the index visit compared to other specialties: infectious diseases (46.2% vs. 42.6%, $p = 2.9 \times 10^{-4}$), psychiatry (48.3% vs. 42.3%, $p = 7.4 \times 10^{-13}$), renal (49.8% vs. 40.9%, $p < 2.2 \times 10^{-22}$) and rheumatology & immunology (54.8% vs. 41.7%, $p < 2.2 \times 10^{-22}$). Patients prescribed ≥5 drugs at index visit had a 5-year CI of 51.7% compared to those prescribed 0-4 drugs (41.7%, $p < 2.2 \times 10^{-22}$).

Conclusions: Medical outpatients have a substantial probability of benefiting from pre-emptive PGx testing. Certain subgroups of patients have higher probability of receiving PGx drugs, but predictive modelling may be needed for yielding insights into risk stratification for pre-emptive genotyping implementation programs.

2548 | Predicting persistent high-dose opioid use after total knee replacement

Chandrasekar Gopalakrishnan[1], Jessica M Franklin[1], Yinzhu Jin[1], Daniel H Solomon[2], Jeffrey N Katz[3,2], Yvonne C Lee[4], Patricia D Franklin[5], Joyce Lii[1], Rishi J Desai[1] and Seoyoung C Kim[1,2]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [4]Northwestern University, Chicago, IL; [5]Northwestern University, Chicago, IL

Background: Patients undergoing total knee replacement (TKR) are at increased risk of persistent opioid use and dependence

Objectives: To identify patients with persistent high-dose opioid use after TKR using group-based trajectory models (GBTM) and determine predictors of persistent high-dose opioid users using pre-TKR patient characteristics

Methods: Using US Medicare Parts A, B and D claims (2010-2014), we identified patients aged ≥65 years who underwent a TKR and had no history of cancer or high-dose opioid use (>25 mean morphine equivalents (MME)/day) in the year prior. All patients were continuously enrolled in Medicare for ≥360 days prior to and ≥30 days after the TKR. To determine opioid filling patterns, patients were followed up to 360 days from the day of TKR. We modeled 12 monthly indicators of opioid prescription fills as a continuous (MME/day) variable using a censored normal GBTM and categorized patients into 4 groups. The primary outcome was persistent high-dose opioid use defined as patients in trajectory Group 3 (38.8 MME/day) or Group 4 (22.4 MME/day). We split the data into training (2010-2013 data) and test (2014 data) sets and used logistic regression to predict high-dose opioid use vs. low-dose opioid use (Groups 1 and 2) as a binary outcome utilizing pre-TKR patient characteristics as candidate predictors using the least absolute shrinkage and selection operator (LASSO) regression for variable selection. A reduced model with only 10 prespecified variables readily available for clinical use was also considered

Results: The final study cohort included 142,089 patients. The GBTM identified 4 distinct trajectories (Group 1- Short-term, low-dose, Group 2- long-term, low-dose, Group 3- medium-term, high-dose, Group 4-long-term, high-dose) of opioid use in the year after TKR. Using logistic regression and LASSO, we predicted the probability of persistent high-dose opioid use (N=17,171) in the training set (N=101,810) for an AUC=0.80. The AUC in the test set (N=40,279) predicting high opioid use (N=5,893) was 0.77. The final model selected 33 variables and identified baseline history of opioid use as the strongest positive predictor of high-dose persistent opioid use. The reduced model with only ten predictors also performed equally well (AUC=0.77)

Conclusions: In this cohort of older patients with no history of cancer or high-dose opioid use at baseline, 16.2% became high dose (28.1 MME/day) opioid users during the year after TKR. Our prediction model with 10 readily available clinical factors may help identify patients at high risk of future adverse outcomes from persistent opioid use and dependence after TKR

2556 | Trends in gabapentinoid prescriptions and coprescription with opioids in the four UK nations

Alvi Rahman[1,2], Joseph Kane[3], François Montastruc[4] and Christel Renoux[2,5]

[1]McGill University, Montreal, QC, Canada; [2]Lady Davis Institute for Medical Research, Montreal, QC, Canada; [3]Queen's University Belfast, Belfast, United Kingdom; [4]Faculty of Medicine and Toulouse University Hospital, Toulouse, France; [5]McGill University, Montreal, QC, Canada

Background: Gabapentinoid drugs, namely gabapentin and pregabalin, were approved in the United Kingdom in 1993 and 2004, respectively, for the treatment of epilepsy, neuropathic pain and generalised anxiety disorders (pregabalin). In the last decade, the rate of patients

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

newly treated with gabapentinoids has tripled but the potential differences in prescription and coprescription with opioids between the four UK nations is unknown.

Objectives: To estimate the annual rate of patients newly prescribed gabapentin and pregabalin in each UK nation (England, Northern Ireland, Scotland, and Wales) and the proportion of patients concomitantly prescribed opioids.

Methods: We used the Clinical Practice Research Datalink, a UK primary care database, to identify patients registered between 1993 and 2017. We fitted Poisson regression models to estimate the annual rate (per 100,000 person-years (PY)) of patients newly prescribed gabapentin and pregabalin in each UK nation, and the rate ratio (RR) from 2007 to 2017. We also calculated the proportion of patients with same-day coprescription with opioids.

Results: The annual rate of patients newly prescribed pregabalin increased steadily during the study period. Between 2007 and 2017, the rate rose from 118 to 351 per 100,000 PY (RR: 2.97; 95% CI: 2.85-3.11) in England, from 96 to 418 per 100,000 PY (RR: 4.37; 95% CI: 3.96-4.82) in Scotland, and from 104 to 370 per 100,000 PY (RR: 3.55; 95% CI: 3.23-3.91) in Wales. However, in Northern Ireland, we observed a rapid escalation from 546 (95% CI: 511-582) per 100,000 PY in 2007 to 1,139 (95% CI: 1,088-1,193) per 100,000 PY in 2010, at which point the rate was 5 times higher than in the other nations. This peak was followed by a decline to 532 (95% CI: 493-573) per 100,000 PY in 2017, but the rate remained higher than in the other nations. We observed a regular increase in patients newly prescribed gabapentin in England, Scotland, and Wales, which stabilized from 2015 onwards. In Northern Ireland however, following a plateau from 2005 to 2009, the rate of first gabapentin use sharply increased and surpassed rates in the other nations in 2017. The proportion of concomitant prescription of opioids remained relatively constant through the study period. In 2017, 16 to 19% of patients newly prescribed gabapentinoids in each of the four nations were concomitantly prescribed opioids.

Conclusions: Since their introduction in the UK, the use of gabapentinoids has notably increased in all nations, more so in Northern Ireland with an unprecedented peak in pregabalin prescriptions. A substantial proportion of patients were concomitantly prescribed opioids in all nations.

2574 | Incidence of anorexia nervosa and the prescribing of psychotropic medications from UK Primary Care, 1996-2016: A retrospective database study

Maedeh Y Beykloo[1], Dasha Nicholls[2], Ian Wong[1], Mima Simic[3], Elizabeth Mills[1] and Ruth Brauer[1]

[1]University College London (UCL), London, United Kingdom; [2]Imperial College London, London, United Kingdom; [3]South London and Maudsley NHS Foundation Trust, London, United Kingdom

Background: Anorexia nervosa (AN) is a psychiatric disorder characterised by restrictive eating and an intense fear of weight gain (1). The most recent study reporting the incidence of AN was conducted using primary care records from 2000 to 2009 and found the incidence to be stable by gender despite minor fluctuations across the years (2). There is currently a lack in evidence for the efficacy of psychotropic medications in AN, however, they are sometimes prescribed if there is a less than optimal treatment response with first line psychological treatments.

Objectives: This study aimed to comprehensively assess trends in the incidence of AN in order to provide up-to-date results and to measure the use of psychotropic medications in individuals with AN over two decades.

Methods: A retrospective database study was conducted using The Health Improvement Network (THIN) database which consists of anonymised medical records from general practices throughout the UK. Individuals aged 12-50 years and with recorded AN diagnosis were identified between 1996 and 2016. The incidence of AN were calculated annually and Kaplan Meier analyses were used to measure the prescribing duration and cessation of psychotropic medications in this cohort.

Results: A total of 17,597 individuals were identified from 1996-2016, of which 80.28% were females. The incidence of AN remained fairly constant for females and males from an overall incidence of 15.21/100,000 person years in 1996, to 21.84/100,000 person years in 2006, followed by a decrease in 2016 to 18.25/100,000 person years. Almost half of individuals with AN (47.44%) received a prescription for psychotropic medication in the study period. Most individuals receiving medication were prescribed antidepressants (98.13%), whilst under a fifth (17.29%) were prescribed antipsychotics, which is in line with our previous study (3). The most common antidepressant prescribed was fluoxetine (59.73%) and the most common antipsychotic was olanzapine (8.90%). Under half of individuals (46%) initiated on a psychotropic medication continued with a psychotropic prescription after six months.

Conclusions: This study provides the most up-to-date trends for AN incidence and highlights the use of psychotropic medications for the treatment of AN in UK primary care, despite lack of sufficient evidence. As our study is limited to patient data as recorded in primary care, we call for greater investigations into the benefits and harms associated with psychotropic medications in this population.

2619 | The impact of changing biosimilar policies for rheumatic conditions and inflammatory bowel disease in Ontario, Canada

Mina Tadrous[1], Daniel McCormack[2], Sophie Kitchen[3], Martins Diana[3] and Tara Gomes[3]

[1]Women's College Hospital, Toronto, ON, Canada; [2]ICES, Toronto, ON, Canada; [3]Ontario Drug Policy Research Network, Toronto, ON, Canada

Background: Biologic drugs are important treatment options for several conditions, including rheumatic conditions, gastrointestinal disease, and diabetes. Yet, these medications are associated with high costs. Recently available biosimilars are similar, lower cost medications

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

with no clinically meaningful differences compared to their innovator biologics. Two drugs currently have available biosimilars but are listed differently. We sought to determine the impact on biosimilar utilization when different listing strategies are used.

Objectives: We sought to determine the impact on biosimilar utilization when different formulary listing strategies are used.

Methods: We conducted a population-based time-series study between January 2010 and June 2019 to assess the quarterly utilization of biologics used for the treatment of rheumatic conditions and inflammatory bowel disease (IBD) with currently available biosimilars (etanercept and infliximab) through the public drug program in Ontario, Canada. Utilization was defined as the number of individuals who were dispensed a prescription for a publicly-funded biologic or biosimilar per quarter. Trends in utilization and expenditures for biologics were forecasted to June 30, 2022. We used Holt-Winters' exponential smoothing models to forecast utilization and costs.

Results: Between Q1 2010 and Q2 2019, the number of biologic users for rheumatic and IBD indications increased by 133% from 5,225 to 12,178 users. Among biologics indicated for rheumatic conditions and IBD with a currently available biosimilar, 16.7% of users (N=1,196 of 7,158) were treated with a biosimilar in Q2-2019. By Q2-2022, this was similar for both drugs. It is estimated that 2,717 users (95% CI: 1,899, 3,536) out of 8,142 biologic users (95% CI: 7,438, 8,847) with a currently available biosimilar will be treated with biosimilars, representing a proportion of 35.1% (95% CI: 24.5%, 45.6%).

Conclusions: The utilization of biologic drugs for rheumatic and IBD indications are substantial and expected to rise over time. Biosimilars current uptake is low and did not different greatly between drugs. Traditional formulary-based policies may not be effective at significantly altering biosimilar uptake.

2633 | Trends in oral anticoagulant co-prescription with antiepileptic drugs among adults with epilepsy, 2010-2018

Emily K. Acton[1,2,3], Allison W. Willis[1,2,4,3], Michael A. Gelfand[4], Sean Hennessy[3,1,5], John R. Pollard[4,6] and Scott E. Kasner[4]

[1]*University of Pennsylvania School of Medicine, Philadelphia, PA;* [2]*University of Pennsylvania School of Medicine, Philadelphia, PA;* [3]*University of Pennsylvania School of Medicine, Philadelphia, PA;* [4]*University of Pennsylvania, Philadelphia, PA;* [5]*University of Pennsylvania School of Medicine, Philadelphia, PA;* [6]*ChristianaCare, Newark, DE*

Background: Adults with epilepsy often have pro-thrombotic conditions necessitating concurrent treatment with antiepileptic drugs (AEDs) and oral anticoagulants (OACs). However, with growing evidence that many widely used AEDs interact with warfarin, and potentially with newer direct oral anticoagulants (DOACs), treatment considerations for epilepsy patients requiring anticoagulation are changing, and actual prescribing practices are not well understood.

Objectives: To estimate the prevalence and characterize the patterns of outpatient prescriptions for concurrent OACs and AEDs in adults with epilepsy.

Methods: We conducted a retrospective assessment of OAC and AED dispensing using the 2010-2018 OptumInsight Clinformatics™ Data Mart, a large claims database. Included enrollees were 18 years of age or older with ICD-9/10 codes for epilepsy. Episodes of AED use lasting ≥14 contiguous days in a given year were counted and classified in terms of presence of ≥1 enzyme-inducing AEDs (EI-AEDs, potentially interacting), or presence of only non-enzyme inducing AEDs (NEI-AEDs, presumably non-interacting). Annual prevalences of contiguous, concomitant prescriptions for OACs with AEDs for ≥14 days were compared over successive years with the Cochran-Armitage test for trend. Multivariable logistic regression was used to evaluate the associations of sociodemographic characteristics with concomitant prescribing patterns.

Results: Among adults with epilepsy on studied AEDs, the prevalence per 1,000 patients of concurrent OACs increased from 58.4 in 2010 to 92.0 in 2018 (odds ratio (OR) 1.63, confidence interval (CI) 1.58-1.69; P<0.001). DOAC use in this population rapidly increased from 2010 to 2018, with yearly % changes in co-dispensing with AEDs of +0.29, +0.30, +0.41, + 0.57, +0.59, +0.84, +1.06, +1.31 (P < 0.001). Simultaneously, warfarin use with AEDs decreased, with yearly % changes of +0.02, -0.01, -0.08, -0.35, -0.30, -0.20, -0.34, -0.39 (P < 0.001). In 2018, DOACs were less likely than warfarin to be co-dispensed with potentially interacting EI-AEDs versus NEI-AEDs alone (OR 0.67, CI 0.63-0.72). Characteristics independently associated with ≥1 episode of concurrent EI-AED use with OACs in 2018 were older age, female sex, white race, and net worth <$250K.

Conclusions: The rapid rise in the concomitant use of OACs with AEDs, including those with demonstrated warfarin and potential DOAC interactions, highlights the need to better characterize and optimize prescribing practices for the concomitant use of these drug classes.

2651 | Correlation between antibiotic consumption and resistance at an intensive care unit in Serbia

Radmila Popović[1], Ana Tomas[2], Sanja Vicković[1], Gordana Jovanović[1], Olga Horvat[2], Zdenko Tomić[2] and Ana Sabo[2]

[1]*University of Novi Sad, Novi Sad, Serbia;* [2]*University of Novi Sad, Novi Sad, Serbia*

Background: The paucity of information on quantity and quality of antimicrobial prescribing is one of the important barriers to the successful development and implementation of antimicrobial stewardship programs in Serbia.

Objectives: To describe antimicrobial prescribing practices and antimicrobial resistance among gram negative pathogens and to relate exposure to antimicrobials to the development of antimicrobial resistance.

Methods: A retrospective, observational study was performed in an intensive care unit in the largest tertiary health care center in Vojvodina, Serbia from 2014 to 2018. Antibiotic prescription data were analysed according to the WHO anatomical therapeutic chemical (ATC)/defined daily dose (DDD) methodology; antibiotic resistance

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

was expressed as incidence density adjusted for total inpatient-days, Targeted organisms included Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter spp. Individual trends were determined by linear regression, while possible associations between antibiotic prescription and resistance were evaluated using cross-correlation analysis.

Results: Overall decrease in antibiotic utilization was observed. The prescription rates of piperacillin-tazobactam increased significantly, while consumption of 3rd and 4th generation cephalosporins and fluoroquinolones decreased. Results over 5 years indicated significantly rising incidence densities of doripenem resistant Acinetobacter spp., piperacillin/tazobactam resistant P. aeruginosa and doripenem, ertapenem, meropenem and colistin resistant Klebsiella pneumoniae. Cross-correlation analysis demonstrated positive association between the use of glycopeptides (R=0.76) and resistance to piperacillin/tazobactam in P. aeuruginosa. Strong positive correlation (R=0.97) has been found between the colistin use and resistance to doripenem in Acinetobaccter spp. For K. pneumoniae, resistance to colistin was strongly positively associated with use of colistin (R=0.89), carbapenems (R=0.73) and imidazoles (R=0.75). Positive association between the use of colistin and carbapenems and carbapenem resistance in K. pneumoniae was identified. There was an inverse relationship between the use of 1st and 2nd generation cephalosporins with the resistance to colistin and carbapenems in K. pneumoniae.

Conclusions: In conclusion, our data demonstrated increase in resistance and a correlation between prescription of and Gram-negative bacterial resistance to several antimicrobial agents in Serbian hospital.

2657 | Sensitivity of treatment patterns to grace period selection in medications with tolerability issues: A real-world example of hedgehog inhibitor use in basal cell carcinoma

Wenzhen Ge[1], Ning Wu[1], Chieh-I Chen[1], Matthew G Fury[1], Emily Ruiz[2] and Jessica J Jalbert[1]

[1]*Regeneron Pharmaceuticals, Inc., Tarrytown, NY;* [2]*Brigham and Women's Hospital, Boston, MA*

Background: Hedgehog inhibitors (HHIs) are oral targeted therapies approved for the treatment of advanced basal cell carcinoma (BCC). As patients commonly experience adverse events that may be managed through treatment interruptions, we hypothesized that HHI treatment patterns may be sensitive to grace period (GP) duration.

Objectives: To assess the impact of GP selection on patterns of HHI treatment interruptions (TI), treatment duration, and re-initiations (RI) among patients with BCC.

Methods: This was a retrospective cohort study using MarketScan Commercial/Medicare databases (01/01/2013-09/30/2018). We identified new users of HHIs (index date = date of the first dispensation), ≥18 years of age who were continuously enrolled for ≥6 months prior to the index date (i.e. baseline) with ≥1 baseline BCC diagnosis. TIs were defined as a lack of dispensation following the exhaustion of days' supply and allotted GP. RI was defined as ≥1 HHI dispensation after TI. The Kaplan-Meier method was used to estimate time to HHI TI and, among patients with a TI, incidence of RI. HHIs are generally dispensed in 30-days' supply and indicated as long as a patient derives a clinical benefit, however, since TIs are commonly employed during HHI therapy, sensitivity analyses were conducted using GPs of 14, 30, 60, 90 and 120 days.

Results: We identified 469 patients with a BCC diagnosis initiating HHIs. The mean (SD) age was 67.6 (15.8) years, 64.2% were men, 51.2% were covered by commercial insurance and 99.2% initiated vismodegib. Using a GP of 14, 30, 60, 90 and 120 days, the risk of HHI TI was 79.2%, 68.8%, 60.0%, 55.4% and 51.4% at 6 months and 94.8%, 91.3%, 88.2%, 83.2% and 80.2%, at 1 year, respectively. Median HHI treatment duration ranged from 94 days (95% CI: 90-109) using a GP of 14 days to 173 days (95% CI: 156-194) using a GP of 120 days. At 6 months following TI, incidence of RI was 35.8%, 19.8%, 11.3%, 6.9% and 4.9% using a GP of 14, 30, 60, 90 and 120 days, respectively. The incidence of HHI RI at 1-year following TI ranged from 40.8% using a 14-day GP to 13.4% using a 120-day GP.

Conclusions: Characterizing real-world persistence on HHIs is challenging due to the use of drug holidays, as TIs, treatment duration, and RIs were sensitive to the duration of the GP selected. Real-world studies of medications with tolerability issues should consider the use of drug holidays in order to accurately characterize drug exposures.

2661 | Medication of diabetes in middle-aged and elderly: Survey data from the china health and retirement longitudinal study (CHARLS)

Lili Liu, Shengfeng Wang and Siyan Zhan

Peking University, Beijing, China

Background: Compared to the increasing prevalence of diabetes in middle-aged and elderly, the blood glucose control rate is extremely low. Medication with lifestyle intervention was recommended in the national guideline for the prevention and control of diabetes in primary care (2018).

Objectives: This study aims to provide reliable estimates of medication trends and related influencing factors in the middle-aged and elderly diabetes in China.

Methods: The China Health and Retirement Longitudinal Study (CHARLS) is a cross-sectional survey using a four-stage, stratified, cluster sampling to select eligible individuals. We analyzed the wave1-3 national survey data from 2011~2016. Diabetes was considered as a fasting plasma glucose ≥ 126mg/dl or a glycosylated hemoglobin (HbA1c) ≥ 6.5% or self-reporting. Multivariable logistic regressions were used to identify medication related influencing factors. The ethics committee of Peking University Health Science Center approved this study, and all participants gave written informed consent before participation.

Results: From 2011 to 2016, the age standardized prevalence of diabetes increased from 13.04% to 16.20% in all respondents ≥ 45 years included. The medication rate was similarly going up from 30.08% to

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

33.97%, and utilization rates of both western medicine and insulin were increasing, except slightly decline of traditional Chinese medicine. Among all patients with diabetes in 2015~2016, only 1323 (19.27%) had been examined by community/village doctors regularly. In the medication, only 1172(33.97%) of whom were treated with medicine (68.94% with western medicine, 24.23% with insulin, and 6.83% with traditional Chinese medicine). After controlling for covariates, heart disease, drink and type of residents are significantly influenced the medication of diabetes. Compared with patients without medication, the patients with medication drunk more frequently in daily life (OR = 1.71, [95% CI 1.34-2.18]). Meanwhile, obesity, highly educated and those with heart disease were more likely to take medicine.

Conclusions: The medication rate of diabetes in the Chinese middle-aged and elderly population is delightfully increasing, despite the prevalence rises unsatisfactorily. In the future, we should strengthen the education of life intervention and chronic disease management, promote the blood glucose control rate, and then to improve the quality of life.

2667 | Drug utilization for symptom management by patients with multiple sclerosis by phenotype in Germany

Denise Oleske, 60064[1], Lou Barbato[2] and Bruce Barger[3]
[1]*AbbVie, Inc, North Chicago, IL;* [2]*AbbVie, Inc, North Chicago, IL;* [3]*AbbVie, Inc, North Chicago, IL*

Background: Knowledge of drug utilization for symptom management by multiple sclerosis (MS) phenotype provides context for safety assessments and potentially impacts efficacy profiles of new disease modifying therapies in development for MS. Little information exists about non-disease modifying drug utilization by MS phenotype owing to the relative rarity of some of its subtypes. Data from a large health insurance claim database in Germany where MS phenotype diagnosis coding has been in place for nearly 20 years can provide reliable insight into the current drug use for symptom management.

Objectives: To evaluate drug utilization for symptom management in patients with MS by disease phenotype.

Methods: This observational study used data from Betriebskrankenkassen. It is comprised of those with Statutory Health Insurance (SHI) in Germany containing adjudicated healthcare claims data on more than 5 million patients (7% of the German SHI population) who are representative, in terms of age and sex, to the larger insured population. Female and male patients aged 18+ years having ≥1 MS diagnosis (ICD-10-GM codes G35.0, G35.1, G35.2, G35.3, or G35.9) and who were continuously enrolled within 2017 are included. The first MS diagnosis is considered for the assignment into the phenotype grouping. Drugs in the database were coded by the WHO Anatomical Therapeutic Chemical (ATC) classification. Chi-square tests evaluated the significance of proportions and ANOVA for continuous variables.

Results: Of those whose MS phenotype was specified (n=7,814), 78.8% had the relapsing remitting (RRMS) form, 15.1% with the secondary progressive (SPMS) form, and 6.1% with primary progressive (PPMS). There was no significant difference among the groups regarding gender. RRMS patients were significantly younger compared to those with SPMS or PPMS ($P<0.01$, for both comparisons). Antidepressants were the most commonly prescribed drug class (RRMS, 24.7%, SPMS, 34.2%, PPMS, 31.1%). A significantly ($P<0.05$) higher proportion of patients with SPMS or PPMS were prescribed antiepileptics, muscle relaxants, urinary antispasmodics, or medications to manage fatigue than RRMS patients. No differences among the three groups were noted for the proportion of prescriptions for anti-dementia drugs, tremor, gastrointestinal disorders, hypnotics or sedatives, or anti-Parkinson drugs.

Conclusions: Some different drug utilization patterns emerged by MS phenotype. More patients with SPMS or PPMS were prescribed drugs for symptom management than those with RRMS. Antidepressants were the most commonly prescribed regardless of MS phenotype.

2672 | Factors associated with concurrent use of prescription opioids and benzodiazepines: A population-based assessment

Erin Y Liu[1], Robyn Tamblyn[1], Kristian B. Filion[1,2] and David L. Buckeridge[1]
[1]*McGill University, Montreal, QC, Canada;* [2]*Jewish General Hospital, Montreal, QC, Canada*

Background: Opioid overdoses have resulted in over 700,000 deaths in North America over the last 20 years. Concurrent use of opioids and benzodiazepines has emerged as a risk factor for these deaths. Given this safety concern, we seek to characterize patients who are prescribed these drugs concurrently.

Objectives: To identify characteristics associated with the concurrent use of prescription opioids and benzodiazepines.

Methods: We conducted a nested case-control analysis within a retrospective cohort of 193,512 new prescription opioid users from 2000 to 2014. The source population was a 25% random sample of residents from Montreal, Canada who had linked data on patient demographics, inpatient and outpatient physician billings, hospitalizations, and dispensed medications. We used risk-set sampling to match cases, defined as concurrent users of opioids and benzodiazepines, to 5 controls on follow-up time and cumulative days' supply of prescription opioids. We defined a concurrent user as anyone with at least 1 day of overlap between dispensed prescriptions for an opioid and benzodiazepine. The first date of concurrent use defined the index date. We used conditional logistic regression to identify patient demographic and clinical characteristics associated with concurrent use.

Results: Cohort members were followed for a mean of 4.9 years. A total of 41,274 patients (21.3%) became concurrent users. The average age of concurrent users was 61.8 years and 64.7% were female. A total of 54.9% of concurrent users were prescribed their opioid and benzodiazepine from different physicians. Previous long-term (60 or more days vs 1-30 days) use of benzodiazepines (OR 3.31, 95% CI 3.13-3.49), 2 vs 1 opioid prescribers (OR 2.46, 95% CI 2.11-2.85),

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

opioid dependence/abuse (OR 1.96, 1.22-3.17), and opioid overdose (OR 1.49, 95% CI 0.90-2.47) at cohort entry, alcohol dependence/abuse (OR 1.48, 95% CI 1.33-1.64) and drug insurance plan for social deprivation (OR 1.40, 95% CI: 1.32-1.49) were highly associated with concurrent use. Non-opioid drug dependence/abuse (OR 1.30, 1.19-1.42), having an opioid prescriber who was a doctor vs dentist (OR 1.17, 95% CI 1.10-1.24) and initiating an opioid prescription that lasted more than 7 days (OR 0.85, 95% CI 0.81-0.88) were modestly associated, whereas age, sex, average daily dose of initiating opioid, and mental health disorders were minimally or not associated.

Conclusions: Concurrent users are more likely to be chronic users of benzodiazepines, have multiple opioid prescribers, be socially deprived, and have a substance use disorder.

2681 | Asthma maintenance medication users in the sentinel distributed database

Marie C Bradley[1], Elnara Fazio-Eynullayeva[2], Yan Li[3], Jianmeng Chen[4], Stacy Chin[4], Sandra Deluccia[2], Efe Eworuke[1], Katherine Freitas[2], Judith Maro[2], Catherine A Panozzo[2], Yunzhao Ren[5], Chandrahas Sahajwalla[6], Rongmei Zhang[7], David Martin[8], Sally Seymour[9], Kenneth Quinto[9] and Robert Busch[9]

[1]FDA, Silver Spring, MD; [2]Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; [3]FDA, Silver Spring, MD; [4]FDA, Silver Spring, MD; [5]FDA, Silver Spring, MD; [6]FDA, Silver Spring, MD; [7]FDA, Silver Spring, MD; [8]FDA, Silver Spring, MD; [9]FDA, Silver Spring, MD

Background: Recent legislation mandates that the US Food and Drug Administration evaluate the potential use of real-world evidence (RWE) to support regulatory decision making. The feasibility of using the Sentinel Distributed Database (Sentinel) to evaluate comparative effectiveness and safety of asthma maintenance medications (AMM) in real world settings is unclear.

Objectives: To examine demographic and clinical characteristics of asthma patients dispensed AMM in Sentinel.

Methods: We conducted a retrospective cohort study in Sentinel from 2008 to 2018. We defined asthma patients as enrollees aged 18 years or greater with an index event of an ICD-9 or -10 code for asthma and with 1 or more dispensings of AMM during the 12 months prior to the index event (baseline period). AMM included inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), inhaled combination products, leukotriene receptor antagonists (LTRA), and biological products for asthma. Asthma patients with ICD codes for common respiratory comorbidities in the baseline period were excluded. We calculated summary statistics for selected demographic and clinical characteristics during the 12-month baseline period and 12-month follow-up periods.

Results: A total of 3.32 million asthma patients met our eligibility criteria; their mean age was 57 years (standard deviation [SD] = 15.2 years) and 69.3% were female. During the baseline period, the mean Charlson/Elixhauser combined comorbidity score was 1.8 (SD = 1.8), and the mean number of ambulatory encounters and filled prescriptions were 19 (SD = 16.4) and 42.3 (SD = 35.5), respectively. In the combined baseline and follow-up periods, the proportion of patients that filled ≥2 prescriptions for ICS was 34.1%, for ICS/LABA combination products was 43.8%, and for LTRA 37.2%. During the follow-up period, 14% of patients had ≥1 respiratory event coded as asthma exacerbation (AEx), 37.9% of patients filled ≥1 oral corticosteroid (OCS) prescriptions, and 1.9% had an AEx that required hospitalization.

Conclusions: To our knowledge, these data represent the first comprehensive characterization of asthma patients in Sentinel. The burden of healthcare encounters, prescriptions, and comorbidities provides insight on the health status of these asthma patients. The inconsistency between the proportion of patients with ICD codes for AEx and the proportion filling OCS prescriptions warrants further examination. These exploratory data inform the feasibility of using Sentinel for future analyses of the potential benefits and risks of asthma medications.

3717 | Utilization of spironolactone in patients with reduced or preserved ejection fraction heart failure

Sruthi Adimadhyam[1], Austin Cosgrove[1], Qoua L. Her[1], Jennifer Lyons[1] and Efe Eworuke[2]

[1]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [2]Food and Drug Administration, Silver Spring, MD

Background: Spironolactone is an aldosterone antagonist indicated for the management of reduced ejection fraction (rEF) heart failure (HF). In the TOPCAT trial, spironolactone significantly lowered the incidence of HF hospitalizations among patients with preserved ejection fraction (pEF) HF. Real world utilization of spironolactone in pEF is unknown.

Objectives: To evaluate the use of spironolactone following a diagnosis of rEF or pEF and characterize the first treatment episode.

Methods: We conducted a retrospective cohort study using data from the MarketScan® Research Databases (7/2010 - 9/2018). We identified patients with rEF or pEF using diagnosis and procedure codes from a previously validated algorithm. Patients with a diagnosis of left or systolic HF with a history of cardiomyopathy, implantable cardioverter defibrillator, or myocardial infarction in 183 days prior HF diagnosis were classified as rEF, while those with diastolic or unspecified HF with no history of cardiomyopathy or implantable cardioverter defibrillator were classified as pEF. We required patients to be continuously enrolled in the 183 days prior to cohort entry and have no history of spironolactone use. Follow-up started on the day of diagnosis and ended at the earliest occurrence of a spironolactone dispensing, disenrollment, death, or end of data. We calculated the proportion of HF patients initiating spironolactone. For those initiating treatment, we estimate the dose and duration of the first treatment episode. Results were stratified by age group, sex, and year of HF.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Among 178,334 patients with rEF, 65.3% were male, and mean age was 68.5 ± 14.6 years. Among 1,361,449 patients with pEF, 49.8% were male, and mean age was 64.4 ± 15 years. Proportion of patients that initiated spironolactone following rEF was 17.2% versus 4.2% after pEF. The median time to initiation of spironolactone after rEF was 79 (12 - 319) days versus 226 (40 - 668) days after pEF. The median duration of first treatment episode in rEF was 120 (34 - 306) days with a median dose of 25 (25 - 25.3) milligrams/day. The median duration of first treatment episode in pEF was 100 (30 - 271) days with a median dose of 25 (25 - 50) mg/day.

Conclusions: Our study indicates low utilization of spironolactone in patients with pEF compared to rEF. Future utilization studies will be needed to evaluate the influence of the TOPCAT trial findings in the management of patients with pEF HF. We intend to replicate this study in the Sentinel Distributed Database.

3738 | How marketing approval changed the use of tranylcypromine in the Netherlands

Angela van der Salm, Magdalena Gamba and Toine Egberts
Utrecht University, Utrecht, Netherlands

Background: Tranylcypromine (TCP) is an old MAO-inhibitor used in patients with treatment-resistant depression. It was taken off the market due to its safety profile in the mid-1960's and later reintroduced but only available in the Netherlands on a named patient basis. Since June 2016 it is available again as authorized medicine.

Objectives: Our aim was to investigate differences in patient characteristics of TCP users on a named patient basis versus those taking the authorized medicine.

Methods: From the Out-patient Pharmacy Database of the PHARMO Database Network, all patients were identified to whom TCP had been dispensed between 1 January 2009 and 31 December 2018. Patients were divided into 3 groups: new users up to July 2016 (new user-pre; using TCP on a named patient basis), new users after June 2016 (new user-post; using authorized TCP), and patients that switched from named patient TCP to authorized TCP after June 2016 (switchers).

Patient characteristics of interest included age, gender, prescriber specialty, concomitant use of cardiovascular (CV) medication, and history of antidepressant (CNS) drug use.

Results: There were 529 patients in the new user-pre group, 216 patients in the new user-post group, and 186 patients switched. The three groups showed a similar mean age (54 years; with switching occurring at the age of 59 years), and gender distribution (33% men vs 67% women). The vast majority of prescriptions was done by psychiatrists/specialists, but in switchers, TCP was prescribed three times more frequently by general practitioners (36% vs 12-13%).

In the new user-post group, 36% of patients used 1 or more CV medications, vs 30% in the new user-pre group, and only 6% in switchers. TCP was prescribed to patients that did not meet the label requirement (i.e. previous use of two other antidepressants and lithium; ≥ 3 other CNS drugs) 1.5 times (95% CI of 1.02 to 2.17) more often in the new user-pre than in the new user post-group (22% vs 14%).

Conclusions: This study has shown that characteristics of patients using TCP changed after the availability changed from a restricted named patient basis to an authorized medicine. Our results indicate a lack of specialist monitoring during switching, and improved but residual lack of adherence to the label requirement for initiating treatment.

3761 | Trend of pattern change of antihypertensive medications using real-world data in Korea

Minji Jung, Eunjung Choo and Sukhyang Lee
Ajou University, Suwon, Republic of Korea

Background: The prevalence of hypertension in persons older than 30 years is as high as 30% in Korea. Hypertension is a risk factor of cardiovascular disease, which is the leading cause of mortality in globally, as well as Korea. Antihypertensive treatments can lower high blood pressure and prevent stroke, heart attacks, heart failure, or kidney disease.

Objectives: To estimate the actual status of antihypertensive medication use and patterns based on drug exposure preparation algorithm using national claims data in Korea.

Methods: We obtained national claims data from the Health Insurance Review and Assessment Service (HIRA), which covers almost all Koreans. A total of 11,193,969 patients were included after being used antihypertensive drugs at least 30 consecutive days from 2015 to 2018. We included both inpatients and outpatients in all ages.

Results: During the study period, patients with monotherapy were 48.1%, dual therapy were 38.0% and more than triple therapy were 13.8%. Among mono therapy, angiotensin II receptor blockers (ARBs) (34.7%) and calcium channel blockers (CCBs) (32.5%) were the most frequently prescribed classes. Male subjects accounted for 50.4% of the study populations. To compare patients prescribed antihypertensive medications in 2016 with those in 2015, 75.1% of study patients maintained their treatments, 8.3% newly started, 5.8% added to different classes of antihypertensives, 5.4% discontinued and 5.4% switched to other classes. Of those with maintained therapy, ARBs (37.6%) and CCBs (32.9%) were the most frequently prescribed classes.

Conclusions: We evaluated antihypertensive medication use and trend to achieve further improvement in hypertension treatment.

3771 | Changes in prescribing of hormone replacement therapy in Germany between 2004 and 2016

Miriam Heinig[1], Malte Braitmaier[1] and Ulrike Haug[1,2]
[1]*Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany*; [2]*University of Bremen, Bremen, Germany*

Background: After publication of the Women's Health Initiative's (WHI) findings in 2002, short-term studies suggested a drastic

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

decrease in the use of hormone replacement therapy (HRT), but studies on longer-term trends and details of use are scarce.

Objectives: To describe trends and details of HRT use based on German claims data over a span of thirteen years.

Methods: We used the German Pharmacoepidemiological Research Database (GePaRD) containing health insurance claims data from ~25 million persons since 2004. We determined the prevalence of any as well as type-specific (combined vs. estrogen-only) HRT prescriptions by route of administration and age. We additionally compared the total number of Defined Daily Doses (DDDs) prescribed to HRT users within 5 years between different time periods (2005-2009 vs. 2012-2016).

Results: Between 2004 and 2016, the prevalence of any type of HRT prescription decreased by 46% in women aged 50 years and was 96 per 1000 in 2016. In women aged 60 years, it decreased by 49% (153 per 1000 in 2016) and in women aged 70 years it decreased by 35% (134 per 1000 in 2016). The prevalence of oral combined HRT prescriptions decreased by 72%, 72%, and 61% in women aged 50, 60 and 70 years between 2004 and 2016 (22, 32 and 19 per 1000 in 2016), respectively. With respect to prescription of estrogen-only HRT, the prevalence and time trends varies according to route of administration. Comparing the prevalence among women aged 50, 60, and 70 years, respectively, in 2016 to 2004 the pattern was as follows: A) oral estrogen -79%, -74%, and -59% (5, 13 and 16 per 1000 in 2016); B) transdermal estrogen +/- 0%, -43% and -42% (25, 27 and 20 per 1000 in 2016); C) vaginal estrogen: -6%, +8% and +3% (32, 85 and 83 per 1000 in 2016). Prevalence of oral gestagen HRT prescriptions (usually combined with an estrogen) increased by 44% and 60% in women aged 50 and 60 years (27 per 1000 and 11 per 1000 in 2016), respectively, and decreased by 10% in 70-year-old women (4 per 1000 in 2016).

Comparing the time periods 2012-2016 to 2005-2009, the median total number of Defined Daily Doses (DDDs) prescribed to 50, 60 and 70-year-old HRT users in the next 5 years decreased by 8%, 32% and 12% for any HRT. For combined oral HRT it decreased by 33% in 50-54-year-old women, increased by 3% in 60-64-year-old women, and did not change in women 70-74 years.

Conclusions: For most types of HRT, prevalence of prescriptions declined considerably between 2004 and 2016 in Germany. In 2016, 10-15% of women aged 50-70 were prescribed any HRT. The fairly high prevalence in 70-year-old women is mainly due to vaginal estrogen.

3787 | Antidiabetic medication use in children and adolescents from 2004 to 2019: Real world data from a commercially insured population in the United States

Jenny W Sun[1], Sonia Hernández-Díaz[1], Florence T Bourgeois[2], Sebastien Haneuse[3], Brian T Bateman[4], Elisabetta Patorno[4] and Krista F Huybrechts[4]

[1]Harvard T.H. Chan School of Public Health, Boston, MA; [2]Boston Children's Hospital and Harvard Medical School, Boston, MA; [3]Harvard T.H. Chan School of Public Health, Boston, MA; [4]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: Over the past several decades, the incidence and prevalence of type 2 diabetes in children and adolescents has nearly doubled, yet little is known about the use of antidiabetic medications and the uptake of newer agents.

Objectives: To describe the patterns of non-insulin antidiabetic medication use and initiation in children and adolescents.

Methods: Using real world data from the Optum© Clinformatics® Data Mart (January 2004-June 2019), we identified a cohort of pediatric patients (10-18 years) and evaluated changes over time in non-insulin antidiabetic medication use overall and by class. Then, we identified new users of non-insulin antidiabetic medications and followed patients until the end of insurance coverage or end of available data. Among new users, we evaluated trends over time in the proportion of patients who initiated metformin compared to other antidiabetic agents, and examined time to discontinuation using a Kaplan-Meier analysis.

Results: In a cohort of over 1 million pediatric patients, the prevalence of any non-insulin antidiabetic medication use was 70.3 per 100,000 patients in 2004 and doubled to 145.0 per 100,000 in 2019. Across all years, biguanides (metformin) was the most widely used medication class, with the prevalence per 100,00 patients increasing from 63.2 in 2004 to 140.0 in 2019. The second most widely used class was thiazolidinediones from 2004-2011 and glucagon-like peptide-1 agonists from 2012-2019, but the prevalence was low in these classes (<10 per 100,000). There were 16,433 new users of non-insulin antidiabetic medications between 2004 and 2019 (mean age at initiation: 14.6 years). Metformin represented 89.3% of initiations in 2004 and rose to 97.3% of initiations in 2019. Recently, the second most frequently initiated antidiabetic was liraglutide (1.1% in 2018, 1.3% in 2019). After treatment initiation (mean follow up: 2.5 years), patients filled a median of 2 (interquartile range [IQR]: 0-6) subsequent non-insulin antidiabetic prescriptions. No refills were observed in 27% of initiators. Patients continuously used any antidiabetic for a median of 67 days (IQR: 30-154).

Conclusions: The use of non-insulin antidiabetic medications in children and adolescents has increased substantially between 2004 and 2019. Nearly all patients initiated metformin, which is consistent with treatment guidelines, whereas use of newer agents remains low. Short treatment periods were observed, which justifies further research to assess whether this represents undertreatment or switch to non-pharmacologic treatment options.

3799 | Use of levothyroxine for the treatment of subclinical hypothyroidism among pregnant women in the United Kingdom: A population-based assessment

Ya-Hui Yu[1,2], Sonia M Grandi[3], Robert W Platt[1,2], Oriana HY Yu[2] and Kristian B Filion[1,2]

[1]McGill University, Montreal, QC, Canada; [2]Jewish General Hospital, Montreal, QC, Canada; [3]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Subclinical hypothyroidism (SCH) affects 2.5% of pregnant women. Although clinical guidelines recommend levothyroxine to sustain optimal fetal growth in women with hypothyroidism, its use among pregnant women with SCH is poorly understood.

Objectives: To describe levothyroxine prescription patterns among pregnant women with SCH and to identify characteristics associated with levothyroxine use in a population-based cohort of women in the United Kingdom.

Methods: Our study cohort used linked data from the Clinical Practice Research Datalink, its pregnancy register, and Hospital Episode Statistics. We included pregnancies of women diagnosed with SCH in the year before or during pregnancy from 1998 to 2017. Cohort entry was defined by the date of SCH diagnosis or by the start of pregnancy, whichever occurred last. Levothyroxine use was defined as ≥1 prescription during pregnancy. We used multivariable logistic regression to estimate characteristics associated with levothyroxine use, including age, race/ethnicity, socioeconomic status, obesity, smoking, alcohol use, diabetes, hypertension, infertility, rheumatoid arthritis, polycystic ovary syndrome, obstetric history, and thyroid-simulated hormone (TSH) level.

Results: Our cohort included 18,113 pregnancies from 15,949 women with SCH. A total of 3,152 (17%) pregnancies from women with SCH received levothyroxine. The average daily dosage of the first prescription during pregnancy was 50-75 mcg in 33% of women and ≥75 mcg in 49% of women. The majority of women were first prescribed levothyroxine in the first trimester (76%). The overall median treatment duration was 185 days (IQR: 84, 256). Among women newly diagnosed with SCH during pregnancy, the initial prescription was, on average, a higher dosage and a shorter duration than among women with prevalent SCH. The levothyroxine prescription rate varied with calendar year; rates decreased from 24% to 17% in 1999 and 2000, remained stable until 2015, when it rose to 20% and then to 24% in 2016. Characteristics independently associated with levothyroxine prescription included higher TSH (4-10 mIU/L) at cohort entry (OR: 4.9, 95% CI: 4.5, 5.4), SCH diagnosis at prior pregnancy (OR: 1.9, 95% CI: 1.7, 2.1), SCH diagnosis during pregnancy but not in the year before (OR: 1.9, 95% CI: 1.7, 2.1), diabetes (OR: 1.7, 95% CI: 1.4, 2.1), and obesity (OR: 1.3, 95% CI: 1.1, 1.4).

Conclusions: Our study suggests that few women with SCH receive levothyroxine during pregnancy and the choice of whether to prescribe may be related to preexisting comorbidities and TSH.

3807 | trends in the use of pharmacologic treatments for pulmonary arterial hypertension from 2013-2017

Rob F Walker[1], Thenappan Thenappan[2], Kurt W Prins[2], Neil A Zakai[3], Joel F Farley[4], Richard F MacLehose[1], Alvaro Alonso[5], Pamela L Lutsey[1] and Pamela L Lutsey[1]

[1]University of Minnesota School of Public Health, Minneapolis, MN; [2]University of Minnesota Medical School, Minneapolis, MN; [3]University of Vermont, Burlington, VT; [4]University of Minnesota College of Pharmacy, Minneapolis, MN; [5]Emory University Rollins School of Public Health, Atlanta, GA

Background: Pulmonary arterial hypertension (PAH) is a rare but debilitating disease with a five-year mortality rate of approximately 40%. Since 2013, several new drugs have been approved by the U.S. Food and Drug Administration (FDA) to treat PAH, which act via vasodilation, platelet aggregation inhibition and/or antiproliferative effects on vascular smooth muscle cells. Trends in the adoption and use of PAH medications are not well documented.

Objectives: To estimate temporal trends in FDA-approved PAH prescription fills among PAH patients from 2013 through 2017 in the U.S.

Methods: MarketScan databases for years 2013 through 2017 were used to identify PAH cases using International Classification of Diseases (ICD) 9 and 10 codes 416.0 and I27.0, respectively. Prescriptions for PAH medications were identified via outpatient pharmaceutical claims data. PAH drugs were categorized into five classes: phosphodiesterase-5 inhibitors (PDE5i), endothelin receptor antagonists (ERAs), prostacyclin derivatives (PDs), guanylate cyclase stimulators (sGCs) or IP receptor agonists. Prescription fill counts for each category were assessed and aggregated into one year intervals to describe the temporal trends.

Results: We identified 30,729 individuals with PAH. Mean age of this population at date of PAH diagnosis was 64.5 years (SD: 20.2) and 62.7% were female. Of those with ICD codes for PAH, only 19.4% (n = 5,959) ever filled prescriptions for FDA approved PAH treatments. These patients received a cumulative 137,890 prescription fills. Patients who filled prescriptions for PAH medications tended to be younger in age (58.5 years, (SD: 19.0) and were 62.1% female. In 2013, 50.9% of prescriptions were for PDE5is and 43.2% for ERAs, while the remainder were prescribed PDs (5.7%) and sGCs (0.2%). By 2017, 44.1% were prescribed PDE5is and 36.8% PDE5s while percentages of those prescribed PDs, sGCs, and IP receptor agonists increased to 8.7%, 6.2%, and 4.2%, respectively.

Conclusions: PDE5i and ERA therapies make up the majority of prescriptions that PAH patients receive, though their use decreased moderately between 2013 and 2017. Recently approved treatment categories such as sGCs and IP receptor agonists were used with increasing frequency in recent years while PD prescription frequency has remained steady across time. With the shift towards prescribing new PAH treatments, opportunities exist to examine the comparative effectiveness and safety of new PAH therapies in real-world settings.

3832 | Prevalence and prescribing trends in bipolar disorder in Hong Kong from 2001-2018

Vanessa Ng[1], Kenneth Man[1,2], Le Gao[1], Esther Chan[1], Edwin Lee[3] and Ian Wong[1,2]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong; [2]UCL School of Pharmacy, London, United Kingdom; [3]Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Bipolar disorder (BD) is a chronic mental disorder characterised by fluctuating manic and depressive episodes hence lifelong treatment is needed for mood stabilisation. The exact prevalence of BD and trend of local prescribing of treatment in Hong Kong are still unknown.

Objectives: To describe the prevalence and time trends of BD and the use of psychotropic medications in BD in Hong Kong from 2001-2018.

Methods: A population-based observational study was conducted using the electronic health records in Clinical Data Analysis and Reporting System (CDARS) authorised by Hong Kong Hospital Authority. Patients with BD aged ≥6 between 2001 to 2018 were identified using ICD-9-CM codes. Psychotropic medications including lithium, antipsychotics, antidepressants, and antiepileptics with mood stabilising properties: valproate, lamotrigine, carbamazepine were investigated. The annual prevalence of BD diagnosis and medications use were calculated in percentage with 95% confidence interval (CI) using Poisson method and stratified by age and gender. All analyses were performed by SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results: A total of 17,247 individuals with BD were identified, of which 16,018 were prescribed at least one psychotropic medications from 2001 to 2018. The prevalence of BD increased by 3 times [from 0.071% (95% CI 0.069-0.073) in 2001 to 0.221% (95% CI 0.217-0.224) in 2018]. Overall, the prevalence of antipsychotics and antiepileptics increased by 52.4% [from 22.5% (95% CI 21.6-23.4) in 2001 to 74.9% (95% CI 73.4-76.4) in 2018] and 41.6% [from 10.4% (95% CI 9.86-11.1) in 2001 to 52.1% (95% CI 50.9-53.4) in 2018] respectively. Valproate has the greatest increase in usage (36.4%), followed by quetiapine (27.7%) and olanzapine (17.7%). By 2018, 39.5% of women of childbearing age were prescribed valproate. The prevalence of lithium increased from 8.93% (95% CI 8.36-9.54) in 2001 to 17.0% (95% CI 16.3-17.8) in 2009, then remained stable till 2018. The prevalence of antidepressants increased by 19.5% [from 7.25% (95% CI 6.73-7.80) in 2001 to 26.7% (95% CI 25.8-27.6) in 2018].

Conclusions: Lithium use as first line treatment for BD remained relatively constant. Prescribing of antipsychotics, antiepileptics and antidepressants in patients with BD increased from 2001 to 2018. Valproate has been frequently prescribed to women of childbearing age, against advice from international treatment guidelines. Further studies are needed to assess the comparative efficacy and safety of different psychotropic medications among patients with BD, and to investigate the reasons of over-prescribing valproate to women.

3838 | Trends in HbA1c thresholds for initiation of hypoglycaemic agents: Impact of changed guideline recommendations for older and/or frail patients with type 2 diabetes

Martina Ambroz[1], Sieta de Vries[1], Klaas Hoogenberg[2] and Petra Denig[1]

[1]*University Medical Center Groningen, Groningen, Netherlands;* [2]*Martini Ziekenhuis, Groningen, Netherlands*

Background: Since 2011, guidelines have recommended less strict glycated haemoglobin (HbA1c) thresholds in older and/or frail type 2 diabetes (T2D) patients than in younger and less frail patients for initiating hypoglycaemic agents.

Objectives: To assess 1) trends in HbA1c thresholds at initiation of a first hypoglycaemic agent in T2D patients and 2) the influence of age and frailty on these trends.

Methods: The Groningen Initiative to Analyze Type 2 diabetes Treatment (GIANTT) database was used, which includes primary care T2D patients from the north of the Netherlands. Patients who initiated hypoglycaemic agent between 2008 and 2013 and had an HbA1c measurement within 120 days before initiation were included. Treatment initiation was defined as a prescription of a non-insulin hypoglycaemic agent without such a prescription in 365 days before. The influence of calendar year (trend), age (<60 years; 60 - 69 years; 70 - 79 years; and reference group ≥80 years) or frailty (electronic frailty index (eFI); tertiles with the highest tertile as reference group) and the interaction between calendar year and age or frailty were assessed using multilevel linear regression analyses adjusted for confounders (e.g. sex, duration of diabetes, chronic medication, blood pressure).

Results: We included 3,800 patients. The mean HbA1c threshold at treatment initiation was 7.4% in 2008 to 2010, 7.1% in 2011, 7.2% in 2012 and 7.3% in 2013. This trend was significant (p=0.006). On average, patients aged <60 years, 60 - 69 years, 70 - 79 years and ≥80 years initiated treatment at 7.4%, 7.2%, 7.2% and 7.4%, respectively. No significant differences were observed (p values 0.895, 0.269 and 0.626 for each of the younger age groups, respectively). Frailty groups initiated hypoglycaemic treatment at similar HbA1c thresholds (7.3% in the lowest two tertiles and 7.2% in the highest tertile). Again, there were no significant differences between groups (p values 0.581 and 0.383 for the lowest and middle tertile, respectively). The interactions between calendar year and age and calendar year and frailty were not significant (p>0.05).

Conclusions: The HbA1c thresholds at initiation of hypoglycaemic agents decreased significantly over the years, particularly between 2010 and 2011. This trend was not influenced by the patients' age or frailty, which is in contrast with changed treatment recommendations from guidelines in the study period. Additional efforts may be needed to get personalized diabetes care implemented in practice.

3840 | Statin use and discontinuation in older Danes: A nationwide drug utilization study

Wade Thompson, Dorte Jarbøl, Jesper B. Nielsen, Peter Haastrup and Anton Pottegård

University of Southern Denmark, Odense, Denmark

Background: There is limited evidence on the clinical effects of statins in older persons. Therefore, characterizing statin use in this population is of interest.

Objectives: Explore statin use and discontinuation patterns in older Danes between 2011 and 2016 using data from Danish health registries.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: We measured (1) monthly prevalence and (2) quarterly incidence of statin use, each according to sex, age, and primary versus secondary prevention, as well as (3) characteristics of new users, (4) total amount of statin redeemed, and (5) the proportion of long-term statin users (taking statins 5+ years) who discontinued therapy between 2014 and 2016. Finally, we determined (6) factors associated with discontinuation in long-term users, using logistic regression. The study population was all Danes age ≥70 years.

Results: The prevalence of statin use increased from 30% in 2011 to 33% in 2016. At the end of 2016, the prevalence was 23% in the primary prevention population and 56% in the secondary prevention population. The quarterly incidence fell from 11 per 1000 persons in early 2011 to 7 per 1000 persons in late 2016. For incident users, the proportion age ≥80 years dropped from 30% in 2011 to 25% in 2016, while the proportion initiating for primary prevention decreased slightly from 58% to 53%. Around 19% of long-term statin users discontinued therapy between 2014 and 2016. Increasing age was the strongest predictor of statin discontinuation, while use of cardiovascular medications decreased the odds of discontinuation.

Conclusions: Statin use continues to be common among older Danes, with approximately 1 in 3 Danes age ≥70 years taking statins in 2016. Between 2011 and 2016, the prevalence of statin use was relatively stable while the incidence fell slightly. The characteristics of incident users changed over the study period, with a lower proportion starting a statin for primary prevention or starting after age 80 by 2016.

3850 | Use of antipsychotics in Denmark 1997-2018: A nation-wide drug utilization study with focus on off-label use and associated diagnoses

Mikkel Højlund[1,2], Jacob H Andersen[1], Kjeld Andersen[3,4], Christoph U Correll[5,6] and Jesper Hallas[1]

[1]University of Southern Denmark, Odense, Denmark; [2]Mental Health Services Region of Southern Denmark, Aabenraa, Denmark; [3]University of Southern Denmark, Odense, Denmark; [4]Mental Health Services Region of Southern Denmark, Odense, Denmark; [5]The Zucker Hillside Hospital/ Zucker School of Medicine at Hofstra/Northwell, Glen Oaks, NY; [6]Charité Universitätsmedizin, Berlin, Germany

Background: Antipsychotics (APs) are primarily licensed for the treatment of schizophrenia, bipolar disorder, and insufficiently responding unipolar depression. Prior drug utilization studies have found considerable and increasing use of APs among other groups.

Objectives: To 1) describe current AP use and associated diagnoses in Denmark, and 2) characterize the subgroup of users without diagnoses labelled for AP treatment.

Methods: We conducted a nation-wide drug utilization study by identifying all AP users in Denmark from 1997 to 2018 in the Danish National Prescription Register. Information on hospital contacts, use of other medications, and health care utilization were obtained from the Danish National Patient Register, the Danish National Prescription Register, and the National Health Insurance Services Register. Possible indications for AP treatment were evaluated using an indication hierarchy: Severe mental illness, other mental disorders, neurological disorders, and cancers (e.g., palliative care). Time trends in prevalence of these groups were evaluated. Users without any of the diagnoses mentioned above were described regarding type and duration of AP therapy, other psychopharmacological treatment, medical comorbidities, and health care utilization.

Results: We identified 630,234 AP users between 1997 and 2018. In 2018, the number of AP users in Denmark was 127,632, of whom 12% had recorded diagnoses of severe mental illness, 21% of other mental illness, 3.5% of only neurological disorders, 2.5% of only cancer diagnoses, and the remaining 61% had none of these diagnoses. "Neurotic or stress-related disorders (ICD-10 F40-49)" was most commonly associated with incident use (8.5% of incident users), followed by unipolar depression (ICD-10 F32-33) (8.2%). The majority of users without psychiatric, neurological, or cancer diagnoses were treated with one AP (87%), most commonly quetiapine (50%), and redeeming either one (21%) or more than five AP prescriptions (41%). APs in this population were commonly co-prescribed with antidepressants (47% of users). In 2018, a general practitioner was the likely initiator of AP treatment in 67% of incident users, and only 15% of incident users were seen by a psychiatrist during 2018.

Conclusions: Most AP users in Denmark did not have psychotic disorders, and more than half of AP users have no psychiatric, neurological or cancer diagnosis. Health insurance data indicate that a considerable proportion of APs is prescribed in general practice. Reasons for and the risk-benefit ratio of such use require urgent study.

3870 | National variation and factors associated with the transition from first use to long-term opioid use for non-cancer pain

Meghna Jani, Belay Birlie-Yimer, Therese Sheppard, Mark Lunt and William Dixon

University of Manchester, Manchester, United Kingdom

Background: Prescribing behaviour has been described as a key driver of rising opioid prescriptions and long-term opioid use. However the effect of prescribers requires interpretation within context. No studies have investigated the extent to which regions, practices, prescribers, vary in opioid prescribing accounting for case-mix by considering this hierarchy together.

Objectives: (i) Quantify and identify risk factors for the transition from new-user to long-term opioid user (ii) Quantify variation of long-term use attributed to region, practice and prescriber, accounting for patient mix and chance variation.

Methods: A retrospective observational UK study between 2006-2017 using CPRD was conducted. Opioids new users, ≥18 years, without cancer were identified. Long-term opioid use was defined as ≥3 opioid prescriptions issued within a 90-day period from index date, or ≥1 opioid prescription lasting at least 90 days in the 1st year. A multi-level random-effects logistic regression model was used to examine the association of patient characteristics with the odds of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

becoming a long-term opioid user. To examine variation in opioid use amongst prescribers, GP practices and region after adjusting for patient case-mix, we used a nested random-effect structure. A 'high-risk' region, prescriber or practice was defined as those where the entire adjusted 95% CI lay above population average.

Results: 1,968,742 new opioid users were included; 14.6% patients transitioned to long-term use. In the fully adjusted model, factors associated with higher odds of long-term opioid use included high MME/day [OR 7.6 (95% CI 6.3, 9.2), older age [OR 4.4 (4.3, 4.5), deprivation [OR 1.5 (1.4, 1.6)], fibromyalgia [OR 1.8 (1.5, 2.2)], rheumatological conditions [OR 1.5 (1.4, 1.6)], major surgery [OR 1.1 (1.05, 1.13)]. The North-West, Yorkshire and South-West were found to be high-risk regions for long-term use. 103 practices (25.6%) and 540 prescribers (3.5%) were associated with a significantly higher risk of long-term use. The odds of becoming a long-term user for a patient belonging to these prescribers reached up to >3.5 times than the population average.

Conclusions: Prescribing factors, age, deprivation, fibromyalgia and rheumatological conditions were associated with highest odds of long-term opioid use. In the first UK study evaluating long-term prescribing with adjustment for case-mix, variation in regions and especially practices and prescribers were observed. Our findings support greater calls for action to reduce practice and prescriber variation by promoting safe practice in opioid prescribing.

3891 | Use of hormonal therapy before and after diagnosis of breast, endometrial and colon cancer

Lina Mørch[1], Charlotte Skovlund[1], Amani Meaidi[2], Christian Dehlendorff[1], Søren Friis[1], Irene Petersen[3] and Anne Katrine Duun-Henriksen[1]

[1]Danish Cancer Society Research Center, Copenhagen, Denmark; [2]Copenhagen University Hospital, Copenhagen, Denmark; [3]University College London, London, United Kingdom

Background: Hormonal therapy is known to increase the risk of some types of cancers, while reducing the risk of others. We anticipate that women with breast and endometrial cancer discontinue hormone therapy around time of diagnosis, while we do not expect discontinuation in women with cancers on which hormone therapy has a neutral or even a protective effect; such as for colon and rectal cancer. Vaginal estrogens are anticipated to have local effect, thus discontinuation is not expected to the same extend as with other types of hormone therapy

Objectives: To examine patterns of hormone therapy use before and after a diagnosis of breast, endometrial or colon cancer in Denmark.

Methods: From Danish nationwide registries, we identified all women aged 50 years or older at diagnosis of incident breast, endometrial and colon cancer during 2000-2016, and comparison cohorts of birth year-matched women without cancer. We calculated rates of hormone therapy as prescriptions/person-year and examined use in 6 months intervals from two years before to two years after diagnosis. Prescription rates were calculated for all types of hormone therapy and for vaginal estrogens separately.

Results: We identified 54,206 women with breast, 9,817 women with endometrial and 18,356 women with colon cancer. Among women with breast cancer, the rates of hormone therapy prescriptions declined from 0.97 [0.95-0.98] per person-year 2-1.5 years before diagnosis to 0.36 [0.35-0.36] prescriptions/person-year 1.5-2 years after diagnosis. During the same period, also rates of vaginal estrogen prescriptions declined from 0.53 [0.52-0.53] to 0.34 [0.33-0.35]. Similarly, among women with endometrial cancer, the rates of hormone therapy prescriptions declined (0.90 [0.87-0.92] vs 0.70 [0.67-0.73]), whereas the rates of vaginal estrogen prescriptions remained stable (0.57 [0.55-0.59] vs 0.65 [0.63-0.68]). Among women with colon cancer, a slight decline in use of hormone therapy (0.60 [0.58-0.61] vs 0.51 [0.50-0.53]) was seen, while use of vaginal estrogen was unchanged (0.45 [0.44-0.46] vs 0.44 [0.42-0.45]). The comparison cohorts exhibited approximately stable rates of hormone therapy and vaginal estrogen prescriptions in the period.

Conclusions: In accordance with expectations use of hormone therapy declined markedly after diagnoses of breast and endometrial cancer, however, surprisingly also slightly after colon cancer. Use of vaginal estrogen declined after a diagnosis of breast cancer, but not after diagnosis of endometrial cancer or colon cancer.

3898 | Racial/ethnic Disparities in Pharmacotherapy and Recurrence of Urinary Tract Infections Among Medicare Beneficiaries

Erline E. Martinez-Miller[1,2], Julia B. Ward[1,3], Brian R. Matlaga[4], Kevin C. Abbott[5], Tamara Bavendam[5], Ziya Kirkali[5], John Lim[1], Casey Pierce[1] and Lydia B. Feinstein[1,3]

[1]Social & Scientific Systems, Durham, NC; [2]University of Texas Southwestern Medical Center, Dallas, TX; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Johns Hopkins University School of Medicine, Baltimore, MD; [5]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Background: Urinary tract infections (UTIs) are highly prevalent among older adults and increasingly difficult to treat with multidrug resistance on the rise. In the United States, racial/ethnic minorities have less access to quality healthcare. Yet little is known about racial/ethnic disparities in UTI burden or its medical management.

Objectives: We examined racial/ethnic disparities in prescribed medications and UTI recurrence among Medicare beneficiaries aged ≥65 years with a UTI diagnosis.

Methods: We used the Centers for Medicare & Medicaid Services (CMS) Medicare 5% Sample from 2007-2016 (N=63,533). UTI episodes were defined as an outpatient claim with a relevant diagnosis code followed by a pharmacy claim for an anti-infectious agent within 72 hours. Anti-infectious agents were categorized using American Hospital Formulary Service classes. We estimated prevalence and duration of UTI-relevant prescription fills and cumulative probability

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of recurrent UTI within 12 months of the initial episode. Analyses were conducted overall and by race/ethnicity.

Results: Race/ethnicity among beneficiaries with UTI was distributed as follows: non-Hispanic White (88%), non-Hispanic Black (7%), Asian (2%), Hispanic (2%), American Indian/Alaska Native (AI/AN; 1%), and Other (1%). Overall, the most commonly prescribed medications were quinolones (42%), urinary anti-infectives (18%), sulfonamides (15%), and cephalosporins (11%). Of these, quinolones and sulfonamides had the lowest cumulative probability of UTI recurrence (39% and 41%, respectively), and urinary anti-infectives and cephalosporins had the highest (47% and 48%, respectively). Quinolones were most commonly prescribed among Asians (51%) and least among AI/ANs (39%). Cephalosporins were most commonly prescribed among AI/ANs (15%) and least among Asians (9%). AI/ANs and Hispanics had the highest cumulative probability of UTI recurrence (46% and 41%, respectively), while Asians had the lowest (34%). Those with medication duration ≥7 days, longer than recommended by guidelines, had the highest cumulative probability of UTI recurrence (44%). Accordingly, Hispanics and AI/ANs were most commonly prescribed medications for ≥7 days (41% and 42%, respectively, vs. 38% overall).

Conclusions: We identified racial/ethnic disparities in UTI pharmacotherapy and recurrence among older adults in the United States, particularly among AI/ANs. Future studies should determine whether improper use of anti-infectious agents for UTI treatment contributes to high frequency of recurrence in understudied minority populations.

3906 | Utilization of antidepressants in Brazil: A study based on private and public consumption data

Lívia Teixeira de Mattos[1], Cláudia Du Bocage Santos-Pinto[2] and Claudia Garcia Serpa Osorio-de-Castro[1]

[1]*Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil;* [2]*Federal University of Mato Grosso do Sul, Campo Grande, Brazil*

Background: Disease burden in Brazil shows that mental health disorders, especially depression, are on the rise. Economic recession has generated impoverishment and austerity measures have impacted on government health expenditures.

Objectives: This study profiles private and public consumption and expenditures of antidepressants considering context of recession and austerity in Brazil.

Methods: In a time-series analysis, from 2011 to 2017, public and private drug purchase data were used as *proxi* for consumption. Ten commonly prescribed antidepressants were selected, based on evidence for treatment of major depression, recommendation by national and international organizations and availability for retail and for government purchases, which were obtained from Brazilian Health Regulatory Agency SNGPC database for controlled substances and from the Federal SIASG database respectively. Socioeconomic and fiscal data were obtained from the Brazilian Institute for Geography and Statistics (IBGE) and from the Brazilian Central Bank. The ATC/DDD system standardized medicines and consumption output, in DDDs /1000 inhab per year. Linear regression and the Prais-Winsten technique for correction of autocorrelation were used for trend analysis.

Results: Time series showed variation in consumption and expenditures. Private and public consumption, and public expenditures, were expressed in tiers, according to range of DDDs/1000 inhab per year and of BRL per year, respectively. Results showed downward or constant trends for public purchases and rise in private purchases of all antidepressants, with marked decrease in GDP variation. Fluoxetine was the top drug in consumption from retail and government purchases, although trend was downward for public purchases and upward for retail.

Conclusions: Rising out-of-pocket expenditures for depression and decreasing government purchases reflect budget health cuts, possibly herding users to the private sector for their medicines. Increased antidepressant use may reflect disease burden as well as despondency and disenfranchisement in Brazil.

4024 | A population-based cohort study on the associations between selective serotonin reuptake inhibitor use before, during, and after pregnancy using data from the health improvement network

Jet WT Scheffers[1] and Irene Petersen[2,3]

[1]*Utrecht Institute of Pharmaceutical Sciences, Utrecht, Netherlands;* [2]*University College London, London, United Kingdom*[3]*Aarhus University, Aarhus, Denmark*

Background: Although depression is common in pregnancy, some women discontinue selective serotonin reuptake inhibitor (SSRI) treatment before or during pregnancy for various reasons. Limited information is available on how many of these women restart SSRI therapy after pregnancy.

Objectives: To examine the associations between selective serotonin reuptake inhibitor (SSRI) use in women before, during, and after pregnancy. In addition, we studied the effects of age and social deprivation on these associations.

Methods: We conducted a retrospective cohort study using data from The Health Improvement Network (THIN) UK primary care database. Women who had given live birth between 1 January 2000 and 31 December 2016 were identified and one random pregnancy was selected per woman. We estimated the number of women who were prescribed SSRIs in the 18 to 6 months before start of pregnancy, during pregnancy, and in the 12 months after delivery. We used Poisson regression to estimate risk ratios (RRs) of receiving SSRIs during pregnancy and after birth given prior treatment. Then, we studied the effects of social deprivation and age on the calculated RRs.

Results: In total, 210,603 pregnancies were included in this study. Of the 19,332 women who received a prescription for an SSRI before pregnancy, 2,840 (14.7%) were also prescribed SSRIs in the second trimester, while 9,630 (49.8%) received an SSRI in the year after delivery. Previously exposed women were 5.34 (95% confidence interval

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(CI), 5.24, 5.45) times more likely to receive postnatal SSRI treatment compared to women not on SSRIs before pregnancy. There was a strong effect of age and social deprivation on the risk of receiving SSRIs after delivery among women who were not exposed to SSRIs before pregnancy. Women below 20 years of age were 2.4 times (95% CI, 2.27, 2.56) more likely to receive SSRIs after delivery than women aged 30 or over. Moreover, women from the most deprived Townsend quintile were almost twice as likely as women from the least deprived quintile to receive a prescription for an SSRI after pregnancy.

Conclusions: While there is a strong association between SSRI treatment before pregnancy and after delivery, only half of the women treated before pregnancy received prescriptions for SSRIs in the year after delivery. These findings suggest that postnatal SSRI treatment is not just a continuum of previous episodes of SSRI treatment. More research is needed to determine the reasons why women stop AD therapy before or during pregnancy, and to identify women in need of postnatal treatment.

4029 | Methodological considerations and learnings from setting up the SABINA program

Cassandra Nan[1], Sofie Arnetorp[1], Maarten JHI Beekman[2], Niklas Lindarck[3], Jennifer K. Quint[4] and Claudia S. Cabrera[1]

[1]AstraZeneca, Gothenburg, Sweden; [2]AstraZeneca, The Hague, Netherlands; [3]AstraZeneca, Södertälje, Sweden; [4]Imperial College London, London, United Kingdom

Background: Recent international asthma management guidance recommends the addition of inhaled corticosteroids to short-acting β_2-agonists (SABAs) to address the underlying inflammation of asthma. The SABA use IN Asthma (SABINA) program describes SABA use globally using primary and secondary data collection methods.

Objectives: To describe methodological considerations and learnings from designing the SABINA program across countries with different healthcare systems and data availability.

Methods: A core protocol (SABINA I) was developed for the Clinical Practice Research Datalink (CPRD), a UK primary healthcare database. Two umbrella protocols were developed based on the core one: a distributed protocol for 8 countries where medical records, pharmacy dispensing databases, or patient registries were available (SABINA II), and a cross-sectional primary data collection protocol for 25 countries with no national healthcare databases (SABINA III). Key definitions (e.g., asthma severity, SABA use), inclusion criteria, and core tables were standardized to maximize between-country comparisons. Protocols were developed in collaboration with local investigators and clinical experts to ensure appropriate study implementation and applicability of results.

Results: Five countries across SABINA I and II have completed analyses comprising >1 million patients, while data has been collected for >8500 patients in SABINA III. Available results from studies with varying levels of complexity show consistent SABA use patterns and its consequences, despite different data sources, healthcare and reimbursement policies. Developing an umbrella distributed program with a tailored framework, including standard definitions, tables, and adaptable algorithms, required several iterations to achieve as data in each country were progressively better understood.

Conclusions: Early involvement of knowledgeable collaborators is key for the efficient development of a large program across multiple healthcare settings and countries to ensure clarity of study objectives and specific country needs. Development of a lexicon for use across countries could help minimize variability in regional terminologies. Granularity of data in the CPRD is rare in most other countries. Although initial feasibility assessments might have facilitated more sophisticated clustering of cross-country results, the step-wise approach of adapting the CPRD protocol to other countries ensured scientific robustness and a point of reference for individual studies within SABINA, maximizing the use of the included databases for this and future studies in asthma.

4036 | Trends in benzodiazepine utilization in Romania during 1998-2018

Irina Cazacu[1], Anamaria Cristina[1], Andreea Maria Farcaş-Călugăr[2], Sinziana Gheorghe-Cetean[3], Cristina Pop[1], Irina Brumboiu[4] and Cristina Mogosan[1]

[1]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania; [2]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania; [3]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania; [4]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania

Background: Increasing concerns on benzodiazepine (BZD) utilization regarding the misuse, dependence, tolerance and difficulty in treatment discontinuation highlight the importance of conducting drug utilization studies in Romania, data on BZDs utilization being scarce.

Objectives: To examine 20-year trends (1998-2018) of BZDs utilization (for all pharmaceutical forms and all indications) in Romania using WHO Defined Daily Doses (DDD).

Methods: We analyzed estimated data from Pharma & Hospital Report CEGEDIM study during 1998-2018, which includes primary data from a panel of retail and hospital pharmacies in Romania. The results are presented in DDD/1000people/day for each BZD International Nonproprietary Name (INN) and in total.

Results: Global BZD utilization increased by 10.8% from 1998 to 2018 (13.8 to 15.3 DDD/1000people/day). We observed major increases in alprazolam (0.2 to 5.5) and lorazepam (0.1 to 3.5) during the same time. The most used BZD in the 20-year period was diazepam (39.0%), followed by alprazolam (22.7%), nitrazepam (11.5%) and medazepam (6.8%). Between 1998 and 2003, we noticed an overall 24.6% decrease in BZDs utilization in Romania, driven by a fall in diazepam utilization (42.1% decrease), and important reductions in oxazepam (decrease by 91.0%), chlordiazepoxide (79.6%) and flunitrazepam

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(78.6%) use, the last three losing their market availability starting 2005. Diazepam, despite an increase in utilization by 30.6% in 2004 compared to 2003, had a steady decrease during 2005-2018, from 6.4 in 2005 down to 3.1 DDD/1000people/day in 2018. Simultaneously, alprazolam and lorazepam had steady increases, from 2.7 and 0.3 in 2005 reaching 5.5 and 3.5 respectively in 2018. Consumption of nitrazepam remained almost static during 1998-2018 (on average 1.5), while for medazepam it decreased from 2.1 in 1998 to 0.2 in 2018, and for bromazepam more than tripled, from 0.3 to 1.0.

Conclusions: Romania faced an increasing use of BZDs during 1998-2018. Even if consumption of diazepam and medazepam decreased during this time, other BZDs gained popularity (alprazolam, lorazepam, and bromazepam). These variations in BZDs use could have been influenced by multiple factors: the release of the modern hypnotics (e.g. zolpidem) which gained popularity starting 2003 in Romania, the ageing population, which largely uses BZDs, the market withdrawal of some BZDs (flunitrazepam, oxazepam, chlordiazepoxide) in Romania, the changes in the national drug reimbursement list or the increased awareness of anxiety disorders and their treatment, mainly involving BZDs.

4037 | Use of analgesics among breast cancer patients in Denmark: A nationwide cohort study

Charlotte Skriver[1], Anne Katrine Duun-Henriksen[1], Irene Petersen[2,3], Christian Dehlendorff[1] and Søren Friis[1,3,4]

[1]Danish Cancer Society, Copenhagen, Denmark; [2]University College London, London, United Kingdom; [3]Aarhus University Hospital, Aarhus, Denmark; [4]University of Copenhagen, Copenhagen, Denmark

Background: An increasing number of breast cancer (BC) patients survive their disease, but some patients may experience chronic pain due to sequela of cancer disease and/or treatment.

Objectives: To examine the use of analgesic drugs among BC patients compared with women from the general population in Denmark.

Methods: We conducted a population-based cohort study using Danish nationwide cancer, prescription, and demographic registries. We identified all Danish women aged ≥30 years with a primary diagnosis of localized BC during 2000-2015. For each BC patient, we randomly selected five women of similar age from the general population who were alive and without cancer history at diagnosis of the corresponding patient (index date). BC patients and comparison women were followed from index date until date of cancer diagnosis (second cancer diagnosis for BC patients), emigration, death, or end of follow-up on 31 December 2016. We assessed use of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol among BC patients and comparison women by estimating prescription rates with 95% confidence intervals (CIs) for each drug group within three prespecified time intervals of 0-5, 5-10, and 10-15 years postdiagnosis. In Denmark, opioids are available on prescription only, whereas some NSAIDs (aspirin and low-dose ibuprofen) and paracetamol are also available over the counter.

Results: We identified 33,991 BC patients and 157,523 comparison women (mean age at index date, 64 years). Median follow-up from index date was 6.3 years (interquartile range: 3.3-10.0 years). The prescription rate for opioids was higher among BC patients than among comparison women within 0-5 years after diagnosis (1.26 [95% CI: 1.26-1.27] vs. 1.06 [95% CI: 1.05-1.06] prescriptions/person-year) and remained higher 5-10 years (1.38 [95% CI: 1.37-1.39] vs. 1.15 [95% CI: 1.15-1.16]) and 10-15 years (1.35 [95% CI 1.33-1.36] vs. 1.20 [95% CI: 1.19-1.20]) after BC diagnosis. Among long-term BC survivors, the higher use of opioids was solely seen for strong opioids (10-15 years: 0.55 [95% CI: 0.54-0.56] vs. 0.42 [95% CI: 0.41-0.42] prescriptions/person-year). For NSAIDs and paracetamol, no major differences in prescribing rates were seen between BC patients and comparison women.

Conclusions: Women with localized BC had persistently higher use of opioids during 15 years after diagnosis compared with women in the general population. Our finding of higher use of strong opioids more than 10 years after BC diagnosis indicates that some women surviving BC suffer from severe long-term pain related to the disease or its management.

4066 | Substantial differences in the anticholinergic burden across sex and age groups in a large population-based sample

Jonas Reinold[1], Oliver Riedel[1] and Ulrike Haug[1,2]

[1]Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany[2]University of Bremen, Bremen, Germany

Background: Several drugs used to treat diseases such as depression, cardiovascular diseases, asthma, and COPD inhibit the effect of acetylcholine. Given that the cumulative effect of anticholinergic medications (also called anticholinergic burden) can lead to functional and cognitive decline, falls, and death, monitoring the anticholinergic burden is of high public health relevance. However, large comprehensive studies on the anticholinergic burden are scarce.

Objectives: To provide a detailed description of the anticholinergic burden by age and sex in a large population sample.

Methods: We used the German Pharmacoepidemiological Research Database (GePaRD) with health insurance claims data from ~17% of the German population. We included persons with ≥1 day of insurance coverage in 2016 preceded by ≥1 year of continuous enrollment and excluded persons hospitalized for ≥3 months in 2016. Based on outpatient drug dispensations in 2016 and the Anticholinergic Cognitive Burden (ACB) scale, we classified persons into four categories: no (ACB=0), low (ACB=1), intermediate (ACB=2), and high (ACB≥3) anticholinergic burden. We also determined the cumulative ACB score as continuous variable.

Results: Among 16,470,946 persons (54% female), the prevalence of ACB≥3 was 832 per 10,000 in women and thus 48% higher compared to men (564 per 10,000). In women, the prevalence of ACB≥3 was highest in the age groups 50-59 (1,087 per 10,000) and 70-79 (1021 per 10,000), while in men it was highest among those <18 (543 per

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

10,000) and in the age group 70-79 years (501 per 10,000). Regarding ACB-relevant medication, we focused on persons in each age and sex group whose cumulative ACB score was in the upper quartile. Among these persons, ACB-relevant medications were mainly prescribed by general practitioners with differences across sex and age groups regarding the type of ACB-relevant medication. For example, in women aged 35-49, the main contributors to the ACB were antidepressants (46%) and antipsychotics (25%) compared to medication for urinary incontinence and overactive bladder (27%), antidepressants (24%), and cardiovascular medication (23%) in women aged 65-79.

Conclusions: This comprehensive overview showed that a high anticholinergic burden is common in the German general population, particularly in vulnerable age groups. Given that the ACB-relevant medication substantially differs between age and sex groups, targeted interventions at the prescriber level are needed to increase awareness of this topic, as well as further studies on potential risks of a high ACB in specific subgroups.

4087 | Trends in the use of disease-modifying therapies among reproductive-aged women with multiple sclerosis in the United States 2001-2017

Emilie D Duchesneau[1], Michele Jonsson Funk[1], Alan C. Kinlaw[2] and Jennifer L Lund[1]

[1]University of North Carolina, Chapel Hill, NC; [2]University of North Carolina, Chapel Hill, NC

Background: Multiple sclerosis (MS) is a chronic disease of the central nervous system. MS preferentially affects women and typical disease onset occurs during reproductive years. Orally administered disease-modifying therapies (DMTs) were first FDA-approved for MS in 2010, but no DMTs of any kind have been approved for MS treatment during pregnancy.

Objectives: To describe the monthly prevalence of DMT use among commercially-insured, reproductive-aged women from 2001-2017.

Methods: This study used the IBM Watson Health MarketScan Commercial Claims and Encounters data from 2000-2017. The population of interest (denominator) included all women age 12-45 years with ≥12 months of continuous enrollment and ≥1 inpatient or ≥2 outpatient diagnosis codes for MS during the 12 months prior to the index month. The monthly prevalence of DMT use was calculated separately for each injectable/infused DMT (glatiramer acetate [GA]; interferon [IFN] β-1a; IFNβ-1b; pegIFNβ-1a; and natalizumab) and each oral DMT (dimethyl fumarate; fingolimod; and teriflunomide). DMTs were identified using National Drug Codes in outpatient prescription claims and Healthcare Common Procedural Coding System codes in the inpatient or outpatient services files. The numerator included women meeting the denominator criteria with any days supply of DMTs overlapping with the index month. Monthly prevalence was standardized by age and region.

Results: The number of reproductive-aged women with MS in the population of interest ranged from 467-9847 across months of the study period and peaked in 2012. The mean age was stable over time at 37 years. Each month, 40%-60% of reproductive-aged women with MS received at least one DMT. IFNβ-1a was the most common before 2010, with a peak prevalence of 31% in 2001, declining thereafter. GA prevalence increased from 10% in 2001 to 20% in 2010; GA use decreased after 2010 but remained second-most common during 2014-2017. After 2010, use of fingolimod and dimethyl fumarate increased drastically, with fingolimod prevalence peaking at 11% in 2016. Dimethyl fumarate was the most common DMT in 2014-2017, with prevalence ranging from 13-17%. Prevalence of natalizumab increased steadily after its FDA approval in 2004, plateauing at ~8% in 2012. Use of pegIFNβ-1a and teriflunomide was low in all years (<3% each).

Conclusions: Use of oral and injectable/infused DMTs in reproductive-aged women with MS is high. Additional research is needed on the safety of DMTs during pregnancy, particularly for DMTs such as dimethyl fumarate, GA, and fingolimod, which have been highly utilized in recent years.

4098 | Controlled drug prescribing of opioids by private prescribers in England, 2014-2018

Georgia C. Richards[1], Helen J. Curtis[2], Brian MacKenna[2], Alex Walker[2] and Ben Goldacre[2]

[1]University of Oxford, Oxford, United Kingdom[2]University of Oxford, Oxford, United Kingdom

Background: The prescribing of opioids has increased by 127% since 1998 in England. To date, most research on opioids has focused on prescriptions dispensed in the public sector. Little is known about the volume of opioids being prescribed privately.

Objectives: We aim to assess the trend of controlled drug prescriptions for opioids dispensed by private prescribers in England between 2014 and 2018.

Methods: We conducted a retrospective observational study. We obtained private prescription data through a freedom of information (FOI) request to the NHS Business Services Authority (BSA). The data was provided as summarised items for Schedule 2 and Schedule 3 controlled drugs dispensed privately at the area team level for drugs with a British National Formulary (BNF) chemical substance code of 4.7.2 (i.e. opioid analgesics) and 4.10.3 (i.e. opioid dependence) in quarterly splits from January 2014 to December 2018. We calculated the number of controlled opioid items dispensed for each calendar year (in crude terms) and determined the percentage change from 2014 to 2018. We stratified the data by the type of opioid using the BNF chemical substance codes to calculate the number of items for each opioid in each calendar year. We calculated the average number of items dispensed for each type of opioid over five years and ranked the opioids from most to least dispensed. We did not standardise the items dispensed by population data as the proportion of the English population who obtain medicines from prescribers registered with private prescriber codes is not publically available.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Controlled opioids dispensed privately decreased by 46% since 2014 (from 23,339 items in 2014 to 12,724 items in 2018). Methadone (7,772 items per year) was the most commonly dispensed controlled opioid followed by morphine (3,444 items per year), buprenorphine (2,637 items per year), tramadol (2,045 items per year) and oxycodone (1,812 items per year).

Conclusions: This is the first analysis of controlled opioids dispensed privately in England. Our findings indicate that the trend is decreasing. Opioids predominately used for the treatment of dependence (i.e. methadone and buprenorphine) are commonly dispensed by private prescribers in England.

4099 | Psychotropic medications utilization in adult cancer patients in China: Based on National Health Insurance database

Lin Bai[1], Cong Huang[1], Haishaerjiang Wushouer[2,3,4], Ziyue Xu[1], Xiaodong Guan[1,4] and Luwen Shi[1,4]

[1]Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, China; [2]Center for Strategic Studies, Chinese Academy of Engineering, Beijing, China; [3]School of Medicine, Tsinghua University, Beijing, China; [4]International Research Center for Medicinal Administration, Peking University, Beijing, China

Background: Psychotropic medications are useful to treat psychiatric disorders which are frequently underdiagnosed and undertreated in cancer patients. The evidence on utilization of psychotropic medications in cancer patients was absent in China.

Objectives: To determine the prescription rates and types of psychotropic medications in cancer patients in China.

Methods: We used the data from China Health Insurance Association database in 2015-2017, which contained health care utilization data for a national representative sample of basic medical insurance beneficiaries. Cancer patients aged 18 and over were identified by International Classification of Disease 10th revision (ICD-10) code C00-C97. We calculated the prescription rates of psychotropic medications in cancer patients. Outcomes were compared by demographics and clinical variables, using Chi-square test.

Results: A total of 260,364 adults with cancer were identified in the database, of which 19.1% were prescribed at least one psychotropic medication, comprising hypnotics and sedatives (11.0%), anxiolytics (9.8%), antipsychotics (1.4%), antidepressants (0.9%) and mood stabilizers (0.7%). Among sample patients prescribed psychotropic medications, the most commonly prescribed were midazolam (43.8%), diazepam (23.9%) and estazolam (22.5%). The 31.7% of the cancer patients with psychotropic medications were on more than one psychotropic medication, and 2.4% were on more than three. The prescription rate of psychotropic medications in cancer patients decreased significantly from 2015 to 2017 (20.6% vs. 18.0%, P<0.001). Cancer patients covered by the Urban Employee Basic Medical Insurance were more likely to use psychotropic medications than those covered by the Urban Rural Resident Basic Medical Insurance (19.5% vs. 18.1%, P<0.001). Cancer patients in Eastern regions were more likely to use psychotropic medications than those in Western regions (28.8% vs. 10.7%, P<0.001). The prescription rate of psychotropic medications in patients with malignant neoplasms of eye, brain and other parts of central nervous system (ICD-10 code C69-C72) (35.0%) was the highest among sample patients. Patients with malignant neoplasms of mesothelial and soft tissue (ICD-10 code C45-C49) (10.8%) and malignant neoplasms of ill-defined, secondary and unspecified sites (7.1%) had the lowest prescription rate.

Conclusions: The prescription rates of psychotropic medications in Chinese adult cancer patients were still low. The appropriate use of psychotropic medications in cancer patients needed to be further addressed in China.

4113 | Infection-related hospitalisations after common infections are associated with antibiotic prescribing in primary care

Birgitta van Bodegraven[1], Victoria Palin[1], Chirag Mistry[1], Matthew Sperrin[1], Andrew White[2], William Welfare[3], Darren M. Ashcroft[4] and Tjeerd P. van Staa[1]

[1]The University of Manchester, Manchester, United Kingdom; [2]NHS Greater Manchester Shared Service, Oldham, United Kingdom; [3]Public Health England North West, Manchester, United Kingdom; [4]The University of Manchester, Manchester, United Kingdom

Background: Research on antimicrobial resistance (AMR) and antibiotic prescribing often focus on reducing inappropriate prescribing. There is doubt with regards to the link between antibiotic prescribing levels and complications that can arise after common infections.

Objectives: Determine the association of incident antibiotic prescribing levels for common infections with infection-related complications and hospitalisations by comparing high with low prescribing GP practices.

Methods: This was a retrospective cohort study using UK primary care records from the Clinical Practice Research Datalink (CPRD GOLD) and SAIL Databank (SAIL) linked with Hospital Episode Statistics (HES) data. These databases hold anonymised patient-level electronic health records. 546 CPRD practices, 346 CPRD-HES linked and 338 SAIL-HES practices were included. Patients had a GP consultation and clinical READ code for a common infection. This was the first consultation for common infection in 6 months and without an antibiotic prescription in the previous 1 month. Six common infections were included: upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), otitis externa, otitis media, sinusitis, and urinary tract infection (UTI). Two outcomes were included in the analysis: infection-related hospital admission and infection-related complication as recorded in primary care records. Outcomes were evaluated for 30 days after the consultation. Negative binomial regression was used to model the rate of complications. All variables were scaled with their interquartile range (IQR: 75th to 25th percentile) to create a comparison between high and low prescribing practices.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: A 10.4% higher antibiotic prescribing rate (IQR) was associated with an IRR of 0. 943 (0.920 to 0.967), meaning a 5.7% lower infection-related hospital admission rate. The observed association varied by infection. The largest difference in the incidence of hospital admission was observed in LRTI (IRR: 0.839; 16.1%; 95%CI: 12.4% to 19.7%), UTI (IRR: 0.853; 14.7%; 95%CI: 7.6% to 21.1%), and URTI (IRR: 0.935; 6.5%; 95%CI: 3.5% to 9.5%). The association of antibiotic prescribing levels and hospital admission was largest in younger patients (6.0%; 1.6% to 10.1%).

Conclusions: Higher levels of incident antibiotic prescribing by GP practices were associated with lower risk of hospital admission and GP diagnosed infection-related complications. Indiscriminately reducing antibiotic prescribing may lead to harm. Greater focus is needed to optimise antibiotics to patients most likely to benefit.

4127 | Self-reported misuse of oral tramadol in the U.S.A.: Analysis of the National Survey on Drug Use and Health (NSDUH), 2002-2017

Thomas Rhodes[1], Sydney T. Thai[2,1], Molly Aldridge[1], Suzanne F. Cook[1] and Cynthia J. Girman[1]

[1]CERobs Consulting, LLC, Wilmington, NC; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Oral tramadol, a weak opioid, was approved in the USA in 1995 and designated a Schedule IV drug in 2014. Population-based estimates of oral tramadol misuse are limited.

Objectives: Describe self-reported misuse of oral tramadol and comparator oral opioids.

Methods: NSDUH is an annual, cross-sectional, population-based survey of self-reported alcohol, drug, and tobacco use among non-institutionalized persons (≥12 years old). NSDUH was used to assess misuse of oral tramadol and oral analgesics containing tramadol. Misuse is defined as use of a drug "in any way a doctor did not direct [the respondent] to use it". Lifetime (ever) misuse (2002-2014) or past-year misuse (2015-2017) for oral tramadol were self-reported. Misuse of morphine, oxycodone, and hydrocodone was also assessed. Counts were weighted to approximate the USA population and reported as a percent. Analyses were stratified by demographics and by responders who report misuse of oral tramadol alone versus those who also misuse comparators. Prescription volume data (Symphony Health Solutions, PRA Health Sciences) were used to estimate misuse per units dispensed (prescriptions or pills) to estimate public health impact.

Results: For 2002-2014, lifetime misuse (as a % of USA population) of oral tramadol and morphine remained <2%; reported misuse increased over time corresponding to increased media attention on abuse of more potent opioids. Lifetime misuse ranged from 4-10% for hydrocodone and oxycodone. For 2015-2017, 0.6-0.7% of the study population reported past-year misuse of oral tramadol. Past-year misuse of oral tramadol was higher in females, predominately in young-to-middle-aged adults, and was often in combination with other opioids. Past-year misuse of morphine, oxycodone, and hydrocodone was reported by 0.2-0.3%, 1.4-1.6%, and 2.3-2.7% of respondents, respectively. Among all self-reported users of oral tramadol, 9-10% reported past-year misuse of tramadol compared to past-year misuse of comparator opioids among self-reported users of morphine (8-9%), hydrocodone (12-13%), and oxycodone (14-15%). Based on dispensing data, the frequency of past-year misuse was lower for tramadol (41-46 cases/1,000 prescriptions; 5-6 cases/10,000 pills) compared to comparator opioids (68-84 cases/1,000 prescriptions; 10-12 cases/10,000 pills).

Conclusions: Among non-institutionalized USA residents, the prevalence of self-reported oral tramadol misuse is low relative to other opioids. Based on dispensing data, the frequency of past-year misuse was lower for oral tramadol relative to comparator oral opioids.

4141 | Hormonal contraception before and after a breast cancer diagnosis

Charlotte Skovlund[1], Anne Katrine Duun-Henriksen[1], Christian Dehlendorff[1], Søren Friis[1], Irene Petersen[2] and Lina Mørch[1]

[1]Danish Cancer Society, Copenhagen, Denmark; [2]University College London, London, United Kingdom

Background: Use of hormonal contraception is known to slightly increase the risk of breast cancer, while it remains unclear if hormonal contraception use influences survival after breast cancer. Recently, use of hormonal intrauterine devices (IUD) was found to increase the risk of breast cancer. It is known that use of oral contraceptives decreases after a diagnosis of breast cancer, however, we do not know if use of hormonal IUD decreases.

Objectives: To examine patterns in use of hormonal contraception, including IUD, before and after a diagnosis of breast cancer in Denmark.

Methods: From the Danish Cancer Registry, we identified 11,865 women aged 13-49 years with incident breast cancer during 2000-2016. The women with an incident breast cancer in this period were matched on birth year to women without cancer (n=52109). Eligible control women had to be alive and cancer free on the date of diagnosis of the corresponding breast cancer woman. Prescriptions of hormonal contraception were identified in the Danish Prescription Registry and divided into two groups: hormonal IUD and other hormonal contraception. Prescription rates per person-year were calculated from 2-0 years before and 0-2 years after the cancer diagnosis in intervals of 3 months.

Results: For hormonal contraceptives overall, there was a rapid decline in prescription rates after breast cancer diagnosis. The prescription rates of hormonal IUD were similar among women with breast cancer and women without cancer before the diagnosis, i.e., 0.02 prescriptions [0.02-0.03] per person-year for women with breast cancer and 0.02 [0.02-0.02] for women without cancer). After breast cancer diagnosis the prescription rate declined to 0.01 [0.00-0.01]/person-year for hormone IUD, while it was unchanged for women without cancer. The prescription rate for other hormonal contraception products was slightly higher before the diagnosis of breast

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

cancer (0.70 [0.69-0.71]) compared to women without breast cancer (0.57 [0.56-0.57]). After the breast cancer diagnosis there was a rapid decline in the prescription rate to 0.05 [0.05-0.05].

Conclusions: Prescription rates of hormonal intrauterine devices (IUD) and other hormonal contraception products declined rapidly after a breast cancer diagnosis and remained low two years after the diagnosis.

4148 | Utilisation of oral anticoagulants for stroke prevention in older people in the UK

Anneka Mitchell[1,2], Margaret C. Watson[3], Tomas J. Welsh[4,5,6], Julia Snowball[1] and Anita McGrogan[1]

[1]University of Bath, Bath, United Kingdom; [2]University Hospital Southampton, Southampton, United Kingdom; [3]University of Strathclyde, Glasgow, United Kingdom; [4]Research Institute for the Care of Older People (RICE), Bath, United Kingdom; [5]University of Bristol, Bristol, United Kingdom; [6]Royal United Hospitals, Bath, United Kingdom

Background: International guidelines recommend that oral anticoagulants (OACs) are prescribed to patients with atrial fibrillation (AF) who have additional risk factors for stroke. Advancing age is a significant risk factor and most guidelines recommend that OACs are considered for all patients ≥75 years. Historically, OACs have been underused in this group; it is not known how the introduction of direct OACs have affected overall OAC prescribing to older adults.

Objectives: To evaluate the effect of age and comorbidities on OAC prescribing to older individuals with AF.

Methods: A cohort of patients was identified in the Clinical Practice Research Datalink (CPRD). The study period was 1/1/2013-27/12/17 as DOACs and warfarin were available. To enter the cohort, patients needed: 1 year of research standard data, a diagnosis of AF, ≥75 years, and a year free of OAC prescribing before entering. Comorbidities for evaluation were selected *a priori* based on clinical factors likely to affect OAC use. Multivariate logistic regression was used to determine adjusted odds ratios of being prescribed an OAC.

Results: There were 43 984 people in the cohort, 45.4% were newly started on an OAC during the study. In the multivariate analysis, the odds of being prescribed an OAC were strongly influenced by advancing age OR = 0.85 (95% CI 0.80-0.89) in 80-84 years, OR 0.56 (95% CI 0.53 - 0.59) in 85-89 years, OR = 0.20 (95% CI 0.19-0.22) in ≥90 years compared with those aged 75-84 years. Comorbidities associated with a significant decrease in the odds of receiving an OAC were dementia (OR 0.26, 95% CI 0.24-0.29); falls compared with no falls (1-2 falls OR 0.74, 95% CI 0.69-0.79; 3+ falls OR 0.53 95% CI 0.43-0.64); previous fracture (OR 0.82, 95% CI 0.78-0.87); acute kidney injury (OR 0.71, 95% CI 0.63-0.80); chronic renal impairment (OR 0.92, 95% CI 0.88-0.96); liver disease (OR 0.68, 95% CI 0.57-0.82). A history of intracranial (OR 0.32, 95% CI 0.27-0.39) or gastrointestinal bleeding (OR 0.85, 95% CI 0.80-0.90) decreased OAC prescribing. Comorbidities associated with an increase in the likelihood of receiving an OAC were hypertension (OR 1.37, 95% CI 1.31-1.43) or history of stroke or transient ischaemic attack (OR 1.39, 95% CI 1.31-1.46).

Conclusions: OACs are underused in older people, with use declining with age. Fear of bleeding is commonly cited as a reason for under use of OACs in this group, however the association remained after adjusting for comorbidities. A history of falls decreased the odds of receiving an OAC, there is little evidence to support the link between falls and bleeding risk and UK guidelines specifically state that OACs should not be withheld due to falls risk.

4153 | Identifying cohorts of patients with type2 diabetes mellitus initiating dapagliflozin in three data sources

J. Bradley Layton[1], Cindy K. Zhou[2], Heather E. Danysh[3], Daniel C. Beachler[2], Ryan Ziemiecki[1], Jade Dinh[2], Ruihua Yin[2], Brian Calingaert[1], Phillip R. Hunt[4], Alicia W. Gilsenan[1] and Catherine B. Johannes[3]

[1]RTI Health Solutions, Research Triangle Park, NC; [2]HealthCore, Wilmington, DE; [3]RTI Health Solutions, Waltham, MA; [4]AstraZeneca, Gaithersburg, MD

Background: A multi-database study of dapagliflozin, a sodium-glucose cotransporter 2 inhibitor, utilized United Kingdom- and United States (US)-based data sources to identify historical cohorts of patients with type 2 diabetes mellitus (T2DM) initiating dapagliflozin. While the data sources differ in patient populations, data systems, and health care delivery and practice, a common protocol and statistical analysis plan were applied with data source-specific adaptations.

Objectives: To describe differences in patient characteristics and initiation patterns among new users of dapagliflozin with T2DM in three data sources.

Methods: Dapagliflozin initiators were identified in US-based administrative claims databases—Medicare (aged ≥ 65 years, years 2014-2017) and the HealthCore Integrated Research Database (HIRD) (aged 18-64 years, years 2014-2017)—and the Clinical Practice Research Datalink (CPRD), United Kingdom-based general practice records (aged ≥ 18 years, years 2012-2018). Clinical and demographic characteristics of the resulting study cohorts were described.

Results: We identified 46,801 dapagliflozin initiators (CPRD, 12,051; HIRD, 16,671; Medicare, 18,079). Across data sources, the proportion of patients using insulin at the time of dapagliflozin initiation was similar (CPRD, 13%; HIRD, 13%; Medicare, 17%), but the CPRD had higher proportions of dapagliflozin initiators adding dapagliflozin to other diabetes treatments (CPRD, 89%; HIRD, 66%; Medicare, 72%) and lower proportions initiating dapagliflozin as monotherapy (CPRD, 2%; HIRD, 13%; Medicare, 10%). The older Medicare cohort had higher baseline prevalences of most indicators of diabetes severity, comedication use, and comorbidity, including coronary heart disease (CPRD, 12%; HIRD, 9%; Medicare, 31%) and other cardiovascular disease (CPRD, 9%; HIRD, 3%; Medicare, 14%). The CPRD had lower recorded diagnoses of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

hypertension than either US data source (CPRD, 54%; HIRD, 70%; Medicare, 90%).

Conclusions: Characteristics of patients with T2DM initiating dapagliflozin vary based on the source population and data source, potentially due to differences in age, data coding and record structures, and practice patterns. The Medicare cohort had higher levels of most comorbidities, as expected due to age. The patterns of dapagliflozin initiation in the CPRD differed from the US samples, which could be due in part to differing diabetes treatment approaches in the two countries. Using patient information from a variety of populations and practice settings is helpful in evaluating the safety of dapagliflozin.

4154 | Development of antipsychotic doses among persons with newly diagnosed schizophrenia - Ten years of follow-up

Antti Tanskanen[1], Marjaana Koponen[2], Markku Lähteenvuo[1], Jari Tiihonen[3] and Heidi Taipale[1]

[1]Niuvanniemi Hospital, Kuopio, Finland; [2]University of Eastern Finland, Kuopio, Finland; [3]Karolinska Institutet, Stockholm, Sweden

Background: Knowledge on antipsychotic dose trends in treatment of schizophrenia is scarce.

Objectives: The aim of this study was to investigate the development of antipsychotic dose in patients with incident schizophrenia over up to ten years of follow-up.

Methods: The study cohort included all persons newly diagnosed with schizophrenia during 1996-2014 in Finland, without antipsychotic use during the preceding year (N=8,342, median age 36, IQR 26-53; 56.3% men). The study cohort was identified based on first schizophrenia diagnosis recorded in inpatient care, and register-based data linkage covered years 1972-2017. Antipsychotic dispensings were modelled into drug use periods with PRE2DUP method, and local dose estimate was calculated at 6 month intervals up to 10 years after first schizophrenia diagnosis. Dose was calculated by sliding average of defined daily doses (DDDs), summed up from all antipsychotic drugs and using up to three purchases before the time point. Similarly, the number of concurrent antipsychotics (no use, monotherapy and polytherapy, referring to concurrent use of more than one antipsychotic) was measured at every time point.

Results: Six months after diagnosis, 74.7% of persons used at least one antipsychotic and the prevalence of polytherapy was 14.1%. At this point, mean antipsychotic dose was 1.27 (SD 0.91) DDDs per day and 17.5% were categorized to have a high dose (>1.5 DDDs per day). After ten years of follow-up, 80.1% used antipsychotics, 22.5% were defined as having antipsychotic polytherapy, mean dose was 1.43 (SD 1.10) DDDs per day and 26.5% had a high antipsychotic dose.

Conclusions: Antipsychotic dose, prevalence of polytherapy and high dose use increased during ten years of follow-up among persons with initially newly diagnosed schizophrenia.

4157 | Do early prescribers of new drugs have different risk management practices?

Nabarun Dasgupta[1], John R Brown[2], Patricia Rippetoe Freeman[2], Maryalice Nocera[1] and Svetla Slavova[2]

[1]University of North Carolina, Chapel Hill, NC; [2]University of Kentucky, Lexington, KY

Background: Uptake of new technology occurs first in "early adopters." We hypothesized that early prescribers of new medicines could likewise be identified, possibly influencing interpretation of early post-market assessments.

Objectives: Conduct a statewide prescriber survey to evaluate if self-described early prescribers have differences in risk management practices compared to later prescribers.

Methods: Planned hypothesis generating analysis of a larger survey on opioid prescribing, fielded by state licensing authority in Nov 2019. **Setting**: All DEA-registered Kentucky (US) physicians. **Exposure**: Self-reported affirmation of any of 3 statements: I prescribe new medications before others; I enjoy the variety of prescribing new medicines; I like to share with colleagues about new medicines I've prescribed. (Other options: I feel more comfortable using familiar medications, etc.). **Outcome**: Physician characteristics, opioid prescribing. **Analysis**: Descriptive univariable/bivariable stats

Results: Emails were delivered to 7631 physicians, with 651 respondents (8.5% - similar to other unincentivized physician surveys). After limiting to controlled substance prescribers and removing incommpletes, the analysis sample was n=349, with 83 (24%) early prescribers. Early adopters were disproportionately in early or late career (less than 15 or 35+ practice-years). The male:female ratio was 2:1 among respondents, but proportionately more females (26%) than males (19%) were early adopters. There were no differences in patient load, practice setting, or medical specialty except emergency medicine and general surgery were less likely; and oncology and OB/GYN were more likely to be early adopters. Early prescribers were more likely to use opioid risk stratification tools (OR 1.5; 0.85, 2.7). Abuse deterrent formulation (ADF) opioid prescribing was similar (OR 1.1; 0.65, 1.8). However, early adopters were more likely (OR 1.4; 0.73, 2.6) to prescribe newer non-OxyContin ADFs, with 93% endorsing "innovative nature of abuse-deterrence mechanisms" as a consideration. They supported legislation mandating insurance coverage for ADFs (OR 3.5; 1.6, 8.9), and more strongly endorsed technical solutions like electronic prescription monitoring programs and urine drug screens, while opposing prescribing limits.

Conclusions: In addition to prescribing newer medications, early adopters may differ in other healthcare delivery aspects that may impact care. The survey is being replicated in other states. Quantitative assessments will follow. Studies with historical controls may want to consider impacts of early adopters.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4190 | Sociodemographic and clinical predictors of prescription opioid use in a longitudinal community-based cohort study of middle-aged and older adults

Kristin Y Shiue[1,2], Nabarun Dasgupta[1,2], Rebecca B Naumann[1,2], Amanda E Nelson[3,4] and Yvonne M Golightly[1,3]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Chronic pain prevalence in the United States is likely to increase with an aging population. While opioids have commonly been prescribed to manage pain, their use may be more likely in certain patients.

Objectives: Assess predictors of prescription opioid use in an adult population with a high prevalence of chronic pain.

Methods: Data were from a community-based cohort of White and African American adults aged 50-90 years residing in predominantly rural Johnston County, North Carolina. Univariable and multivariable logistic regression models were used to evaluate sociodemographic and clinical factors in non-opioid users (n=795) at baseline (2006-2010) as predictors of opioid use at follow-up (2013-2015). Variables included age, sex, race, obesity (BMI≥30kg/m^2), polypharmacy (5+ medications), educational attainment (<12, ≥12 years), employment (unemployed, employed/retired), insurance (uninsured, public, private), Census block group household poverty rate (<12%, 12-24%, ≥25%), depressive symptoms (Center for Epidemiologic Studies Depression Scale ≥16 or depression diagnosis), perceived social support (moderate/poor [<19], strong [≥19]; Strong Ties Measure of Social Support, range 0-20), pain sensitivity (sensitive [<4kg], normal [≥4kg] pressure pain threshold), and pain catastrophizing (high [≥15], moderate/low [<15]; Pain Catastrophizing Helplessness Subscale, range 0-25).

Results: At follow-up, 13% (n=102) of participants were using prescription opioids. In univariable models, younger age, female sex, obesity, polypharmacy, unemployment, public (vs. private) health insurance, higher poverty, depressive symptoms, poorer perceived social support, pain catastrophizing, and elevated pain sensitivity were independently associated (p<0.05) with opioid use. In the multivariable model, younger age (60 vs. 70 years; adjusted odds ratio, 95% confidence interval=1.76, 1.12–2.77), polypharmacy (2.21, 1.27–3.85), high pain catastrophizing (2.12, 1.29–3.48), and depressive symptoms (1.93, 1.12–3.31) remained significant independent predictors.

Conclusions: The simultaneous assessment of a breadth of clinical and sociodemographic factors identified polypharmacy, pain catastrophizing, and depressive symptoms as modifiable predictors of prescription opioid use. These findings support the incorporation of pharmacological review and behavioral approaches into chronic pain management strategies. Further research is warranted to track changes in these factors as prescription opioid use declines nationwide

4232 | Understanding real-world use and survival with the use of anaplastic lymphoma kinase (ALK) inhibitors for ALK-positive non-small cell lung cancer: A Hong Kong-wide cohort study

Swathi Pathadka[1], Jesse Zhao[1], Joseph E. Blais[1], David C. L. Lam[2], Jessica P. Shami[1] and Esther W. Y. Chan[1]

[1]The University of Hong Kong, Hong Kong, Hong Kong; [2]The University of Hong Kong, Hong Kong, Hong Kong

Background: Anaplastic lymphoma kinase (ALK) inhibitors have advanced the treatment of ALK-positive non-small cell lung cancer (NSCLC). There is limited real-world data on the treatment and outcomes in patients with ALK-positive NSCLC in the Asian population.

Objectives: To assess the treatment patterns and survival outcomes with the use of ALK inhibitors in Hong Kong.

Methods: We conducted a population-based cohort study using electronic medical database managed by the Hong Kong Hospital Authority. Patients treated with ALK inhibitors between 2013 and 2017 were followed-up until 2018. Patient characteristics and treatment patterns of ALK inhibitors, including a switch in therapy and treatment discontinuation were described. Using the Kaplan-Meier method, overall survival (OS) of patients treated with crizotinib was analyzed.

Results: Among 417 patients who received ALK inhibitors (median age, 57 years; 59.2% women), crizotinib was initiated as the first-line ALK-targeted therapy in 387 (92.8%), for a median treatment duration of 39 weeks. The majority of patients had confirmed lung adenocarcinoma (81.7%) and 15.3% of patients had brain metastases before receiving ALK inhibitors. More than half of the patients on crizotinib switched to either chemotherapy (18.8%) or a second-generation ALK inhibitor (36.2%) after a median period of 10 months. Nearly 20% of patients on crizotinib, 16% on ceritinib and 7% on alectinib discontinued therapy for more than 3 months. The median OS of patients treated with crizotinib was 10.4 months (95% confidence interval, 7.97-12.7).

Conclusions: In Hong Kong, crizotinib was the most common initial choice of treatment for ALK-positive NSCLC. Crizotinib appears to be associated with 10 months OS, but treatment discontinuation and switch in therapy due to disease progression occur frequently.

4262 | Prescribing pattern of antibiotics in children

Ching-Lan Cheng[1,2], Ju-Ling Chen[3], Yea-Huei Kao Yang[3] and Wen-Liang Lin[4]

[1]National Cheng Kung University, Tainan, Taiwan; [2]National Cheng Kung University Hospital, Tainan, Taiwan; [3]National Cheng Kung University, Tainan, Taiwan; [4]National Cheng Kung University Hospital, Tainan, Taiwan

Background: Antimicrobial Resistance (AMR) is a worldwide problem with the public. "Taiwan Antimicrobial Resistance, Prescribing and Efficacy in Neonates and Children Project (TARPEC)" is a multicenter study to estimate the magnitude of antimicrobial resistance in pediatrics in Taiwan.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To evaluate the utilization of neonatal and pediatric AMR blood stream infection (BSI) in survey study and the trend of antibiotic use in children stratified by age group in Taiwan by using claim database.

Methods: We conducted a prospective cohort study to collect clinical data by using the online surveillance system in four centers. We enrolled admitted children who aged younger than 18 years during August 2017 to July 2019. The 1-day point prevalence of prescription were calculated among all hospitalized neonates and pediatric patients at 8 am since at least midnight. The pattern of neonatal and pediatric AMR blood stream infection was evaluated. In addition, we conducted a retrospectively study by using National Health Insurance Research Database from January 1 2012 to December 31 2016, to analyze the utilization of antibiotics, focusing on the pediatric population. We also identified the antimicrobial regimen for bacteremia, sepsis of newborn (ICD-9/ICD-10 code:790.7/R78.81, 771.8/P36) among hospitalization children.

Results: In survey study, *Escherichia coli* (*E. coli*) (26%) was the most isolated pathogen among 105 subjects with BSI, followed by *Staphylococcus aureus* (*S. aureus*) (21%) and *Salmonella* (16%). More than 50% isolated *E. coli* was resistant to ampicillin/sulbactam and trimethoprim/sulphamethoxazole. *S. aureus* was resistant to clindamycin, erythromycin and oxacillin. Amoxicillin/beta-lactamase inhibitor and cefazolin were two highest prescribed abxs among inpatient setting. Prescription pattern was similar between medical center and regional hospital. Prescription rate was highest in 6~18 yrs old age group (around 61%), followed by 2~5 yrs old, 0~1 yrs old and lowest in 1~2 yrs old group (51%) during hospitalization. For children with bacteremia or sepsis, ampicillin and gentamicin were most prescribed (54 %) empirical combination therapy. In addition, third generation cephalosporins, such as cefotaxime, ceftazidime and ceftriaxone, were most frequently prescribed abxs for monotherapy.

Conclusions: *E. coli* was the most isolated pathogen in patients with BSI and resistant to ampicillin/sulbactam and trimethoprim/sulphamethoxazole inn survey study. In claim data study, different abxs prescription pattern was observed might due to different patient's characteristics between inpatients and outpatients.

4269 | Secular trends in first line treatment with disease modifying antirheumatic drugs in rheumatoid arthritis: An international real-world study by the OHDSI and EHDEN networks

Anthony G. Sena[1,2,3], Nigel Hughes[1], Emily S. Brouwer[1], Edward Burn[4,5], Jennifer Lane[5], Marcel de Wilde[3], Katia Verhamme[3], Peter R. Rijnbeek[2,3], Daniel Prieto-Alhambra[5] and Patrick B. Ryan[1,2,6]
[1]Janssen Europe, Middle East and Africa, United States of America, Titusville, NJ; [2]Observational Health Data Sciences and Informatics, New York, NY; [3]Department of Medical Informatics, Erasmus MC, Rotterdam, Netherlands; [4]Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain; [5]Centre for Statistics in Medicine (CSM), Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; [6]Department of Biomedical Informatics, Columbia University, New York, NY

Background: International guidelines increasingly recommend early initiation of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) following diagnosis of rheumatoid arthritis (RA), with methotrexate (MTX) advised as the first line treatment. There is a scarcity of data on secular trends in the real-world use of csDMARDs in treatment of RA internationally.

Objectives: To characterize secular trends in first-line csDMARD treatment patterns during the first year following an RA diagnosis.

Methods: Fourteen real world databases from 9 countries mapped to the OMOP Common Data Model were included from the OHDSI network and EHDEN European project: Australian (IQVIA), Belgian (IQVIA), Estonian, France (IQVIA), Japanese (JDMC), Dutch (IPCI), Spanish (SIDIAP), UK (IQVIA THIN), and USA (IBM: CCAE, MDCR, MDCD, Optum: DOD and EMR). Patients were included starting at the earliest of: first diagnosis of RA or first DMARD with an RA diagnosis within 30 days. Patients must be 18 years or older and required 1+ year pre-index observation, and at least 1-year of follow-up after diagnosis of RA. The study period covered 2000-2018. Patients with previous non-RA inflammatory arthritis history were excluded. 15 DMARDs and minocycline were included for analyses, but only MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ) and leflunomide (LEF) monotherapy were available in all databases, with all others grouped as "other" for the analyses.

Results: We identified 323,547 newly diagnosed RA patients with a first-line csDMARD in the first year from index. Across all databases, MTX was the most prevalent first-line therapy with consistent usage. HCQ was the next most prevalent first-line therapy in Australia, Belgium, Estonia, France, Netherlands, and USA, with LEF as second most used in Spain until 2012 then changing also to HCQ. Despite consistent guidelines, the use of MTX as a first line treatment remained low (around 50%) in the US, Australian and UK data with no clear change over time. MTX as first-line therapy increased in Spain and the Netherlands until 2012, then decreased in favor of HCQ. Japan and Estonia had low use of MTX (<50%) initially, but slowly increased over time.

Conclusions: We observed evidence of heterogeneity in the management of RA across 9 countries. Despite published guidance for MTX to be first line therapy, data suggest that a large proportion of patients receive another csDMARD. The proportion of first-line MTX initiators has not increased over time despite international recommendations.

4273 | Geographical variation and prescribing trajectories of opioids in the Scottish primary care setting

Teng-Chou Chen[1], Amanj Kurdi[2,3] and Li-Chia Chen[1]
[1]Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom, Manchester, United Kingdom; [2]Strathclyde Institute of Pharmacy and Biomedical Science, University of Strathclyde, Glasgow, United Kingdom; [3]Department of Pharmacology, College of Pharmacy, Hawler Medical University, Erbil, Iraq

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: From 2015, opioid prescribing remained stable in Scotland due to the rising concerns of abuse and the implementation of deprescribing strategies. Although variation in opioid prescribing across practices has been identified associating with policies across health boards and population characteristics, the variation in longitudinal opioid prescribing trend and its associated factors have not been investigated.

Objectives: This study aimed to identify the longitudinal trajectory of opioid utilisation and its associated population factors in general practices in Scotland.

Methods: This cross-sectional study used the practice-level dispensing data from the NHS National Services Scotland and published statistics from 2016 to 2018. Practices that prescribed opioid analgesics and could be assigned characteristics of registrants were included. Monthly opioid utilisation in each practice was quantified using defined daily dose (DDD)/1000 registrants. The monthly opioid utilisation in 2017 and 2018 were compared with utilisation in 2016 and the difference between each calendar month was calculated. Group-based trajectory models were used to identify groups of practices with a similar trajectory based on the difference in monthly opioid utilisation. The association between characteristics of registrants and the trajectory groups was analysed by logistics regression and reported as odds ratio (OR) and 95% confidence interval (95%CI).

Results: Overall, 813 practices were included and categorized into four trajectories from 2016 to 2018. Of the 813 practices, most of them were grouped into the trajectory with stable (31.7%), decreased (29.4%) and largely decreased (10.3%) monthly opioid utilisation. However, 28.7% of practices were grouped into the trajectory with increasing opioid prescribing. More than 30% of practices in the Southern and Western Scotland were categorised into trajectory group with increasing opioid prescribing. Practices with more than 20% of registrants coming from the most deprived area were associated with a higher risk (OR: 2.3, 95%CI: 1.7, 3.1) of grouping into the trajectory with increasing opioid utilisation.

Conclusions: Increasing opioid utilisation over time was related to depriving socioeconomic status despite existing strategies to deprescribe opioids across general practices in Scotland. Further studies should explore the determinants associated with decreased opioid prescribing by applying individual-patient data.

4278 | Trajectories of use of biologic disease modifying anti-rheumatic drugs in rheumatoid arthritis: A cohort study of Tuscan patients, Italy

Irma Convertino[1], Sabrina Giometto[2], Rosa Gini[3], Massimiliano Cazzato[4], Giulia Valdiserra[1], Emiliano Cappello[1], Sara Ferraro[1], Marco Fornili[2], Giuseppe Turchetti[5], Valentina Lorenzoni[5], Leopoldo Trieste[5], Marta Mosca[4], Corrado Blandizzi[1,6], Marco Tuccori[6,1] and Ersilia Lucenteforte[2]

[1]Unit of Pharmacology and Pharmacovigilance, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Unit of Medical Statistics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [3]Tuscan Regional Healthcare Agency, Florence, Italy; [4]Unit of Rheumatology, University Hospital of Pisa, Pisa, Italy; [5]Institute of Management, Scuola Superiore Sant'Anna, Pisa, Italy; [6]Unit of Adverse Drug Reactions Monitoring, University Hospital of Pisa, Pisa, Italy

Background: Adherence to biologic Disease Modifying Anti-rheumatic Drugs (bDMARDs) in rheumatoid arthritis (RA) patients is poorly reported, and its interpretation is complex due to recommended discontinuation of the drugs when remission of symptoms is achieved.

Objectives: To identify and characterize trajectories of bDMARDs in RA patients.

Methods: This is a population based retrospective cohort study using data collected in administrative healthcare databases of Tuscany, an Italian region. We included patients with a first dispensation of bDMARD (infliximab, adalimumab, certolizumab, etanercept, golimumab, abatacept, tocilizumab) from 2010 to 2015 (index date, ID); at least 1 year (y) of look-back period at ID; a RA diagnosis or a rheumatologic visit within 1y after ID; at least 3 dispensations of bDMARD. We excluded patients with dispensations of antineoplastic drugs or cancer diagnosis at baseline, or less than 3y of follow-up. We censored for cancer or pregnancy. We estimated adherence to bDMARD every three months through the Proportion of Day Covered and clustered longitudinal trajectories of adherence in groups. We described the clusters and compared baseline characteristics of patients across clusters.

Results: Out of 3,468 first bDMARD users with a RA diagnosis or visit and no history of cancer, 292 (8.4%) had less than 3 dispensations and 79 (2.3%) had less than 3y of follow-up. In the cohort of 3,097 patients, 67.2% were female. The mean age was 52.90 (SD 16.6). The index bDMARDs (ibD) were etanercept (1184 patients, 38.2%), adalimumab (998, 32.2%), infliximab (259, 8.4%), golimumab (234, 7.6%), abatacept (159, 5.1%), certolizumab (149, 4.8%), tocilizumab (114, 3.7%). We identified 3 clusters: in the 1st, including 1,213 patients, adherence was high for 2y, followed by a slow decrease; in the 2nd, 1,744 patients, adherence showed a steady state with moderate decrease over time; in the 3rd, 135 patients, adherence fell abruptly after 9 months. Gender and age did not predict cluster membership. History of fractures and number of specialist visits predicted the 2nd and the 3rd trajectory, respectively. The most common ibD were etanercept (35.7%), adalimumab (32.8%) and golimumab (10.1%) in the 1st group; etanercept (40.3%), adalimumab (32.5%) and infliximab (9.1%) in the 2nd; etanercept (34.8%), adalimumab (23.0%) and abatacept (13.3%) in the 3rd.

Conclusions: Three trajectories of adherence were identified: late decrease, slow and steady decrease, early and sudden decrease. Specialist visits, fractures, and ibD were predictive of the cluster membership.

4290 | The associations between personality traits and medication use, dietary supplement use and blood pressure control

Dianna F. M. de Vries[1], Julia C. Stingl[2] and Monique M. B. Breteler[1,3]

[1]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [2]RWTH Aachen, Aachen, Germany; [3]University of Bonn, Bonn, Germany

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Personality traits have been associated with disease burden, adherence to treatment and reporting of adverse drug reactions. It is unknown whether personality is also associated with medication and supplement use.

Objectives: To assess the associations between personality traits and medication use, supplement use, and control of blood pressure.

Methods: We used data from the Rhineland Study, a population based cohort in Bonn, Germany that includes people aged ≥30 years. Information on medication use was collected in an interview. We assessed supplement intake using a Food Frequency Questionnaire and personality traits with the short Big Five Inventory. We quantified the associations between personality traits and the amount of drugs used (regularly, regularly without prescription, and as needed), dietary supplement use, intensive blood pressure lowering (antihypertensive treatment and systolic blood pressure <120 mmHg) and having uncontrolled blood pressure (≥140/90 mmHg), by using either multivariable logistic models or quasi-Poisson regression models (dependent count variables). Models were adjusted for age, sex and educational level. Personality traits were entered as independent variables (one trait per model) comparing persons in the fourth to those in the first quartile.

Results: The analyses were based on 3,502 out of 4,000 participants (mean age 55 years, standard deviation 13.9, 57% women). The main reason for exclusion was missing data on supplement use. Higher neuroticism level was associated with an increased amount of drugs used regularly (IRR 1.47, 95% confidence interval (CI) 1.32-1.64), regularly without prescription (IRR 1.87, 95%CI 1.37-2.57), and as needed (IRR 1.39, 95%CI 1.26-1.54), more use of supplements (OR 1.66, 95%CI 1.37-2.02), and an increased likelihood of intensive blood pressure lowering (OR 2.45, 95%CI 1.48-4.21). Higher agreeableness was associated with a lower amount of drugs used regularly (IRR 0.89, 95%CI 0.80-0.98) and a decreased likelihood of being on intensive blood pressure lowering treatment (OR 0.57, 95%CI 0.36-0.87). Higher openness was associated with increased use of supplements (OR 1.24, 95%CI 1.02-1.50). There were no associations between extraversion and conscientiousness and our outcomes of interest.

Conclusions: Individuals high on neuroticism may be at increased risk of suboptimal medication use due to their increased use of supplements and medication. Especially the increased use of non-prescribed and as needed medication, which is often not known to the physician, may increase the risk of unintended effects.

4291 | Persistently high levels of opioid utilization among older patients with urinary stone disease: Findings from the urologic diseases in America project

Lydia Feinstein[1], Julia B. Ward[1], Kevin C. Abbott[2], Tamara Bavendam[2], Ziya Kirkali[2], Erline Martinez-Miller[1] and Brian R. Matlaga[3]

[1]Social & Scientific Systems, Durham, NC; [2]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; [3]Johns Hopkins University School of Medicine, Baltimore, MD

Background: Urinary stone disease (USD) and its surgical treatment are typically very painful, but the scope of opioid utilization to mitigate USD-related pain is not well understood.

Objectives: To assess trends in the utilization of opioid agents among a U.S. representative sample of USD patients aged ≥65 years.

Methods: We analyzed data from USD patients aged ≥65 years in the 2006-2013 Centers for Medicare & Medicaid Services Medicare 5% Sample with full enrollment in Parts A, B, and D (N≈10,000 annually). A patient was considered to have experienced a kidney stone episode in a given calendar year if they had at least one Evaluation & Management claim with a qualifying ICD-9-CM diagnostic code indicative of kidney stones at any time during that year. The percentage of USD patients prescribed opioid agents was calculated annually over the study period. All results were assessed overall and stratified by age group, gender, and race/ethnicity.

Results: Approximately three-fourths of USD patients filled a prescription of any kind in the course of their treatment. Opioid agents were the most commonly prescribed pharmaceutical (range: 55-58%), followed by alpha blockers (range: 19-29%) and calcium channel blockers (range: 27-30%). The prevalence of opioid agonist prescription fills decreased with increasing age and was higher among women (range: 58-61%) compared to men (range: 51-56%). Black USD patients were also more likely to be prescribed opioid agonists (range: 60-65%) compared to other racial/ethnic groups (range: 45-58%). These trends were consistent across all study years.

Conclusions: Opioid agents are commonly prescribed to older USD patients in the United States, and this practice persisted over the study period. An understanding of the scope of opioid prescription practices among USD patients is the first step in a pathway towards reducing use of opioids for analgesia. Given how commonly opioids are utilized among USD patients, and given the recognized health risks associated with these agents, developing clinical pathways that decrease reliance on opioid agents is particularly important.

4310 | Drug utilization disparities regarding rural-urban area and economic status in primary healthcare in china: A nationwide cross-sectional survey

Mengyuan Fu[1,2], Haishaerjiang Wushouer[1,3], Luwen Shi[1,4] and Xiaodong Guan[1,2,4]

[1]School of Pharmaceutical Sciences, Peking University, Beijing, China; [2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [3]Center for Strategic Studies, Chinese Academy of Engineering, Beijing, China; [4]International Research Center for Medicinal Administration, Peking University, Beijing, China

Background: The primary healthcare institutions (PHIs) in China, which provide basic clinical care to a fifth of the world's population, have 4.4 billion outpatient visits in 2018. However little research has been focused on the nationwide variation of drug utilization quality in Chinese primary healthcare in recent years.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To evaluate the outpatient drug utilization disparities regarding rural-urban areas and economic status in primary healthcare in China.

Methods: We conducted a nationwide cross-sectional survey for PHIs in China from October, 2017 to April, 2018. A total of 283 PHIs (195 rural vs. 88 urban) were randomly selected from 9 provinces, in various regions and at various economic levels (4 levels based on capita GDP of the city), using multi-stage stratified sampling method. Outpatient prescriptions in 2017 were randomly selected from sampled institutions and analyzed retrospectively. Average number of drugs per prescription, antibiotic prescription rate, multi-antibiotic prescription rate, injection prescription rate and national essential medicine (NEM) prescription rate were used as outcome measures to evaluate drug utilization. Generalized estimating equations were applied to generate population-weighted average comparisons using model adjusting for other covariates (region, patient gender, patient disease type, etc.). Ethics approval was obtained from Peking University Institution Review Board.

Results: 388,361 prescriptions were included in total. PHIs in rural areas prescribed larger number of drugs per prescription (adjusted number, 2.6 vs. 2.3), higher proportion of antibiotic, multi-antibiotic, injection and NEM prescribing (adjusted proportion, 23.1% vs. 16.2%; 16.4% vs. 13.9%; 26.5% vs. 16.5%; 71.3% vs. 67.7%). PHIs in lower economic status have relatively more drugs per prescription (adjusted number, lowest quartile of economic level to highest 3.4-1.9), higher proportion of antibiotic, multi-antibiotic, injection and NEM prescribing (adjusted proportion, lowest quartile of economic level to highest 23.2-14.7%; 18.4-11.0%; 21.9-20.3%; 75.7-60.8%).

Conclusions: Substantial variations regarding rural-urban areas and economic status were identified in outpatient drug utilization in primary care in China. More strategies aiming at promoting prescribing practices and quality use of medicines of primary healthcare, especially in rural and economically underdeveloped areas, are required.

4318 | Increasing use of muscle relaxants in the US 2005-2016

Samantha E. Soprano, Sean Hennessy, Warren B. Bilker and Charles E. Leonard
University of Pennsylvania, Philadelphia, PA

Background: Little is known about United States (US)-based trends in skeletal muscle relaxant (SMR) use, despite important safety concerns especially among older adults and in persons concomitantly exposed to opioids.

Objectives: To measure US trends in SMR utilization over a 12-year period.

Methods: We conducted a repeated cross-sectional study using 2005-2016 US Centers for Disease Control and Prevention National Ambulatory Medical Care Survey data. The study population consisted of ambulatory care patient encounters of non-federally funded, office-based physicians. We quantified ambulatory care visits—overall and stratified by calendar year, geographic region, patient age, sex, and race—in which an SMR was newly prescribed or continued. Among visits in which an SMR was newly prescribed, we assessed all diagnoses. Concomitant medications were analyzed We used survey visit weights to estimate nationally representative measures and further generated age-standardized rates by geographic region using US census data.

Results: The number of US ambulatory care visits in which an SMR was either newly prescribed or continued as ongoing therapy nearly doubled from 15.5 million in 2005 to 30.7 million in 2016. While visits for new SMR prescriptions remained stable, office visits with continued SMR therapy tripled from 8.5 million visits in 2005 to 24.7 million visits in 2016. SMR users were predominantly female (52.8%), white (53.7%), and non-Hispanic (81.3%). The most common diagnoses were related to issues of back pain. Older adults accounted for 22% of patients receiving an SMR in 2016, accounting for a 3-fold increase from 2005. Concomitant opioid use was documented in 67.2% of all visits with a continuing SMR prescription. Age standardized rates revealed a 325.1% increase in continued SMRs prescriptions in the Northeast region, followed by the Midwest with a 297.6% increase.

Conclusions: SMR use in the US has increased rapidly, which is worrying given prominent adverse effects and limited long-term efficacy data associated with their use. Use in older adults continued to rise over the study period, despite labeling by the American Geriatric Society as potentially inappropriate in this population. Approaches are needed to limit long-term use of SMRs, especially in older adults, akin to approaches to minimize long-term use of opioids and benzodiazepines.

4328 | Trends of non-insulin antidiabetic medicines prescribing in Romania during 2012-2018

Camelia Bucsa, Adriana Rusu, Andreea Farcas and Cristina Mogosan
"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Background: Several new antidiabetic medicines (ADMs) were authorized during the last decades and this resulted in changes in diabetes therapy.

Objectives: To analyze the market trends of ADMs in Romania during 2012-2018 and to describe the utilization of the new ADMs (glucagon-like peptide-1 receptor agonists [GLP-1], dipeptidyl peptidase-4 inhibitors [DPP-4] and sodium-glucose transport protein 2 inhibitors [SGLT-2]) during 2018.

Methods: We conducted a retrospective analysis of pharmacy claims data from IQVIA Romania database from January 2012-December 2018. For trends analysis, we used nationally extrapolated data (IQVIA proprietary algorithm with maximum 2% error) and for the detailed 2018 analysis, we used exact data retrieved from the approximately 4000 pharmacies (approx. 70% of the overall market). We analyzed the reimbursed prescriptions that included at least one ADM (all

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ATC10 codes) as defined daily doses (DDDs)/1000 inhabitants/day and number of prescriptions (for 2018).

Results: The total number of ADMs DDDs/1000/day increased by 41.74% between 2012 (48.08) and 2018 (68.15) at the national level. A comparison between the successive years showed a continuous increase in ADMs consumption (the highest of 9.20% between 2016-2017), except for the years 2013-2014 where a slight decrease was observed (0.68%). Metformin was the most prescribed ADM and its consumption increased constantly during 2012-2018 (14.01-22.89 DDDs/1000/day), also gaining in share of the non-insulin ADMs (39.81-44.52%). Sulphonylureas (SU) were the 2nd most prevalent ADM with a constant increase in prescribing between 2012-2017 and slight decrease during 2017-2018 (15.91-20.34 and 19.73 DDDs/1000/day, respectively), but a continuous decrease of its share in the non-insulin ADMs during 2012-2018 (45.20-38.36%). A steady increase was observed for the new ADMs (GLP-1, DPP-4, and SGLT-2) throughout the study period with a share of 7.11% of the non-insulin ADMs in 2018. In 2018, a total number of 1060146 ADM prescriptions were registered, mostly issued by diabetologists and family practice physicians. Most of the prescriptions with DPP-4 inhibitors (28%) had a SU co-prescribed, of the SGLT-2 inhibitors (51%) had metformin and of GLP-1 analogs had both metformin or SU in equal proportions (approx.31% each).

Conclusions: An overall trend of market increase was found for ADMs between 2012-2018, corresponding to the increase in the prevalence of diabetes in Romania. As expected, an increased prescription of new ADMs and decreased of SU was found during the time frame of our analysis.

4329 | Utilization characteristics for inhaled corticosteroid-based asthma medications in the sentinel distributed database

Tancy C. Zhang[1], Inna Dashevsky[1], Yan Li[2], Marie C. Bradley[3], Jianmeng Chen[4], Stacy Chin[2], Sandra DeLuccia[1], Efe Eworuke[3], Judith C. Maro[1], Yunzhao Ren[4], Rongmei Zhang[5], Chandrahas Sahajwalla[4], David Martin[6], Sally Seymour[2], Kenneth Quinto[6], Robert Busch[2] and Catherine A. Panozzo[1]

[1]Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; [2]Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD; [3]Division of Epidemiology, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD; [4]Division of Clinical Pharmacology II, Office of Clinical Pharmacology, Office of Translational Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD; [5]Office of Biostatistics, Office of Translational Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD; [6]Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD

Background: In randomized clinical trials, inhaled corticosteroid (ICS)-based medications have demonstrated effectiveness on asthma endpoints. Despite their potential benefit, real-world data describing medication adherence across large asthma populations are limited.

Objectives: To estimate proxies of medication adherence including the number of dispensings and proportion of days covered (PDC) over a one-year follow-up among ICS-based asthma medication users in the U.S. Food and Drug Administration's Sentinel System.

Methods: We conducted a retrospective cohort study and identified two ICS-based asthma medication user cohorts in Sentinel from January 2008 to July 2019, including: 1) ICS monotherapy and 2) ICS/long-acting beta-agonist fixed dose combination therapy (ICS/LABA). Cohort entry was defined by National Drug Codes, indexing on the first qualifying ICS-based dispensing. We selected users aged ≥18 years with continuous enrollment in health plans and an asthma ICD-9/10-CM diagnosis in the 183 days prior to the index date. Users with other respiratory comorbidities, including chronic obstructive pulmonary disease, in the 183 days prior to and including the index date were excluded. We further excluded users with ≥2 dispensings of other long-acting asthma maintenance medications during the 365 days after and including the index date. We required all users to be continuously enrolled in health plans in the 365 days after the index date to facilitate calculation of dispensings and PDC.

Results: We identified 802,627 ICS monotherapy users (mean age ± SD: 54 ± 16 years; 69% female) and 1,188,694 ICS/LABA users (mean age ± SD: 58 ± 15 years; 66% female). During a fixed one-year follow-up, ICS and ICS/LABA users filled their prescriptions a median of 2 (interquartile range (IQR): 1-4) and 3 (IQR: 2-6) times, respectively. The median PDC was 25% (IQR: 8-47%) for ICS and 33% (IQR: 16-61%) for ICS/LABA.

Conclusions: In our data, ICS/LABA users had a higher median number of dispensings and had a numerically higher PDC compared to ICS users. Over the one-year follow-up, we observed a median PDC ranging from roughly one-quarter to one-third for asthma medications intended for chronic daily use. Real-world data on utilization metrics such as the PDC may reveal inconsistencies between clinical recommendations and proxies of adherence, informing the design of future comparative effectiveness analyses.

4334 | Applicability of renal outcome trials of canagliflozin to the real world: Implications from comparisons of characteristics between trial patients and real-life patients

Ling-Chen Hsu[1], Kai-Cheng Chang[1,2], Shih-Chieh Shao[3,2], Hui-Yu Chen[1], Yuk-Ying Chan[4] and Edward Chia-Cheng Lai[2]

[1]Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; [2]National Cheng Kung University, Tainan, Taiwan; [3]Keelung Chang Gung Memorial Hospital, Keelung, Taiwan; [4]Chang Gung Medical Foundation, Taoyuan, Taiwan

Background: A well-known randomized controlled trial (RCT), CREDENCE, demonstrated patients receiving canagliflozin were

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

associated with lower risk of renal failure in type 2 diabetes patients with diabetic nephropathy. However, the RCT was conducted under ideal conditions and included participants who were highly selected and may differ from real-life patients, leaving the question whether the trial is applicable to the real world.

Objectives: To compare the characteristics between trial participants and real-life patients in order to evaluate the applicability of RCT to the real world.

Methods: We analyzed the data from the Chang Gung Research Database (CGRD), which is a multi-institutional electronic medical records database covering approximately 1.3 million individuals (6% of Taiwan's population). We selected a cohort of patients newly receiving canagliflozin for type 2 diabetes treatment from August 2018 to December 2019 from CGRD. We applied additional inclusion criteria to CGRD patients based on criteria from the CREDENCE trial, and calculated the proportion of patients included for each criterion. The additional criteria were: (1) estimated glomerular filtration rate (eGFR) ranging from 30-90 mL/min/1.73 m^2, (2) urine albumin to creatinine ratio (UACR) ranging from 300-5000 mg/g and (3) treatment with renin-angiotensin system (RAS) blockade.

Results: We identified a cohort of 1,479 type 2 diabetes patients receiving canagliflozin from CGRD. We found the mean age of patients was 60.7 (SD 11.9) and 62.9 (SD 9.2) in the CGRD and CREDENCE trial, respectively. The proportion of female patients was 39.0% in CGRD and 34.6% in the CREDENCE trial. When we applied all criteria from the CREDENCE trial, only 5.4% of patients from the CGRD qualified for inclusion. We found 64.1% of CGRD patients' eGFR ranged from 30-90 mL/min/1.73 m^2; 13.3% of CGRD patients' UACR ranged from 300-5000 mg/g, and 63.9% received RAS blockade.

Conclusions: We found that only a low proportion of type 2 diabetes patients receiving canagliflozin in the real-world practice setting was eligible under the selection criteria for the CREDENCE trial. This finding highlights that careful consideration must be placed on applicability of results from trials to real-life patients.

4343 | Changes in therapeutic strategy in metastatic castration resistant prostate cancer between 2012 and 2014 from the French nationwide claims database

Nicolas H. Thurin[1], Magali Rouyer[1], Jérémy Jové[1], Marine Gross-Goupil[2], Thibaud Haaser[2], Xavier Rebillard[3], Michel Soulié[4], Gérard de Pouvourville[5], Camille Capone[6], Marie Pierrès[6], Stéphanie Lamarque[1], Emmanuelle Bignon[1], Cécile Droz-Perroteau[1], Nicholas Moore[1,2] and Patrick Blin[1]

[1]Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France; [2]CHU de Bordeaux, Bordeaux, France; [3]Clinique Beau Soleil, Montpellier, France; [4]CHU de Toulouse, Toulouse, France; [5]ESSEC, Cergy-Pontoise, France; [6]Janssen, Issy les Moulineaux, France

Background: Therapeutic strategy in mCRPC has evolved significantly since 2011 in France, when abiraterone acetate and enzalutamide indication were extended to 1st line mCRPC treatment (respectively in 2012 and 2014). France has a National Healthcare System database (SNDS) covering 99% of the population and allowing the assessment of mCRPC management.

Objectives: To describe the evolution of mCRPC management between 2012 and 2014.

Methods: A validated algorithm was used to identify patients in SNDS (2007-2016) and form two cohorts: mCRPC patients initiating a 1st line treatment in 2012, and mCRPC patients initiating a 1st line treatment in 2014. First line treatments considered were abiraterone acetate, docetaxel and enzalutamide. Previous prostate cancer stages before mCRPC status were defined according to the estimated date of castration resistance and 1st metastases management as non-metastatic hormonosensitive prostate cancer (nmHSPC), metastatic hormonosensitive prostate cancer newly diagnosed (NDx mHSPC) or progressive (progressive mHSPC), and non-metastatic castration resistant prostate cancer (nmCRPC).

Results: In France, patients initiating a 1st line treatment were respectively 2 921 out of 11 668 prevalent mCRPC in 2012 vs. 3 949 out of 12 951 mCRPC in 2014. Respectively in 2012 and 2014, previous stage of prostate cancer before mCRPC were: nmHSPC 47% and 52%, NDx mHSPC. 15% and 15%, progressive mHSPC 18% and 15%, nmCRPC 20% and 18%. In the 2012 cohort, abiraterone acetate was the 1st line treatment for 18% of the patients, while docetaxel was used for 81% of patients with few variations according to NDx mHSCP, progressive mHSCP, nmHSCP and nmCRPC stage: 87%, 77%, 80% and 81%, respectively. In the 2014 cohort, the 1st line treatments were abiraterone acetate for 62% of the patients, docetaxel for 31%, and enzalutamide for 5%. Patients coming from progressive mHSCP, nmHSCP and nmCRPC were mostly treated with abiraterone (respectively 61%, 62% and 72%). Patients coming from NDx mHSCP stage were almost equally treated by abiraterone (48%) and docetaxel (46%).

Conclusions: Between 2012 and 2014, the mCRPC 1st line treatment shifted from docetaxel for 4 out of 5 patients to abiraterone acetate for 3 out of 5.

4348 | Global trends in anti-dementia medications consumption in 66 countries/regions from 2008 to 2018

Chengsheng JU

School of Pharmacy, University College London, London, United Kingdom

Background: Worldwide, around 50 million people have dementia, with nearly 60% living in low/middle-income countries. Anti-dementia drugs are widely prescribed for the symptomatic treatment of dementia. Secular trends of anti-dementia drug consumption are important to understand the changes in clinical practice in managing dementia.

Objectives: To determine trends in anti-dementia medications consumption between 2008 and 2018 in 66 countries regions.

Methods: This is a descriptive study nested within the wholesale data from the IQVIA-Multinational Integrated Data Analysis System

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

database on anti-dementia medications sales in 66 countries and regions from 2008 to 2018, stratified by country income level (Low/Middle-income countries (LMICs), *n*=28; High-income countries (HICs), *n*=36; pooled regions, *n*=2). We analysed data on anti-dementia drugs, namely, donepezil, memantine, rivastigmine and galantamine. The consumption per year was estimated from defined daily dose (DDD: WHO defined daily dose, which takes into account the size, strength and form of each pack and reflects average dosing) per 1000 inhabitants per day. Mid-year population estimates and income levels of each country were obtained from the World Bank. Changes over time were quantified as percentage changes and compound annual growth rates (CAGR) in consumption per person. Percentage of each anti-dementia drug consumption over the total anti-dementia drug consumption was used to assess inter-country differences.

Results: Total anti-dementia drug consumption increased from 1.06 to 1.34 DDD per 1000 inhabitants per day between 2008 to 2018 (LMICs: 0.10 to 0.45; HICs: 4.79 to 5.04) with CAGR=2.30%. The increase was mainly driven by the LMICs (CAGR=15.97%) in comparison to the HICs (CAGR=0.51%). The trends varied between countries with the interquartile range (IQR) of CAGR from 5.63% to 18.98%. The overall consumption from 2008 to 2018 increased for rivastigmine (CAGR=6.45%), donepezil (CAGR=2.59%) and memantine (CAGR=1.30%), but decreased for galantamine (CAGR=-0.14%). In 2018, the most commonly used anti-dementia drug globally was donepezil with 49.75% of total sale volume, followed by memantine (32.65%), rivastigmine (11.24%) and galantamine (6.36%),

Conclusions: There was an overall increasing trend in anti-dementia medication consumption globally. The rate of increase was greater in LMICs. The disparity in the use of anti-dementia drugs between countries and regions suggests a need for consistent and evidence-base guidelines guiding optimal treatment for dementia.

4366 | Treatment patterns in people with Parkinson's disease in the United States and the association with cardiovascular disease

Loes C. A. Rutten-Jacobs[1], Spyros Roumpanis[1], Yutong Liu[2] and Preciosa M. Coloma[1]

[1]F. Hoffmann-La Roche Ltd., Basel, Switzerland[2]Genesis Research, Hoboken, NJ

Background: Limited data are available on how comorbidities impact treatment patterns in people with Parkinson's disease (PD). One such important comorbidity is cardiovascular disease (CVD), but its association with PD treatment patterns has not been described.

Objectives: 1) Describe treatment patterns in people with PD; 2) Evaluate the association of CVD with these patterns.

Methods: This retrospective cohort study used Truven MarketScan Commercial and Medicare Supplemental databases, 2007-2018. We identified people with incident PD by selecting those with two PD-diagnosis claims (ICD-9 332.0 and/or ICD-10 G20) and no PD claim or use of any PD medication for ≥12 months beforehand. Treatments of interest were levodopa and levodopa combination therapies (LD), dopamine agonists (DA) and monoamine oxidase B inhibitors (MAO-Bi). CVD included cerebrovascular, peripheral, cardiac and hypertensive diseases. Presence of a CVD claim within 6 months prior and 6 months post the first PD diagnosis claim was summarized. Events of interest were PD treatment initiation and switch-to or add-on of another PD treatment class. Cox proportional hazards analysis was used to evaluate the age and sex-adjusted association of CVD with the occurrence of the events of interest.

Results: The study cohort comprised 38,828 people with incident PD (40.4% women; median [interquartile range (IQR)] age 74 [64-82] years; median [IQR] follow-up time: 2.8 [1.8-4.4] years). 72.5% of people with PD were treated at any time during the follow-up period; LD was the first-line therapy for most (72.0%), followed by DA (14.9%) and MAO-Bi (10.0%). CVD was present in 73.1%. People with PD and concurrent CVD were less likely to initiate treatment during follow-up (hazard ratio (HR) 0.96 (95% CI 0.93-0.99) for LD; HR 0.82 (95%CI 0.79-0.86) for DA; HR 0.67 (95% CI 0.64-0.71) for MAO-Bi). In those with LD as first-line therapy, the 1-year probability to switch or add-on of PD treatment was 14.2% (95% CI 13.8%-14.7%). The corresponding probabilities for DA and MAO-Bi were 33.2% (95% CI 31.8%-34.7%) and 43.5% (95% CI 41.7%-45.4%) respectively. Concurrent CVD was negatively associated with switch-to or add-on another PD treatment class for people with LD as first-line treatment (HR 0.81 (95%CI 0.76-0.86)) or DA (HR 0.79 (95%CI 0.73-0.87)) but not MAO-Bi (HR 0.96 (95% CI 0.87-1.06)).

Conclusions: LD was the most common first-line treatment in newly diagnosed people with PD. Those with concurrent CVD were less likely to initiate treatment during the study period and less likely to switch-to or add-on another treatment if the initial treatment was LD or DA.

4368 | Antihypertensive medicine use in the Baltic states between 2008 and 2018

Indre Treciokiene[1,2], Nomeda Bratcikoviene[3,4], Jolanta Gulbinovic[5], Bjorn Wettermark[6] and Katja Taxis[2]

[1]Vilnius University, Vilnius, Lithuania; [2]University of Groningen, Groningen, Netherlands; [3]Vilnius Gediminas Technical University, Vilnius, Lithuania; [4]Vilnius University, Vilnius, Lithuania; [5]Vilnius University, Vilnius, Lithuania; [6]Uppsala University, Uppsala, Sweden

Background: High blood pressure is an important risk factor for cardiovascular death and disability. High prevalence of hypertension is seen in all three Baltic States, but little is known about use of antihypertensives.

Objectives: The aim of this study is to compare utilization of antihypertensive medicines in Estonia, Latvia and Lithuania over 11-years.

Methods: Wholesale data from the National retail audit IQVIA was used to determine the use of antihypertensive medicines in 2008-2018. The ATC/DDD methodology was used to calculate utilization of renin angiotensin system (RAS) inhibitors, including

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

angiotensin converting enzyme inhibitors -ACEi (C09A and C09B) and angiotensin II receptor blockers - ARBs (C09C and C09D), calcium channel blockers (C08), beta receptor blockers (C07), diuretics (C03) and central acting antihypertensives (C02A). The results were expressed in DDD per thousand inhabitants per day (DDD/TID). Time series analysis was used to analyze trends. ANOVA and Kruskal-Wallis tests were used to test differences between countries.

Results: The total use of antihypertensive drugs was 372.0 DDD/TID in Estonia, 267.0 DDD/TID in Latvia and 379.5 DDD/TID in Lithuania in 2018. The utilization increased by 10.88 DDD/TID (95% CI: 7.13 - 14.63), 8.04 DDD/TID (95% CI: 4.57 - 11.52) and 6.42 DDD/TID (95% CI: 2.44 - 10.41) annually, respectively. The use of all classes increased, except calcium channel blockers. Most frequently used class in 2018 was RAS inhibitors, followed by beta-blockers in all three Baltic countries. The use of central acting antihypertensives was highest in Lithuania, 30.9 DDD/TID, compared to 3.01 DDD/TID in Estonia and 16.17 DDD/TID in Latvia (p=0.000001) in 2018. Use of fixed-dose combinations increased from 30.3 to 94.9, from 33.7 to 87.1 and from 28.2 to 106.6 DDD/TID in Estonia, Latvia and Lithuania, respectively.

Conclusions: The use of antihypertensive medicines increased in the Baltic states, mostly driven by RAS inhibitors, beta-blockers and fixed-dose combinations. Striking differences in low overall use of antihypertensives in Latvia and high use of central acting substances in Lithuania were detected.

4402 | Characterizing real-world patterns of early childhood vaccination

Anne M. Butler[1], Jason G. Newland[2], John M. Sahrmann[1], Caroline A. O'Neil[1], Sena Sayood[1] and Leah J. McGrath[3]

[1]Washington University School of Medicine, St. Louis, MO; [2]Washington University School of Medicine, St. Louis, MO; [3]NoviSci, Durham, NC

Background: Vaccine hesitancy is increasingly common, but knowledge is limited on the effects of delayed vaccine schedules. Prior to performing comparative effectiveness studies, more information is needed on patterns of childhood vaccination.

Objectives: To characterize patterns of vaccine delay among commercially-insured children in the United States.

Methods: Using the IBM® MarketScan® Commercial Database, we identified infants who received first dose of diphtheria-tetanus-acellular pertussis (DTaP) vaccine at 38 to 92 days of age from October 1, 2009 to June 30, 2017. We ascertained injectable and oral vaccine antigens (DTaP, polio, pneumococcal conjugate, rotavirus, Haemophilus influenza type b (Hib), measles, mumps, rubella, and varicella). We used CPT codes to collect vaccine administration history on antigen, formulation, dose, and date. Timely receipt was defined as concomitant administration of the CDC-recommended number of antigens during the following time windows: 2, 4, 6, and 12-15 months of age (grace period: -7, +21 days). We generated heat maps to illustrate age distributions at receipt of specific antigens and doses. We created Sankey diagrams to illustrate the number of antigens received concomitantly during each time window and depict transitions to different states over time (e.g., no vaccine delay to vaccine delay). For each antigen and dose, we estimated the cumulative incidence of receipt using inverse probability of censoring weights.

Results: Among 1,066,216 eligible infants, the majority (84%) concomitantly received all 5 CDC-recommended antigens at 2 months of age while others only received 1 (1%), 2 (2%), 3 (4%), or 4 (9%) antigens. Many vaccinations were delayed - 30% of children did not receive all recommended antigens concomitantly at 4 months, and 39% did not at 6 months. The heat map shows wide variation in age at vaccination. For several antigens including Hib, measles, mumps, rotavirus, rubella, and varicella, the cumulative incidence increased steeply at ≥2 time points, suggesting vaccine delay for some infants. For example, the first dose of Hib was administered to 85% of infants by 2 months of age, with subsequent small but distinct increases at 4, 6, 12, and 15 months of age.

Conclusions: Using real-world data to study early childhood vaccination patterns, we observed evidence of substantial deviation from the CDC-recommended schedule, consistent with reports of increasing vaccine hesitancy. These results expand current knowledge on the magnitude and timing of antigen- and dose-specific vaccine delay on a population level.

4405 | Prescribing trends of antidepressants and coprescription with other psychotropic medications for children and adolescents in primary care in the United Kingdom, 2000-2018

Dai Cao[1], Lara Fraga[2], Emma Fergusson[3], Sophie Dell'Aniello[4], Hui Yin[4], Soham Rej[5], Laurent Azoulay[1,4,6] and Christel Renoux[1,4,7]

[1]McGill University, Montreal, QC, Canada; [2]Universidade Nove de Julho (UNINOVE), Sao Paolo, Brazil; [3]Oxford University, Oxford, United Kingdom; [4]Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada; [5]McGill University, Montreal, QC, Canada; [6]McGill University, Montreal, QC, Canada; [7]McGill University, Montreal, QC, Canada

Background: An increase in antidepressant prescriptions in children and adolescents has been documented in the United Kingdom (UK) since the 2000s but no information is available on recent trends. Moreover, little is known about the coprescription with other psychotropic medications.

Objectives: To describe time trends in antidepressant prescriptions and coprescription with other psychotropic medications in UK children and adolescents between 2000 and 2018.

Methods: Using the Clinical Practice Research Datalink, we defined a cohort of all patients aged 5-17 years between 1 January 2000 and 31 December 2018. Using Poisson regression, we estimated the yearly rates of patients newly treated with antidepressants from the following classes: selective serotonin reuptake inhibitors (SSRIs), other second-generation antidepressants, and tricyclic antidepressants (TCAs). We also estimated the rate ratio (RR) of patients newly treated

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

with antidepressants over the last 10 years. Finally, we calculated the percentage of patients with a same-day coprescription with other psychotropic medications (antipsychotics, mood stabilizers, anxiolytics, and stimulants).

Results: After a 42% decline from 2000 to 2005 (399.3 to 230.7 per 100,000 person-years), the rate of children and adolescents newly prescribed antidepressants increased from 2006 onwards. From 2008 to 2018, the rate increased from 254.3 to 471.2 per 100,000 person-years (RR 1.97, 95% confidence interval 1.96-1.99). The rate was higher in girls and in adolescents aged 15 to 17 years during the entire study period. SSRIs were the most commonly prescribed antidepressant class (70% of all antidepressant prescriptions), followed by TCAs (28%). In 2018, 81% of prescriptions were for SSRIs, 17% for TCAs and 2% for other antidepressants. Overall, 5% of new users of antidepressants had at least one same-day coprescription for another psychotropic medication during the study period, 51% of which had no previous prescription for a psychotropic medication. The percentage of patients with a coprescription rose from 2.6% of patients in 2000 to 6.4% in 2018. In 2018, coprescription was mostly for anxiolytics (62%) and antipsychotics (25%), and 93% of patients had only one psychotropic drug prescribed with the antidepressant.

Conclusions: Antidepressant prescriptions increased steadily for more than a decade in children and adolescents, accompanied by a rise in coprescription for other psychotropic medications. Further research is needed to offer potential explanations for the trends observed.

4431 | Trends and characteristics in cough prescription use in ambulatory care settings in the United States: 2003-2016

Seonkyeong Yang, Juan M. Hincapie-Castillo, Ching-Yuan Chang, Debbie L. Wilson and Jenny Lo-Ciganic
University of Florida, Gainesville, FL

Background: In response to the US opioid epidemic, numerous policies have been implemented to reduce inappropriate opioid prescribing in recent years. Gabapentin, a prescription with emerging safety concerns due to its potential abuse and risk of overdose, is recommended by the 2015 American College of Chest Physicians guidelines as a treatment option for unexplained chronic cough. It is often used off-label. Little is known of the prescription cough medication utilization patterns over time in light of these factors.

Objectives: To examine the trends, patient and prescriber characteristics in the use of antitussives containing opioids and gabapentinoids in US ambulatory care settings.

Methods: This cross-sectional study used 2003-2016 National Ambulatory Medical Care Survey data. We included adult (≥18 years) visits with infection or non-infection related cough as a visit reason (hereafter cough-related visits). We excluded visits with any cancer or benign respiratory tumor diagnoses. Among cough-related visits, we used logistic regression to examine the trends in the use of antitussives containing codeine or hydrocodone, and gabapentinoids (i.e., gabapentin and pregabalin).

Results: Of 385 million cough-related visits from 2013 to 2016, 24.6% were infection-related. The total number of cough-related visits declined from 42.3/1000 visits in 2003 to 31.6/1000 visits in 2016. Among cough-related visits, the prescribing prevalence was 5.5% for codeine, 4.4% for hydrocodone, and 1.6% for gabapentinoids. Cough-related visits with gabapentinoid prescriptions were more likely in patients aged ≥65 years (codeine: 20.4%; hydrocodone: 21.5%; gabapentinoid: 44.0%) and patients having ≥2 chronic conditions (codeine: 35.0%; hydrocodone: 25.4%; gabapentinoid: 62.2%). Over 60% of cough-related visits with codeine or hydrocodone prescriptions were paid by commercial insurance, and 60% of cough-related visits with gabapentinoid prescriptions were paid by public insurance. Primary care physicians were the major prescribers (>80%) of cough medications in the cough-related visits. The number of cough-related visits where hydrocodone was prescribed substantially decreased (6.0% to 1.7% from 2003 to 2016; P_{trend} =0.003), while codeine use remained stable (5.5% to 5.8%; P_{trend} =0.89) and gabapentinoid use increased significantly (0.6% to 2.4%; P_{trend} =0.003).

Conclusions: Among cough-related office-based ambulatory care visits in the US, antitussive containing hydrocodone prescribing substantially decreased from 2003 to 2016, while gabapentinoid prescribing quadrupled.

4448 | Trends in consumption of psychiatric drugs among patients attended in primary healthcare in Brazil: An ecological time-series study

Julia RasoFerreira de Oliveira[1], Iahel Manonde Lima Ferreira[1], Marcela Jirón Aliste[2], Manuela Roque Siani-Morello[1], Fabiana Rossi Varallo[1] and Leonardo RegisLeira Pereira[1]
[1]*School of Pharmaceutical Sciences of Ribeirão Preto, University of Sao Paulo, Ribeirão Preto, Brazil;* [2]*School of Pharmaceutical Sciences, Universidad de Chile, Santiago, Chile*

Background: Trends in consumption of psychiatric drugs may be a tool to screening adverse drug reactions. The monitoring contributes for patient safety and appropriate use.

Objectives: Characterize the consumption of psychiatric drugs among patients attended in primary healthcare of Ribeirão Preto -São Paulo (Brazil).

Methods: Design: An ecological time series analysis was carried out from 2008 to 2012 to analyze the electronic registration of dispensing of essential psychiatric drugs. Setting: Electronic database contains registries of drugs dispensing for all patients attended in public healthcare facilities. During the period of the study. The municipality had, on average, 591.602 inhabitants. Exposures: All patients who had at least one registry of psychiatric drug dispensing from any primary health unit of Ribeirão Preto were eligible. Main outcome measures: Defined Daily Dose/1,000 inhabitants-day (DDD/1,000PD) and prescribed daily dose (PDD). The variables extracted were psychiatric drug, amount dispensing, sex and age of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients [pediatrics (0-19 years old); adults (20-59 years old) and elderly (above 60 years old)]. Statistical analysis: The Mann-Whitney test was applied to compare the population growth rate with the rate of consumption of psychiatric drugs. To verify the correlation between increasing age and the use of drugs, simple linear regression was performed.

Results: There were 1,577,241 patients with at least one registry of drug dispensation, of those 287,356 (18.2%) used psychiatric(s) drug(s). The majority were female [203,094/287,356 (70.7%)] and adults [185,929/287,356 (64.7%)]. There was an increase in the total consumption of psychiatric drugs. PDDs of lithium carbonate, fluoxetine, haloperidol, naltrexone, nitrazepam phenobarbital, and sertraline were higher than DDD assigned by World Health Organization. Only the consumption rates of sertraline (p=0,0304) and clonazepam (p=0,0304) were higher than population growth rate. There was a correlation with advancing age and consumption.

Conclusions: One out of five inhabitants of Ribeirão Preto consumes psychiatric drugs, being most women. Trends in consumption are related to population growth rate, except for sertraline and clonazepam. Despite of the discrepancies among DDD/1,000PD and PDD, the monitoring of consumption with these metrics may be a strategy to screening patients eligible for pharmaceutical care to early detect drug-related problems.

4451 | Recent trends in first-line glucose-lowering treatment choice for type 2 diabetes in younger and older adults in the U.S.

Hojin Shin[1,2], Sebastian Schneeweiss[2], Robert Glynn[2] and Elisabetta Patorno[2]

[1]Harvard T.H. Chan School of Public Health, Boston, MA; [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: Although metformin is the accepted first-line treatment for type 2 diabetes (T2D), antidiabetic drugs that have demonstrated cardiovascular benefits in recent clinical trials, i.e., GLP-1 receptor agonists (GLP-1RA) and SGLT2 inhibitors (SGLT2i), could be increasingly considered as a first-line treatment, in particular for patients with cardiovascular disease (CVD).

Objectives: To evaluate recent trends in first-line glucose-lowering treatment choice for T2D among patients aged ≤65 versus >65, and to assess the impact of CVD on the initial treatment choice.

Methods: Using claims from two US commercial insurance databases (Optum Clinformatics and IBM MarketScan) and Medicare fee-for-service, we identified T2D patients aged ≥ 18 years (>65 in Medicare), who initiated any antidiabetic treatment from 1/2013 through 12/2017. We restricted to patients without any diabetes treatment in the prior 365 days (or more, depending on data availability). Patients were categorized by the class of their first antidiabetic drug prescription fill within age strata (≤65 versus >65), and results were pooled across databases. Trends in first-line T2D treatment initiation were plotted overall and stratified by baseline CVD and tested by the Cox and Stuart Trend test.

Results: Overall, we identified 409,546 T2D first-line initiators aged ≤65 and 427,483 initiators aged >65. Metformin was the most frequently initiated treatment with increasing trends from 1Q-2013 to 4Q-2017 (adults ≤65: 82.0% to 86.2% (P=.014), adults >65: 69.7% to 79.3% (P=.014)), followed by sulfonylureas, though with decreasing trends (adults ≤65: 6.9% to 3.9% (P=.014), adults >65: 14.4% to 8.6% (P=.014)). Compared to patients ≤65, patients >65 had lower metformin use (79.3% vs 86.2%) but higher sulfonylurea use (8.6% vs 3.9%), at the most recent assessment, i.e., Q4-2017. The initiation of GLP-1RA and SGLT2i increased over time, though their uptake remained low (for GLP-1RA, adults ≤65: 1.3% to 2.9% (P=.014), adults >65: 0.6% to 1.1% (P=.014); for SGLT2i, adults ≤65: 0.3% to 1.1% (P=.289), adults >65: 0.04% to 1.0% (P=.008)). In both age groups, patients with CVD were less likely to initiate metformin but more likely to initiate sulfonylureas, compared to patients without CVD; the uptake of GLP-1RA and SGLT2i did not differ by CVD.

Conclusions: Metformin was the most frequently initiated first-line treatment for T2D, consistent with current treatment guidelines, though sulfonylureas remained frequent among patients aged >65 or with baseline CVD. The uptake of GLP1-RA and SGLT2 inhibitors was low and did not differ by baseline CVD.

4487 | In-hospital post-operative analgesic use in patients undergoing primary total hip or knee replacement: A drug utilization study within the capital region of Denmark

Astrid Blicher Schelde[1], Anne Mette Skov Sørensen[1], Martin Erik Nyeland[1], Anders Odgaard[2] and Espen Jimenez-Solem[1,3]

[1]Department of Clinical Pharmacology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark; [2]Department of Orthopaedic Surgery, Copenhagen University Hospital, Herlev and Gentofte, Copenhagen, Denmark; [3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Background: Total hip and knee replacement (THR and TKR) are common surgical procedures associated with post-operative pain, which can be managed with post-operative analgesics. The in-hospital post-operative analgesic use in THR and TKR patients has to our knowledge not previously been examined in a large Danish setting. This is though important in order to identify patients at risk of potentially inappropriate pharmacotherapy and to ensure rational pharmacotherapy.

Objectives: To explore the pharmacological in-hospital post-operative analgesic use in patients undergoing primary THR and TKR.

Methods: The cohort included all patients with a primary THR or TKR in the Capital Region of Denmark, January 2012 to December 2015. Using a regionwide registry based on electronic health records, we obtained information on patient characteristics and in-hospital post-operative analgesic use, including paracetamol, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), opioids, and gabapentinoids. For each surgical procedure (THR and TKR), we calculated the prevalence of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients having each of these analgesic drugs prescribed and administered during their post-operative in-hospital stay.

Results: We identified a total of 15,164 patients having a primary THR (n=7,724, mean age=69 years, 39% males) or TKR (n=7,440, mean age=68 years, 38% males) performed during the study period. The prevalence of THR and TKR patients having post-operative analgesics administered in-hospital was 99.1% and 99.0% for paracetamol, 24.5% and 72.7% for NSAIDs, 43.6% and 76.0% for opioids, and 50.1% and 58.9% for gabapentinoids, respectively.

Conclusions: We observed differences in the in-hospital use of NSAIDs and opioids between THR and TKR patients. It is of note that half of all patients were administered gabapentinoids. The results call for studies analyzing whether these treatment patterns raise any short- and long-term safety concerns for the patients.

4488 | Patterns of triptan use by gender in tuscany region, Italy

Giulia Hyeraci[1], Rosa Gini[1], Silvia Benemei[2], Francesco De Cesaris[2], Chiara Lupi[2], Pierangelo Geppetti[2] and Giuseppe Roberto[1]
[1]*Regional Agency for Healthcare Services of Tuscany, Florence, Italy;* [2]*Headache Centre, Careggi University Hospital, Department of Health Sciences, University of Florence, Florence, Italy*

Background: Triptans are the most commonly used anti-migraine drugs in clinical practice. However, the potential increased risk of acute cardiovascular events (ACE) related to their vasoconstrictive effect, and the possible occurrence of medication overuse headache (MOH) secondary to an excessive triptan intake, represent the main limitations to their use. Although triptan utilization has been extensively investigated, evidence on the influence of gender on their patterns of use in clinical practice is still poor.

Objectives: To describe the patterns of triptan utilization by gender in the general population of Tuscany, Italy, in 2017.

Methods: The population-based regional administrative database of Tuscany was used. For each subject active into the database at 1 January 2017, demographic information were linked to hospital discharge records and outpatient drugs dispensings. Prevalent triptan users (PU) were subject ≥1 dispensing during 2017. PU with no dispensing before 2017 were new users (NU). Prevalence and incidence of use by age classes were observed. Utilization patterns were categorized as: sporadic (1 dosage unit), occasional (≥1 dosage unit with ≤3 months between 2 dispensings), regular (≥1 dosage unit with ≥3 months between 2 dispensings), and overuse (≥20 dosage units per month for ≥3 consecutive months). Users with prior ACE were identified. All analyses were stratified by gender.

Results: PU were a total of 4109 men and 15400 women, of which NU were 37.7% in men and 29.9% in women. Prevalence (2.1%) and incidence (0.6%) of use showed a peak between 45 and 54 years and 35-44 years, respectively, in both sexes. Elderly users accounted for 1.1% of PU users and 0.39% of NU. The percentage of patients with previous ACE was 7.6% in NU and 5.5% in PU. NU with ACE were 5.5% in men and 2.1% in women. Among NU, sporadic (67.3% vs 63.6%) and occasional (11.7% vs 8.6%) use was slightly higher in men while regular use was more frequent in women (21.0% vs 27.7%). Overusers were 0.1% among NU in both genders, while among PU they were 2.1% of men and 1.5% of women.

Conclusions: Women used triptans more regularly than men. Overusers possibly affected by MOH increased after first year of treatment in both genders. The non-negligible use of triptans in non-recommended populations like elderly and patients with previous ACE warrants analytical studies on triptan safety.

4510 | Trends in truvada (emtricitabine and tenofovir) utilization among HIV positive and HIV negative persons in the U.S. 2011 - 2016

Carter McCormick and Dima Qato
University of Illinois at Chicago, Chicago, IL

Background: Despite its importance in HIV treatment and prevention, there is limited information on trends in Truvada utilization overall and since FDA approval for pre-exposure prophylaxis (PrEP) in HIV-patients.

Objectives: To describe the trends of Truvada usage in the United States from 2011 - 2016.

Methods: This descriptive observational study used a nationally representative sample from IQVIAs LifeLink (LRx) data from 2011 - 2016. Patients using Truvada without the use of another HIV medication were included as HIV- PrEP users and all other Truvada users concurrently using another HIV medication were included as HIV+ treatment users. We examine the share of users overall and by age and gender.

Results: Overall, the percent of HIV+ persons using Truvada decreased from 94% to 61%, and this decrease was most pronounced in men ages 45-49 (19%-8.5%). Among Truvada users, the share of HIV+ users has declined while the share of HIV negative users increased from 6% to 39%. Men are have the most pronounced increase, from 3% to 36%. Women during this time consistently remained between 2 - 3%. When HIV- users are broken into age groups, men age 25 - 39 (2% - 21%) have profound increases while men 24 years and younger have more minimal increases (0.2% to 3.2%). Women across all age groups see minimal to no change, consistently remaining under 1%.

Conclusions: These findings indicate the use of Truvada is increasingly being used as PrEP in HIV-persons. Older men are the group driving the increase in utilization for PrEP, while young men and pediatric users have much lower increases in utilization. In contrast to men, women's use of Truvada, especially among young women, has not changed during this time. With young women and men being at higher risk for HIV, it is important to address these age and gender disparity through targeted interventions and policies to increase utilization among these important risk groups.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4528 | Trends in buprenorphine prescribing among medicare part D providers, 2013-2017

Kristin Shiue[1,2], Mary Figgatt[1,2] and Yvonne Golightly[1,3]
[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: While opioid prescribing has recently declined in the United States, prescription opioid overdose rates have increased among adults >65 years of age. To treat opioid use disorder, there has been significant uptake of buprenorphine nationwide, particularly after the publication of *SAMHSA Federal Guidelines for Opioid Treatment Programs* in 2015. Buprenorphine is covered under Medicare Part D, but little is known about prescribing patterns in Part D beneficiaries, most of whom are older adults.

Objectives: Characterize trends in buprenorphine prescribing among Medicare Part D providers over time, by prescriber specialty, and by state.

Methods: Data from the Medicare Part D Prescriber Public Use Files for 2013-2017 were used for descriptive analyses (n=1404428 unique providers). Providers with >10 claims for buprenorphine were classified as buprenorphine prescribers, with prescribing assessed among all providers, as well as specifically among opioid prescribers (defined as providers with >10 claims for any opioids).

Results: Buprenorphine prescribing increased steadily from 2013-2017, with the number of Part D providers nearly doubling from approximately 9000 to more than 16000 per year. Among opioid prescribers in 2017, <2% were buprenorphine prescribers, of which the majority (75%) had ≤10 beneficiaries receiving buprenorphine. Buprenorphine prescribers were primarily in family practice (25%) and internal medicine (16%), though the percent of providers prescribing buprenorphine within these specialties remained relatively low over time (1%-4%). Neuropsychiatry, pain management, psychiatry, and anesthesiology had the greatest increases in buprenorphine prescribers from 2013-2017 (10% to 13% absolute increase among providers who were opioid prescribers), with pain management and anesthesiology as the top specialties in 2017 with regard to percent of all providers that were buprenorphine prescribers (30% and 11%, respectively). The percent of providers prescribing buprenorphine varied between <1% to 5% during the study, with the greatest increases observed in Maine, Vermont, and West Virginia (1% to 2% absolute change among all providers).

Conclusions: Despite the growing number of buprenorphine prescribers from 2013-2017, the overall proportion of providers regularly prescribing buprenorphine to Medicare Part D beneficiaries remains low. To mitigate a further increase in prescription opioid overdose rates among older adults, further exploration of specialty and state-level differences among Part D providers is warranted to guide efforts to encourage buprenorphine use in this population.

4553 | Sex differences in patterns of systemic agents' use among individuals with psoriasis

Raymond Milan[1], Jacques LeLorier[2], Ivan Litvinov[1] and Elham Rahme[1]
[1]McGill University, Montreal, QC, Canada; [2]Université de Montréal, Montreal, QC, Canada

Background: Psoriasis severity differs between males and females. However, it is not clear if psoriasis management also differs by sex. Severe psoriasis is treated with conventional systemic agents (CSA) and/or biologic agents when CSA are ineffective or inappropriate.

Objectives: We assessed sex differences in the utilization patterns of CSA and switches to biologic agents among individuals with psoriasis.

Methods: We conducted a retrospective cohort study using Quebec health administrative databases (1997 - 2015). Individuals ages ≥ 20 years were included if they received a first psoriasis diagnosis and at least one CSA. Individuals were followed for two years. For each treatment claim, a 60-day grace period between the end of the supply period of the last prescription fill and the beginning of a new prescription fill was considered. Treatment switch occurred when a patient filled a prescription for a different CSA or a biologic agent during the supply or grace period of the initial CSA. Treatment discontinuation occurred when the patient did not have a supply for any systemic agent for a period exceeding 60 days. Analyses were stratified by sex. Multivariate Cox proportional hazard models were conducted to determine the risk of switch to a biologic agent. Multinomial logistic regression models were conducted to identify predictors of treatment switch and discontinuation.

Results: We included 1,272 individuals with psoriasis (55% females). Most individuals were initiated on methotrexate (MTX, 56%), followed by acitretin (37%). During the follow-up, 364 (29%) were persistent, 688 (54%) discontinued and 220 (17%) switched (75% to another CSA and 25% to a biologic agent). Most patients switching to a biologic agent received adalimumab (41%) and infliximab (27%). Compared to females, males tended to switch more to a biologic agent (44/1000 person-years vs 27/1000 person-years, HR=1.66, 95% CI: 0.96-3.03). When compared to persistent patients, males and females who switched were more likely to be younger and initiated on acitretin and sulfasalazine (vs MTX). Initiating on these agents was also associated with treatment discontinuation among male, but not among female individuals. Males with psoriatic arthritis and females with rheumatoid arthritis were less likely to discontinue their initial CSA (OR=0.49, 95% CI: 0.26-0.90 and 0.40, 0.21-0.71 respectively).

Conclusions: MTX was the CSA treatment of choice for both sexes in the management of psoriasis. Persistence on CSA was lower among males and younger psoriasis patients, and higher among those with other inflammatory diseases.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4560 | Injectable paliperidone palmitate showed a higher adherence rate compared to oral atypical antipsychotics in Japan

Ting Zhang[1], Hsingwen Chung[2], Tao Wu[1], Yongjing Zhang[3], Yanfang Liu[4] and Hong Qiu[2]
[1]*Janssen Research and Development, China, Beijing, China;* [2]*Janssen Research and Development, USA, Titusville, NJ;* [3]*Janssen Research and Development, China, Shanghai, China;* [4]*Janssen Research and Development, Singapore, Singapore, Singapore*

Background: Long acting injectable paliperidone palmitate (PP1M) may improve adherence in schizophrenia patients.
Objectives: To compare persistence and adherence of PP1M vs oral atypical antipsychotics (OAAs) for schizophrenia treatment in Japan.
Methods: This was a retrospective cohort study utilizing the Japanese Medical Data Center (JMDC) claims database. The study period was between 2013 and 2018. The overall cohort included patients who were a) diagnosed with schizophrenia, b) with at least one prescription of PP1M or OAAs, c) with continuous care (≥ 3 consecutive visits with at least 7 days in-between visits and no gap > 45 days), and d) ≥ 18 years old. The index date was defined as the date of the first prescription of PP1M or any OAAs. The study cohort included all PP1M patients and 1:1 matched OAAs patients using a propensity score, which was created using baseline characteristics including age, gender, diagnosis, medication usage, and hospital visits. Persistence and adherence were compared between the PP1M and OAAs groups. Persistence was defined as days to first discontinuation (a gap between two consecutive PP1M or OAAs prescriptions ≥ 45 days) plus 28 days (as days' supply of the prescribed drug) within 1-year post-index. A Cox proportional hazards model was used to estimate the hazard ratio (HR) for 1-year persistence. Adherence was assessed by the proportion of days covered (PDC), which was calculated as the number of non-overlapping days covered by PP1M or OAAs divided by total days up to 1-year post-index or first discontinuation, if it happened. Patients with PDC ≥ 80% were considered adherent. A logistic regression model was used to estimate the odds ratio (OR) for adherence.
Results: There were 249 patients in the PP1M group and 40,058 patients in the OAAs group overall. After propensity score matching, 249 patients in OAAs group were matched. In the PP1M group, mean (SD) age was 39.5 (11.4) years, and 39.8% (99 patients) were males. The mean (SD) persistence of the PP1M group was 235.0 (139.2) days; in the matched OAAs group, the corresponding result was 197.6 (151.6) days. PP1M was associated with better persistence, with 21% lower risk of discontinuation compared to OAAs (adjusted HR=0.79, 95% CI=0.66-0.95). 66% of patients in the PP1M group were adherent as indicated by PDC, while 54% patients in the matched OAAs group were adherent. PP1M was associated with better adherence, adjusted OR=1.66 (95% CI=1.14-2.42).
Conclusions: Overall, persistence and adherence of PP1M and OAAs in Japanese schizophrenia patients were high, and persistence and adherence of PP1M were better than OAAs in Japan.

4593 | Influencing factors for medications in patients with stroke in a nationally representative sample of older Chinese: Results from CHARLS

Jingnan Feng, Shengfeng Wang and Siyan Zhan
Peking University, Beijing, China

Background: Stroke is the first cause of death among Chinese residents, effective medication after stroke can reduce the functional disability and complications in patients. Thus, accelerate the rehabilitation process and save social resources.
Objectives: To explore the medication rate and its influencing factors in the elderly stroke population in China.
Methods: Data were collected from China Health and Retirement Longitudinal Study (CHARLS) over the period from 2011 to 2015. We analyzed the prevalence of stroke and drug treatment and compared demographic, health status and functioning data between non- medication and medication groups. Influencing factors were estimated by using Logistic regression.
Results: In 2015, a total of 10,162 participants aged 60 years and older were included in this study. The prevalence of stroke slightly increased from 3.57% to 4.91%. As for medication for stroke, more than 28.21% patients didn't take any treatments in the 5 years. Although western medicine was the preferred medication (over 50%), the percentage of patients using Chinese traditional medicine and acupuncture increased by 2% between 2011 and 2015. Compared with medication group, non- medication group showed higher proportion of smoking and memory-related diseases (P<0.05). Logistic regression analysis showed that the major risk factors included drinking (OR=1.46,95%CI:1.02-2.08) and memory-related diseases (OR=1.71,95%CI:1.20-2.45), while heart attack (OR=0.29,95% CI:0.12-0.74) was the protective factor.
Conclusions: As the prevalence of stroke increased, the proportion of taking medication in elderly stroke patients was relatively low in China. Intervention and education should be strengthened for patients without medication, special attention needs to be paid on patients with multiple comorbidities and unhealthy lifestyles.

4610 | Differential prescription patterns of drospirenone-containing combined oral contraceptives in Eastern Europe and North America: Insights from the INAS-FOCUS Study

Clare Barnett, Thai Do Minh, Suzanne Reed and Klaas Heinemann
ZEG Berlin, Berlin, Germany

Background: Combined oral contraceptives (COCs) are a commonly prescribed method of birth control in North America and Eastern Europe; prescription practices and user populations are considered to be homogenous across continents. Using baseline data from the INAS-FOCUS study, we explored whether the drug utilization patterns were similar in North America and Eastern Europe and why differences seen, if any, might exist.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To describe differences in prescription patterns and user demographics in an all-comer, observational, active-surveillance registry.

Methods: Large, prospective, controlled, non-interventional, long-term cohort registry following users of DRSP/EE+ and oCOC for up to seven years. The registry did not interfere with the physicians' prescribing behavior and no medical inclusion/exclusion criteria were applied. Participants were recruited via a network of COC-prescribing physicians in Russia, Ukraine, Canada and the United States of America (US). Demographics, medical and gynecological history were collected at baseline. Follow-up included collection of contraceptive utilization history and identification of adverse events every 6-12 months via an active surveillance approach employing self-administered questionnaires. Patient-reported clinical outcomes of interest were validated via health care professionals.

Results: The registry included 82,780 women, comprising 7,649 users of DRSP/EE+, 13,034 users of DRSP/EE- (DRSP/EE without folate) and 62,098 users of oCOC-. Prescription patterns in eastern Europe showed little overlap with North America. In Russia/Ukraine, DRSP/EE+ users comprised 17.4% of the baseline study population, compared to only 4.1% in the US/Canada. North American study participants tended to be prescribed COCs containing Norethindrone (NETA)- (47.0%), Norgestimate (NGM)- (20.5%) and Levonorgestrel (LNG)- (8.3%), whereas the most commonly prescribed progestogens in eastern Europe were DRSP (53.7%), oCOC (44.5%, mostly DNG) and LNG- (1.8%).

Conclusions: INAS-FOCUS was a long-term, active surveillance registry based on primary data collection methods. Results showed a large discrepancy in COC utilization patterns between eastern Europe and North America; despite LNG being recommended as first-line therapy, only 8.3% of North American study participants and 1.8% of eastern European study participants were prescribed an LNG-containing COC. NETA, NGM (North America) and DRSP (eastern Europe) were more commonly prescribed.

4631 | Nationwide patterns of long-term ranitidine use and its associated factors in Korea

Myo-Song Kim[1], Seung-Hun You[1], Min-Taek Lee[1], Ye-Jin Kang[1], Ye-Jee Kim[2], Joongyub Lee[3] and Sun-Young Jung[1]

[1]*College of Pharmacy, Chung-Ang University, Seoul, Republic of Korea;* [2]*Asan Medical Center, Seoul, Republic of Korea;* [3]*Inha University Hospital, Incheon, Republic of Korea*

Background: Ranitidine, a histamine H2-receptor antagonist, has recently been recalled due to contamination with N-nitroso-dimethylamine. Because ranitidine is used for both for treatment of gastrointestinal disorders and for gastroprotection in long-term NSAIDs use in some chronic diseases, it is necessary to identify the nationwide patterns of long-term use.

Objectives: To assess patterns of long-term ranitidine use and factors affecting the long-term prescribing in the Korean population.

Methods: We analyzed prescribing patterns of ranitidine and characteristics of long-term users using Korea Health Insurance Review and Assessment database between 2007 and 2018. We calculated the annual number of patients who received ranitidine, and each patient's total prescription days and doses for 12 years. Long-term prescription was defined as prescription for more than 365 days considering the distribution of total prescription days in study population. We identified patient's comorbid status including upper gastrointestinal (UGI) disease (ICD-10, K20-K31), rheumatic diseases (M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0), or musculoskeletal diseases (M07-M99 except for the codes included in rheumatic diseases). We categorized patients' type of insurance as medical insurance, medical aid, and veterans. We applied multivariable logistic regression model to examine factors associated with long-term prescription of ranitidine.

Results: A total of 42,311,376 patients received ranitidine prescription between 2007 and 2018 in Korea (51.8% female; mean age 41.7 (±19.1) years), which accounting for approximately 82% of the Korean population. The number of patients has increased steadily from 5,466,816 in 2007 to 19,571,060 in 2018. Of these, 2,300,403 (5.4%) were long-term users. In the multivariable analysis, increased age (OR=1.822; 95% CI 1.820-1.824, 10-year increments), comorbid rheumatic disease (OR=4.37; 95% CI 4.34-4.40), UGI disease (OR=3.54; 95% CI 3.53-3.56), musculoskeletal diseases (OR=2.85; 95% CI 2.84-2.86), medical aid (OR=2.79; 95% CI 2.78-2.81), and veterans (OR=4.45; 95% CI 4.28-4.61) were associated with long-term prescription of ranitidine.

Conclusions: Long-term prescription of ranitidine was associated with increased age, socioeconomic status, and specific comorbidities of patients. Patient characteristics associated with the long-term prescription of ranitidine could aid identifying at-risk patients, and provide information for designing further research assessing cancer risk associated with chronic exposure to ranitidine.

4642 | Overall quality of antibiotic consumption in a middle-income developing country over 16 Years

Maryam Taghizadeh-Ghehi[1], Fatemeh Rezaei[1], Aarefeh Jafarzadeh-Kohneloo[2] and Mona Kargar[1]

[1]*Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran;* [2]*Department of Epidemiology and Biostatistics, Faculty of Health, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran*

Background: Resistance to antibiotics is a global health challenge that mainly resulted from inappropriate antibiotic use. A comprehensive picture from quantity and quality of antibiotic consumption at national level would be necessary to detect irrational use and overcome consequent problems.

Objectives: Our aim was to study trend and pattern of antibiotic consumption considering WHO Access, Watch, Reserve ("AWaRe") categories of antibacterials, over 16 years in Iran.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: 1. Design: This cross-sectional observational study was conducted using data recorded from 2000 to 2016.2. Setting: National pharmaceutical wholesale data in Iran were used.3. Exposures: In according to WHO ATC/DDD system (2018), systemic antibacterial agents in J01 group were targeted. Consumption data of antibiotics were extracted, cleaned, and converted into WHO defined daily doses (DDDs).4. Main outcome measures: DDDs per 1000 inhabitant per day (DID)) was calculated annually for every single antibiotic and summed up for WHO AWaRe categories (2019). Antibiotics from AWaRe categories constituted 90% of consumption (DU-90%) were also determined. Statistical Analysis: Joinpoint regression (Joinpoint, version 4.7.0.0) was used to analyze the trends.

Results: Antibiotic consumption increased over 16 years (β=1.28, P-value=0.000). The share of "Access" antibiotics from annual consumption decreased from 92.63% in 2000 to 59.76% in 2016. However, net DIDs of the "Access" antibiotics did not change significantly (P-value=0.49). Amoxicillin was the most commonly used antibiotic, with DIDs of 45.22 in 2000 and 32.74 in 2016. Consumption of antibiotics in "Watch" category increased significantly (β=1.34, P-value=0.000). The share of "Watch" antibiotics from annual consumption increased from 7.36% in 2000 to 40.22% in 2016. DU-90% comprised median (Min-Max) 9 (8-10) antibiotics. Among nine and 8 DU-90% antibiotics in 2000 and 2016, none and 3 medications were from "Watch" category, respectively. Cefixime, ciprofloxacin, and azithromycin were consistent representatives of "Watch" category among DU-90% antibiotics from 2006 onwards and cefixime remained at the second place of annual antibiotic use in our country, since 2007.

Conclusions: Systemic antibacterial use have increased significantly during past decades in Iran. Although the "Access" antibiotics are still comprised nearly 60% of total antibiotic consumption in our country, high amount of antibiotic consumption, ascending trend and gradual shift of use to "Watch" agents could ring the bells for health policy-makers in our country.

4643 | Increasing tramadol utilisation under strict regulations for opioid prescribing: A Cross-sectional study in Taiwan

Teng-Chou Chen[1], Ting-Chun Wang[2], Chih-Peng Lin[3], Kerina Bonar[4], Darren M. Ashcroft[1,5,6], K. Arnold Chan[2] and Li-Chia Chen[1]

[1]Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom; [2]Health Data Research Center, National Taiwan University, Taipei, Taiwan; [3]Department of Anesthesiology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [4]Mundipharma Research Limited, Cambridge, United Kingdom; [5]NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom; [6]NIHR Greater Manchester Patient Safety Translational Research Centre, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom

Background: Tramadol has been classified as a controlled medicine in several countries due to safety concerns and rising utilisation. Although opioid prescribing to patients with non-cancer pain is strictly regulated in Taiwan, tramadol is not included in the controlled regulation for chronic opioid prescribing.

Objectives: This study aims to identify the utilisation trend of prescription tramadol and other opioid analgesics and investigate the influence of drug regulation on opioids prescribed for managing cancer or non-cancer pain in Taiwan.

Methods: This cross-sectional study used the Taiwan National Health Insurance claims records and the Taiwan cancer registry from 2001 to 2016. Opioid analgesics commonly prescribed for pain relief were identified from prescribing records from outpatient clinic visits, emergency department visits or during inpatient hospitalisations. The annual number of adult opioid users, annual opioid utilisation (Defined Daily Doses [DDDs]/1000 registrants) and the number of supply days were enumerated for each calendar year and further stratified into cancer and non-cancer patients. Descriptive statistics were used to report the trend of outcome measures in each calendar year.

Results: Overall, the annual number of opioids users increased from 606,457 to 1,226,935, and 7,551,250 opioid users were identified between 2002 and 2016. There was a marked increase in the annual opioid utilisation (55.6 to 578.1 DDD/1000 registrants) and mean supply days (from 6.4±14.5 to 28.7±57.9 days) from 2002 to 2016. Taiwan regulations strictly limited chronic opioids prescribed to patients with non-cancer pain, of which only a small proportion of non-cancer fentanyl (20%) and morphine users (<2%) were prescribed with an annual number of supply days greater than 28 days. The annual utilisation of morphine (6.4 to 53.5 vs. 1.1 to 9.6 DDD/1000 registrants) and fentanyl (8.3 to 37.0 vs. 0.16 to 1.8 DDD/1000 registrants) to patients with cancer was consistently higher than patients without cancer. However, in contrast to morphine and fentanyl, the utilisation of tramadol prescribed to patients without cancer increased 92.2-fold (3.7 to 341.2 DDD/1000 registrants) from 2002 to 2016.

Conclusions: Opioid utilisation increased ten-fold due to the increasing number of opioid users and chronic prescribing of tramadol to patients with non-cancer pain. The strict regulation of prescribing potent opioids for patients with non-cancer pain may result in sub-optimal pain management, and the prominent substitution of tramadol for other opioids also raises safety concerns in Taiwan.

4649 | Adherence and persistence of once versus twice-daily direct oral anticoagulants

Claudia Bartolini[1], Rosa Gini[1], Tania Schink[2], Elisabeth Smith[3], Eline Houben[3], Fernie JA Penning- van Beest[3], Georgios Spentzouris[4] and Ron MC Herings[3]

[1]Agenzia regionale di sanità della Toscana, Florence, Italy; [2]Leibniz Institute for Prevention Research and Epidemiology, Bremen, Germany; [3]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands; [4]Daiichi Sankyo Europe GmbH, Munich, Germany

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Direct oral anticoagulants (DOACs) are available for atrial fibrillation (AF) patients as once-daily (QD) (edoxaban and rivaroxaban) or twice-daily (BID) (apixaban and dabigatran) regimens.
Objectives: To compare adherence and persistence of QD vs. BID dosage regimens (DR) in AF patients.
Methods: A cohort study was conducted in 3 databases in Germany (DE), Italy (IT) and the Netherlands (NL). AF patients starting DOACs between approval date and 2018 were included. The index date (ID) was the date of first dispensing. We restricted to patients aged ≥18, ≥1 year database history and ≥1 year follow-up. Adherence to treatment was defined over the first year of follow-up based on the proportion of days covered≥80% during the exposure period. The exposure period was defined as the number of days between ID and date of the last drug dispensing with the index DR in the first year of follow-up. Persistence at one year was defined as absence of a gap between dispensings of the index DR before the end of the first treatment year. The gap was defined as half the duration of the previous dispensing, or 7 days if shorter. Switch between DRs was assessed during the whole exposure period from first to last dispensing in all available follow-up.
Results: 167,445, 32,260 and 6,068 patients were included from DE, IT and NL, respectively. 61%, 40% and 31% were QD users, respectively, and mean age among the two groups was the same in all sites (i.e. 74, 77 and 70 years respectively). Patients with a previous record of vitamin K antagonist treatment were 25%, 43% and 31%, respectively. Mean exposure period of QD/BID users was 23/21, 25/29 and 23/25 months, respectively. Among QD/BID users, patients with≥10 dispensings during the exposure period were 35/43%, 82/86% and 52/54%, respectively. Among QD/BID users, 82/62%, 89/88% and 94/91%, respectively were adherent during the first year. Persistence rates at one year in QD/BID users were 46/31%, 13/14% and 60/59%, respectively, but, based on high adherence, treatment discontinuation was temporary. During the exposure period, switches to the other DR occurred in 13/10%, 5/6% and 8/7% of QD/BID users in DE, IT and NL.
Conclusions: Adherence to treatment was high everywhere, and markedly higher in QD users compared to BID users in DE. Persistence was low, and markedly lower in BID users versus QD users in DE, but discontinuation was temporary. The comparison among sites was biased by different duration of a dispensing period, probably linked to differences in the local regulations regarding number of pills allowed in a single dispensing package, which is lower in IT. Switching between DRs was rare among both QD and BID users.

4651 | A Multidatabase study of trajectories of antidepressant use in Italy

Ippazio Cosimo Antonazzo[1], Olga Paoletti[2], Claudia Bartolini[2], Giuseppe Roberto[2], Valdo Ricca[3], Giovanni Castellini[3], Marco Menchetti[4], Elisabetta Poluzzi[5], Elisa Sangiorgi[6], Giampiero Mazzaglia[1] and Rosa Gini[2]

[1]Center for Public Health Research (CESP), University of Milan – Bicocca, Milan, Italy; [2]Epidemiology Unit, Regional Agency for Healthcare Services of Tuscany, Florence, Italy; [3]Psychiatric Unit, Department of Health Sciences, University of Florence, Florence, Italy; [4]Psychiatric Unit, Department of Biomedical and NeuroMotor Science (DIBINEM), University of Bologna, Bologna, Italy; [5]Pharmacology Unit, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [6]AUSL di Bologna-Dipartimento Farmaceutico, Bologna, Italy

Background: Tuscany (TUS) is the Italian region with the highest consumption of antidepressants (AD): 62 Defined Daily Dose (DDD)/1000 inhabitants/day were recorded in 2018. In the neighboring region Emilia-Romagna (ER), similar to TUS in demographics, socio-economic conditions, and regional healthcare system, consumption in 2018 was 52 DDD/1000 inhabitants/day.
Objectives: To investigate reasons for observed difference in consumption, based on patterns of AD use.
Methods: An observational retrospective cohort study was carried out using administrative data from Florence (FLO) and Bologna (BO), two large, similar areas respectively from TUS and ER. All inhabitants with ≥1 AD pharmacy claim from 2009 to 2013 and without AD claims during the previous 5 years were selected and incidence rate of use (IR) was computed in FLO and BO as well as incidence ratio (IRR) between FLO and BO. Users with ≥5 years of follow-up were included in the next analysis. Gender, age and type of index AD (iAD) were observed. Twenty binary variables were defined, each indicating whether≥1 AD claim was recorded in the corresponding trimester (TRI). Trajectories were clustered and comparison of occurrence of clusters was conducted across area, gender, age and iAD.
Results: The study cohort included 219,393 individuals with ≥1 AD claim: 149,285 in FLO (IR: 2.12/100 person-years) and 70,108 in BO (IR: 1.92/100 person-years), with IRR 1.11 (CI 95%: 1.10-1.12). The majority of the 178,633 individuals with ≥5 years of follow-up were female (64%) and aged between 65 and 84 years (32%), but in FLO patients aged ≤45 were more common (30% vs 28%) and iAD were more commonly selective serotonin reuptake inhibitors (SSRi) (75% vs 72%). 6 clusters of trajectories were identified: (1) 38% were treated for 1 TRI only; (2) 12% had repeated short cycles (1 TRI); (3) 15% had ≥1 cycle of ≥2 after the first 1 TRI; (4) 9% had longer cycles during the first 2 years and then discontinued; (5) 18% had long cycles (between 8 and 19 TRI); and (6) 4% were continuously treated for 5 years. Clusters were distributed similarly across areas, although clusters 5 and 6 were slightly more common in FLO. Clusters 5 and 6 were also more frequent among older individuals and SSRIs users, and more so in FLO.
Conclusions: In FLO higher incidence of new AD users was observed, and slightly higher occurrence of younger patients and SSRi treatments. This may indicate a higher propension in FLO clinicians to prescribe AD for anxiety disorders, more prevalent among younger patients and more commonly treated with SSRi. Lower reluctance in FLO both to initiate and to withdraw from therapy may be due to higher acceptability of AD in the population.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4665 | Channelling bias of initiating fixed ratio combination (FRC) therapy in adults with type 2 diabetes (T2D): A retrospective observational US study

Robert Lubwama, Anders Boss, and Alka Shaunik
Sanofi, Bridgewater, NJ

Background: Channelling bias is a form of confounding that occurs when a drug is preferentially prescribed to patients with different baseline characteristics, and the observed response may not be related to the drug or cannot be generalised to patient populations. Early data on FRC (basal insulin + GLP-1 receptor agonist [GLP-1 RA]) use among people with T2D in the US indicate that channelling bias may be present.
Objectives: To investigate differences in baseline demographic and clinical characteristics in adults with T2D initiating FRCs (iGlarLixi or IDegLira) compared with those initiating GLP-1 RAs or sodium-glucose linked transporter-2 inhibitors (SGLT-2is).
Methods: Data from the US Optum Humedica electronic health records database were captured from January 1, 2017 to June 30, 2018. Adults with T2D initiating FRCs were compared with those initiating GLP-1 RAs and SGLT-2is. Baseline characteristics and clinical variables were extracted using ICD-9-CM/ICD-10-CM and prescription codes. Multivariate logistic regression analyses adjusting for age, sex, number of oral antidiabetic medications and comorbidities in the baseline period were used to estimate odds ratios (OR).
Results: The clinical profile of people initiating FRC treatment (n=3003) differed from those initiating therapy with GLP-1 RAs (n=49,935) and SGLT-2is (n=44,895). When compared with adults initiating GLP-1 RAs, those initiating FRCs were more likely to have a lower body mass index (≥35 kg/m^2; OR = 0.70, p<0.001), be older (age 55-64 years; OR = 1.24, p<0.001) or have serious hyperglycaemia (OR = 1.32, p<0.05) or HbA_{1c} ≥9 % (OR = 1.44, p<0.001). When compared with adults initiating SGLT-2i, those initiating FRCs were less likely to be male (OR 0.73, p<0.01), or more likely to have HbA_{1c} ≥9 % (OR 1.87, p<0.001), serious hyperglycaemia (OR = 1.81, p<0.01), nephropathy (OR = 1.61, p<0.001) or neuropathy (OR = 1.29, p<0.05). When reviewed by the prescribing physician, FRC prescriptions were more likely than GLP-1 RA prescriptions to be written by specialists (OR = 1.50, p<0.001).
Conclusions: The differences observed between the baseline characteristics of adults initiating FRCs and those initiating GLP-1 RAs and SGLT-2is are prognostic factors and confounders for diabetes therapy response and may influence short- and long-term disease outcomes. Therefore, it is important to apply appropriate statistical methods to control for the confounding in comparative-effectiveness observational studies when analysing data from electronic medical or claims databases for people initiating FRC therapies.

4680 | Trend and contributing factors of prescribing antidepressants in primary care in England: 2013-2019

Xinchun Gu, Tehreem Fatima Ahmed, Teng-Chou Chen, Douglas Steinke and Li-Chia Chen
Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

Background: Patients with chronic pain were commonly prescribed with antidepressants and opioids in primary care settings in England. The increase of antidepressants prescribed in primary care ascribes to multiple factors, e.g. socioeconomic status (SES) or strategies for deprescribing opioids, but the trend in utilisation and the associated factors have not been fully studied.
Objectives: This study aimed to categorise the trend of antidepressants prescribed in primary care in England and assess factors associated with the prescribing.
Methods: This cross-sectional study used monthly practice-level prescribing data and publicly available statistics in England from the United Kingdom National Health Service Digital and Office for National Statistics between April 2013 and March 2019. Antidepressants were categorised into selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and others based on the British National Formulary. The annual and quarterly utilisation of antidepressants were measured by Defined Daily Dose (DDD)/1000 registrants. Practices were grouped by a trajectory model analysing their quarterly utilisation between April 2013 and March 2019. Multilevel mixed-effect regression was used to assess the association between one-year utilisation (April 2018 to March 2019) and contributing factors (i.e. demographic characteristics, prevalences of diseases, and SES) after adjusting the cluster-effect of Clinical Commissioning Groups.
Results: The annual utilisation of antidepressants increased from 29484 to 39723 DDD/1000 registrants from 2013 to 2019. Of the five antidepressant categories, SSRIs had the largest increase from 20522 to 28272 DDD/1000 registrants, while the annual utilisation of TCA and MAOIs decreased slightly. Of the 5 utilisation trajectories identified from 8054 general practices, only one (16.9% practices) presented a decreasing utilisation. The greater annual utilisation was associated with a higher proportion of female, elderly, mental health illness, palliative care, depression, smoking, obesity and deprived SES in a practice.
Conclusions: Most practices in England increasingly prescribed antidepressants in the recent 6 years, and the rising utilisation was dominated by the increasing prescribing of SSRIs. SES was one of the factors ascribe to antidepressant utilisation. Further study is needed to identify social determinants and potential harms of the increased antidepressant prescribing.

4681 | Trends in nationwide metamizole utilization in Turkey

Caner Vizdiklar, Volkan Aydin and Ahmet Akici
Marmara University School of Medicine, Istanbul, Turkey

Background: Use of metamizole (dipyrone) is controversial, especially due to serious adverse events, which is more pronounced for use in

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

outpatient setting and via parenteral route. While the drug has been withdrawn or unapproved in several countries, it is still in use in some countries including Turkey.

Objectives: This study aimed to evaluate nine-year nationwide metamizole consumption trend in Turkey.

Methods: In this retrospective descriptive study, we obtained nationwide metamizole consumption data between 2010 and 2018 from IQVIA Turkey. Drug utilization was measured by DDD (defined daily dose)/1000 inhabitants/day (DID) unit.

Results: Overall metamizole utilization decreased from 1.13 to 0.94 DID during the study period. Enteral route (71.2-86.6%) and outpatient setting (87.6-95%) were mostly preferred. Percentage of enteral preparations raised from 78.1% to 83.6%, whereas the share of outpatient preparations remained relatively stable, changing from 93.1% to 92.3%. Outpatient parenteral use showed a mostly steady decline (0.18 to 0.08). Inpatient parenteral consumption levels fluctuated through years (range: 0.04-0.14), yet remained almost unchanged in 2018 compared to 2010 (0.07 DID). Outpatient enteral DID peaked in 2014 (1.52), then lessened to lower than previous levels (0.87 in 2010 and 0.78 in 2018). Inpatient enteral consumption decreased to approximately one-seventh (0.007 to 0.001).

Conclusions: During the nine-year period, metamizole utilization decreased in Turkey mostly regardless of setting and route of administration. More prominent decline in use via parenteral route and outpatient setting might deserve designation of further studies that aim to explore the association of such trend to safety concerns.

4683 | Prescription opioids dispensed in Romania during 2017-2018

Irina Cazacu[1], Camelia Denisa Bucsa[2], Cristina Pop[1], Anamaria Cristina[1], Bogdan Apan[3] and Cristina Mogosan[1]

[1]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania; [2]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania; [3]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania

Background: Opioids provide essential therapeutic options in bringing moderate-to-severe pain relief. Unfortunately, even if published data from different European countries show an increase in opioid use, data pertaining to it are currently very scarce in Romania.

Objectives: To characterize the consumption of prescription opioids (PO) in Romania.

Methods: We retrospectively analyzed data provided by IQVIA Romania, which included prescriptions dispensed from retail pharmacies, originating from all 41 Romanian counties and the municipality of Bucharest, during 2017-2018, for morphine (oral and injectable), fentanyl (cutaneous and sublingual), oxycodone (oral), dihydrocodeine (oral), pethidine (injectable), tramadol (oral, injectable and intrarectal), tramadol+paracetamol (oral).

Results: Total PO consumption, expressed in DDD/1000people/day, was 0.321 in 2017 and 0.359 in 2018. Tramadol+paracetamol (0.186 in 2017 and 0.223 in 2018, respectively) and tramadol (0.085, 0.086), followed by morphine (0.017, 0.015), fentanyl (0.012, 0.014) and dihydrocodeine (0.011, 0.010), were the most dispensed opioids. For both years, tramadol+paracetamol (72.8%) and tramadol (20.9%) had also the highest number of prescriptions, followed by fentanyl (2.7%), morphine (1.7%) and dihydrocodeine (0.9%). The two main indications for tramadol+paracetamol and *tramadol use* were polyarthrosis (7.0% and 8.3%, respectively) and dorsalgia (6.7%, 6.0%), followed by *intervertebral disc disease (6.0%) for* tramadol+paracetamol and gonarthrosis (4.9%) for tramadol. Morphine, fentanyl and dihydrocodeine were mostly prescribed for pain relief in case of lung cancer (13.1%, 11.1% and 13.4%, respectively), breast cancer (10.4%, 10.5%, 11.9%) and prostate cancer (6.9%, 7.1%, 8.7%). The highest regional opioid consumption, during 2017-2018, was in Bucharest (9.2%), followed by the counties Prahova (8%), Hunedoara (7.6%), Constanta (5.4%) and Mures (5.1%).

Conclusions: Tramadol in association with paracetamol or alone was the main PO dispensed in Romania during 2017-2018, and it was mainly indicated for pain management in case of rheumatic diseases. Regarding lung, breast or prostate cancer, morphine was the main opioid prescribed to provide analgesia. Continuous education on opioid use, to ensure safe and effective treatment of painful conditions, is a justified necessity at present in Romania.

4685 | Impact of changes in controlled drugs legislation on benzodiazepine and Z-drug prescribing in Ireland

Cathal A. Cadogan[1], Colin P. Bradley[2] and Kathleen Bennett[1]

[1]Royal College of Surgeons in Ireland, Dublin, Ireland; [2]University College Cork, Cork, Ireland

Background: In May 2017, new controlled drugs legislation targeting benzodiazepines and Z-drugs was implemented in Ireland over concerns relating to diversion of valid prescriptions and drug misuse. The legislation introduced additional prescribing requirements and possession of these medications without a prescription is now a criminal offence.

Objectives: The objective was to examine the impact of the Misuse of Drugs Regulations 2017 on benzodiazepine and Z-drug prescribing in Ireland using national pharmacy claims data.

Methods: A repeated cross-sectional analysis was conducted using publically available monthly dispensing data from the General Medical Services (GMS) pharmacy claims database, the largest public health scheme, maintained by the Primary Care Reimbursement Services. The study population comprised all GMS-eligible individuals aged ≥16 years from January 2016 to September 2019. Monthly prevalence (%) was calculated as the number of patients in receipt of at least one of the medicines divided by the GMS eligible population and trends were examined over time. Segmented regression analyses were used to examine changes in the slope before and after introduction of the legislation stratified by gender and age groups. Odds ratios

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(OR) and 95% confidence intervals (CIs) for monthly change are presented.

Results: The prevalence of benzodiazepine and Z-drug prescriptions issued on the GMS in January 2016 was 8.3% and 6.0%, respectively. Prior to the legislation (January 2016 to April 2017), there was a significant monthly decline in benzodiazepine prescribing (OR 0.998; 95% CI 0.998, 0.999; p<0.001) but no significant change in Z-drug prescribing (OR 1.00; 95% CI 1.000, 1.000; p=0.66). Following introduction of the legislation (May 2017 to September 2019), the decline in benzodiazepine prescribing was not sustained (OR 1.001; 95% CI 1.001, 1.002; p<0.001) and a marginal increase was observed in Z-drug prescribing (OR 1.002; 95% CI 1.001, 1.002; p<0.001). However, there were differences in the youngest and oldest age groups, with significant increases in benzodiazepine and Z-drug prescriptions issued to the youngest subgroup (16-44 years) for both genders and significant decreases post-legislation in the oldest age group (≥65 years) for both genders.

Conclusions: This study indicates that the introduction of new legalisation had limited impact on benzodiazepine and Z-drug prescriptions issued on the main public health scheme in Ireland. Interventions targeting specific population subgroups may be needed if sustained reductions in prescribing are to be achieved.

4692 | Antidepressant use and concurrent psychopathology in Danish children, adolescents and young adults

Rikke Wesselhoeft[1], Peter B. Jensen[1], Lotte Rasmussen[1], Johan Reutfors[2], Lena Brandt[2], Kari Furu[3], Svetlana Skurtveit[4], Randi Selmer[3], Per Damkier[5], Anton Pottegård[1] and Mette Bliddal[6]
[1]University of Southern Denmark, Odense, Denmark; [2]Karolinska Institute, Stockholm, Sweden; [3]Norwegian Institute of Public Health, Oslo, Norway; [4]Norwegian Institute of Public Health, Oslo, Norway; [5]University of Southern Denmark, Odense, Denmark; [6]University of Southern Denmark, Odense, Denmark

Background: The use of antidepressants in children and young adults varies widely between the Scandinavian countries in spite of similar health care systems and medication guidelines.

Objectives: To describe antidepressant use among young Danes, providing information for future comparisons of utilization patterns between the Scandinavian countries.

Methods: Population-based study design including all Danish individuals aged 5-24 years, who filled an antidepressant prescription during 1997-2018. Incidence rates were determined by sex and age groups. Treatment duration was calculated from 2012-2018 using a Kaplan-Meier curve. Concurrent psychiatric disorders were defined as a diagnosis assigned at mental health clinics ± one year of filled antidepressant prescription.

Results: We identified 175,393 antidepressant users. The incident antidepressant use increased from 3 to 10 users/1,000 inhabitants from 1997-2010 and decreased to 6 users/1,000 inhabitants in 2018. New use of selective serotonin reuptake inhibitors (SSRI) was the main driver for the increase in antidepressant use, reaching a peak of 9/1,000 in 2010. Individuals aged 15-19 and 20-24 years constituted the largest user groups, with 9 and 12 female users/1,000, and 4 and 7 male users/1,000, respectively in 2018. Female/male ratios were 2.3 at age 15-19 years and 1.7 at age 20-24 years. Among 10-14-year-old users, 66% and 39% continuously filled antidepressant prescriptions after 12 and 24 months respectively, which was markedly higher than other age groups (42-50% and 21-25%, respectively). Within a two-year time window, 40% of new antidepressant users were assigned with a psychiatric disorder diagnosis. Non-internalizing disorders were the most common diagnoses (21%), followed by any anxiety disorder (20%) and depression (16%).

Conclusions: The incidence of antidepressant use peaked in 2010, and 15-24-year-old females were approximately twice as likely to start antidepressant treatment than males. Somewhat surprisingly, treatment duration was longest for 10-14-year-old individuals. Also, less than half of new users were assigned with a concurrent psychiatric disorder, whereof non-internalizing disorders were the most frequent group. These findings suggest that antidepressant use in young Danes is often initiated without licensed indications. This study will be followed by similar analyses of Swedish and Norwegian data by our group.

4694 | Spatial exploration of deprivation driven inequalities in opioids prescribing in English primary care: A cross sectional analysis

Magdalena Nowakowska, Salwa Zghebi, Rosa Parisi, Li-Chia Chen, Darren M Ashcroft and Evangelos Kontopantelis
University of Manchester, Manchester, United Kingdom

Background: Over 23 million opioid prescription items were dispensed in English primary care in 2018/19. The levels of prescribing are not distributed equally across regions and populations. A greater understanding of the geographical differences and social drivers of opioid prescribing is needed to guide policy responses and interventions.

Objectives: To explore regional variations in opioid prescribing in England and the role of socio-economic deprivation in driving inequalities in opioid prescribing.

Methods: Cross-sectional study using national primary care prescription data. The prescribing of opioids in each general practice was quantified by Defined Daily Doses (DDD) and attributed to 32,844 Lower Layer Super Output Areas (LSOA), geographical units representing approximately 1,500 people. Linear regression was used to model the effect of socio-economic deprivation, measured by the Index of Multiple Deprivation 2019 quantiles, on levels of prescribing. The model accounted for the proportion of females and people over 65 year old, rurality/urbanity of the area, and prevalence of cancer, palliative care, depression, severe mental illness (SMI), rheumatoid arthritis, and obesity. Within higher organisational areas (Clinical

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Commissioning Groups, CCG), adjusted DDD were estimated and compared at each deprivation level.

Results: In total, 5,350,151,699 DDD of opioids were prescribed. Prescribing of opioids, measured by DDD/1000 populations/day, was not distributed randomly between LSOA and varied between 4 and 1,905 DDD/1000 population/day. On average, 93.8 (SD: 1.9, $p < 0.001$) more DDD/1000 population/day were prescribed in the most deprived compared to the least deprived areas. Prevalence of cancer and SMI were negatively associated with opioid prescribing, and the remaining conditions had a positive association. Smaller LSOA and LSOA with a smaller proportion of females prescribed fewer opioids. A higher proportion of population over 65 was associated with higher prescribing. On average, opioid prescribing was 33.6 DDD/1000 populations/day (SD: 2.2, $p < 0.001$) higher in urban compared to rural areas. Within individual CCGs, the difference between prescribing in the least and most deprived areas varied by up to 200%.

Conclusions: Even after adjusting for differences in population structure, opioid prescribing practices differ significantly across the country, and geospatial deprivation is a key prescribing driver. Future policies and interventions should focus on high-prescribing low-geography areas and on tackling deprivation driven inequalities.

4719 | Trends of use of opioids in the period 2010 to 2018: Findings from a real-world cohort of 2 million patients in Spain

Isabel Hurtado, Gabriel Sanfelix-Gimeno, Salvador Peiro and Anibal Garcia-Sempere
FISABIO, Valencia, Spain

Background: the opioid epidemic has been well documented in the USA and Canada, but fewer data are available for Europe.

Objectives: to describe the trends of opioid use -volume of prescription, dosing and patients treated - in a European population with more than 4,2 million inhabitants 18 years and older.

Methods: we included all patients aged 18 and over who had at least one opioid prescription (including morphine, codeine, tramadol, buprenorphine, fentanyl, hydromorphone, oxycodone, petidine and tapentadol) in the region of Valencia, Spain, between 2010 and 2018. We described the trends of number of prescriptions, doses prescribed in Morphine Milligram Equivalents (MME) per inhabitant and volume of patients treated.

Results: more than 36 million treatments were prescribed in the whole period, and the number of treatments per year grew by twofold, from 2,597,727 prescriptions in 2010 to 5,115,498 in 2018. Tramadol use increased from 45.5 prescriptions/100h/year in 2010 to 76.2 in 2018 (84.2% of prescriptions in combination with paracetamol). Fentanyl figures rose from 4.7 to 17 prescriptions/100h/year; tapentadol was launched in 2011 and accounted for 8.5 prescriptions/100h/year in 2018. Total MME per inhabitant grew from 224.5 in 2010 to 644.9 in 2018, almost a threefold increase. Fentanyl MME/h more than tripled in the period (and accounted for 37% of the total MME/h in 2018), while morphine and tramadol increased by twofold. Oxycodone MME/h showed a tenfold increase and tapentadol showed the highest growth figures, overtaking tramadol at the end of the period. The number of patients receiving an opioid prescription every year more than doubled, with 336.193 having at least one prescription in 2010 versus 726.952 in 2018, for a total of 2.107.756 unique patients receiving at least one prescription in the period.

Conclusions: Opioid use increased by twofold from 2010 to 2018, as did the number of unique patients treated per year, while MME/h prescribed tripled in the period. Even if proportions seem still far from epidemic, urgent research is warranted on the appropriateness and health outcomes associated to these observed trends, especially for higher use and higher strength drugs.

4721 | Use of low-dose aspirin for primary prevention from 1998 to 2018: A nationwide danish cohort study

Espen Jimenez-Solem[1], Mikkel B Christensen[1], Erik L Grove[2], Morten Schmidt[3], Martin T Ernst[4] and Anton Pottegård[4]
[1]Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Aarhus University Hospital, Aarhus, Denmark; [4]University of Southern Denmark, Odense, Denmark

Background: Evidence suggests that low-dose aspirin for primary prevention of atherosclerotic cardiovascular disease (ASCVD) has an unfavorable benefit-risk balance.

Objectives: To assess the nationwide use of low-dose aspirin for primary prevention of ASCVD in Danish adults during the past two decades.

Methods: We identified all Danish adults redeeming low-dose aspirin prescriptions 1998-2018 and linked these data with hospital diagnoses of ASCVD. We estimated the incidence and prevalence over time of aspirin use for primary prevention defined as patients without a diagnosis of ASCVD. We also investigated age and co-medications adding to bleeding risk, including other platelet inhibitors, oral anticoagulants, and systemic glucocorticoids.

Results: We identified 1.1 million adults using aspirin during the 20-year study period. Low-dose aspirin was used by 4.1% (1998), 8.3% (2008), and 5.1% (2018) of the adult Danish population. Use for primary prevention was 3.1% (1998), 6.1% (2010), and 3.6% (2018), thus accounting for 70-77% of the total aspirin use. Aspirin use for primary prevention showed a strong age dependency, reaching more than 20% among those aged at least 80 years. Simultaneous use of at least one drug known to increase the risk of gastrointestinal bleeding events was fairly stable over the study period and amounted to 40% in 2018.

Conclusions: Low-dose aspirin use for primary prevention is common and increases with age reaching more than 20% among elderly >80 years. These data suggest a considerable potential for discontinuation of unnecessary aspirin treatment.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4741 | Prescription patterns of denosumab in Spain: A population-based cohort study

Mar Martín-Pérez, Patricia García Poza, Belén Castillo Cano and Elisa Martín-Merino

Spanish Agency for Medicines and Medical Devices (AEMPS), Madrid, Spain

Background: Denosumab (Prolia®) is a human monoclonal antibody for osteoporosis in postmenopausal women and in men at increased risk of fractures. Long-term data on the prescription patterns of denosumab is scarce.

Objectives: To estimate the incident use of denosumab since 2011 and to describe the characteristics of new users.

Methods: A retrospective cohort study was performed in the Spanish Database for Pharmacoepidemiological Research in Primary Care (BIFAP). Patients ≥18 years, from 2011-2018 and ≥1 year of data, were followed until a first ever paper-based prescription or dispensation (for electronic prescriptions) for denosumab 60 mg/ml subcutaneous injection (Prolia®), death, loss to follow-up or end of study period. Incidence rates (IR) of denosumab prescriptions per 10,000 person-years (py) were computed overall, by age and sex and by calendar year. Characteristics of patients were ascertained any time prior or on the date of denosumab first prescription. Potential indications were explored among recorded diagnoses/treatments.

Results: Out of 8.4 million patients in the study population, 62,445 received a first prescription of denosumab. The resulting overall IR of denosumab prescription was 12.3/10,000 py, much higher in women (22.1/10,000 py) than in men (1.6/10,000 py) and peaked in women aged 70-79 years (69.9/10,000 py) and in men at 80-89 years (9.0/10,000py). IR increased from 0.3/10,000 py in 2011 to 16.5 in 2017 and decreased slightly thereafter until 15.4 in 2018. The majority of patients with denosumab prescriptions (93.7%) were women and the mean age was 71.3 (SD ± 10.7). Over 75% of patients had osteoporosis diagnosis recorded, 43.4% a history of fracture (nearly a third being vertebral fractures) and 6.7% osteopenia. Also, 41.8% of patients had glucocorticoids prescribed, 7.0% had breast cancer (of whom 50.3% had prescriptions of aromatase inhibitors) and 0.8% prostate cancer diagnosis (26% with recorded hormone therapy). Most patients (70.3%) had previously received therapy for osteoporosis (80% oral bisphosphonates), with 45.7% having used ≥2 different medications, and 90.4% had been prescribed calcium-vitamin D supplements.

Conclusions: Since its approval in 2011 the uptake of denosumab in Spain has been fast; in the first seven years the prescription rate increased steadily, but the rate observed in 2018 pointed to a negative trend that needs confirmation. As expected, use in women was much greater than in men and the main indication was osteoporosis. The majority of patients with denosumab prescriptions were not naïve to antiosteoporotic medications (mostly oral bisphosphonates).

4745 | Prescribing trend and factors associated with prescribing benzodiazepines in primary care in England: 2013-2019

Xinchun Gu, Laura Hayward, Teng-Chou Chen, Douglas Steinke and Li-Chia Chen

Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

Background: Benzodiazepines (BZDs) are commonly prescribed sedatives in primary care settings in England. The prescribing of BZDs ascribes to multiple factors such as deprivation and deprescribing policy. However, change in utilisation and factors influencing the prescribing of BZDs in general practices have not been fully studied.

Objectives: This study aimed to categorise the longitudinal trend of prescribing BZDs in England and investigate factors that may influence the prescribing of BZDs.

Methods: This cross-sectional study used monthly practice-level prescribing data and publicly available statistics in England between April 2013 and March 2019 from the United Kingdom National Health Service Digital and Office for National Statistics. The utilisation of prescribed BZDs was quantified as Defined Daily Dose (DDD)/1000 registrants. Descriptive statistics were used to report the annual utilisation of BZDs from 2013 to 2019. General practices were categorised by the trajectory model based on their quarterly utilisation of BZDs from April 2013 to March 2019. Mixed-effect multi-level regression was used to associate one-year utilisation of BZDs (April 2018 to March 2019) with contributing factors, i.e. demographic characteristics, the prevalence of diseases, lifestyle indicators and socio-economic status (Index of Multiple Deprivation [IMD] decile) by adjusting for the cluster-effect of Clinical Commission Groups.

Results: Overall, the annual utilisation of BZDs profoundly decreased from 2620 to 1810 DDD/1000 registrants between 2013 and 2019. Of the 5 decreasing trajectories categorised from the utilisation trends of 8050 general practices, quarterly utilisation of BZDs in the trajectory with the largest decrease (13% practices) dropped from 1327 to 856 DDD/1000 registrants from 2013 to 2019. The utilisation of BZDs in the most recent year was associated with the proportion of female or elderly, the prevalence of diseases and socioeconomic status in the practice. For every increase in IMD decile (less deprived), there was a significant decrease in the annual utilisation of BZDs of 26 DDD/1000 registrants.

Conclusions: Prescribed BZDs in primary care decreased from 2013 to 2019 in England, and there was variation in the longitudinal trajectory of prescribing BZDs. Multiple factors, including socioeconomic status, were associated with the prescribing of benzodiazepines. Further study will investigate the prescribing trends between BZDs and other medicines, such as opioids and the potential harms related to the concurrent prescribing.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4752 | Prescribing patterns of antidepressants in Slovenia: A nationwide database study

Nanca Cebron Lipovec, Andrej Anderlic and Igor Locatelli
University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

Background: Antidepressants use is believed to be increasing, however the actual prevalence and incidence is not well known.
Objectives: To evaluate the prevalence and incidence of antidepressants use and antidepressants prescribing patterns between 2008 and 2018.
Methods: This retrospective cross-sectional study analyzed health claims data of all dispensed outpatient antidepressant prescriptions between 2008 and 2018. Data detailing the health claims of medications prescribed and dispensed to outpatients in Slovenia were obtained from a national database held by the Health Insurance Institute of Slovenia. Incidence was calculated based on the number of patients who received their first antidepressants prescription after at least 5 years without antidepressants treatment. Furthermore, we explored the course of treatment in this patient cohort and followed them until 2018.
Results: In 2018, a total of 147,000 patients (7.1% of inhabitants) received antidepressants prescriptions. The average patient age was 60 years and 69% were females. The prevalence was highest among the oldest patients (20% of inhabitants ≥80 years, 13% of inhabitants between 65 and 80 years). In the last decade, the prevalence increased most considerably among the oldest patients (25% increase) and was constant among patients below 50 years of age. The overall prevalence increased for 18%; however, applying the standardised age structure from 2008, the 10-year increase in antidepressants prescribing fell to 8%. The most frequently prescribed antidepressants belonged to selective serotonin reuptake inhibitors (SSRI, 60% share), namely sertraline and escitalopram. A steady increase in the share of duloxetine (11% in 2018, 5% in 2008) as well as mirtazapine (8% in 2018, 4.5% in 2008) has been observed. Similarly, increased shares have been observed for newer antidepressants (eg. agomelatin and vortioxetine), whereas older antidepressants are disappearing from the market. The incidence of antidepressant prescribing was approximately 26,000 patients (in 2013). Of these, almost half patients received up to two consecutive prescriptions and did not continue treatment. Amongst patients who received more than 2 consecutive prescriptions, approximately 40% patients discontinued treatment within the first 6 months.
Conclusions: The prevalence of patients receiving antidepressants is steadily increasing in the last decade, mainly due to the aging of the population. Two thirds of patients with newly prescribed antidepressants discontinue treatment within the first 6 months.

4763 | Trends in the use of systemic anti-inflammatory biologics in Denmark: A nationwide drug utilization study

Mette Reilev[1], Alexander Egeberg[2], Lene Dreyer[3], Jesper Hallas[1], Tine Jess[4] and Anton Pottegård[1]

[1]University of Southern Denmark, Odense C, Denmark; [2]Copenhagen University Hospital Gentofte, Gentofte, Denmark; [3]Aalborg University, Aalborg, Denmark; [4]Statens Serum Institut, Copenhagen, Denmark

Background: The introduction of biological therapy has had a profound effect on the treatment of inflammatory diseases. It is, however, expensive compared to traditional treatment. To promote appropriate, safe and effective use of these drugs, continued monitoring of utilization patterns is necessary.
Objectives: To provide an overview of utilization patterns of systemic anti-inflammatory biologics in Denmark.
Methods: Using nationwide Danish health registries, we investigated use patterns of systemic anti-inflammatory biologics during 2004-2018 among all Danish individuals and in cohorts of individuals treated for inflammatory bowel disease, inflammatory arthritis, or inflammatory skin disease separately. We described incidence rates, prevalence proportions as well as persistence to therapy.
Results: We included 37,961 Danish adults having 960,008 dispensing of a systemic anti-inflammatory biologic during 2004-2018. The study population were 42% male and the median age at receiving the first treatment series of a biologic was 45 years [IQR 31-58]. The assumed indication for receiving biologics were inflammatory arthritis (45% of the study population), followed by inflammatory bowel disease (28%), inflammatory skin diseases (8%), and other indications (19%). The rate of new users of any biologics increased from 0.4 per 10,000 person-years in 2004 to 8.4 per 10,000 person-years in 2018. Concurrently, the point prevalence proportion of any biologics increased markedly from 0.3 to 36 users per 10,000 persons in 2018. The trends in incident and prevalent use was mainly driven by an increasing use of TNF-alfa inhibitors and was evident across all disease entities. Within inflammatory arthritis, we observed the highest prevalent use of biologics with 13% of individuals with a hospital diagnosis of the disease receiving a biologic in 2018. This was followed by inflammatory bowel disease (8% in 2018) and inflammatory skin disease (5% in 2018). Within all disease entities, persistence to therapy was highest among users of TNF-alpha inhibitors, with 35%, 45%, and 47% of individuals with inflammatory bowel disease, inflammatory arthritis and inflammatory skin disease, respectively, being covered by therapy 2 years after initiation.
Conclusions: We document an extensive increase in the use of biologics, both overall and within specific disease entities. Underlying drug use patterns including a detailed evaluation of persistence and switching patterns, and predictors hereof should be investigated.

4765 | Inventory of biological and biosimilar medicine data sources in Europe at a national and hospital level: The EU-inbiobase initiative

Carla Sans[1,2,3], Lina Leguízamo[1,2,3], Judit Riera[1,2,3], Elena Ballarín[1,3], Mònica Sabaté[1,2,3], Alethea Charlton[4,5], Alessia Bonora[6], Xavier Vidal[1,2,3] and Luisa Ibanez[1,2,3]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Clinical Pharmacology, Vall d'Hebron University Hospital, Barcelona, Spain; [2]Autonomous University of Barcelona, Barcelona, Spain; [3]Catalan Institute of Pharmacology Foundation, Barcelona, Spain; [4]Institute for Medical Information Processing, Biometry and Epidemiology - IBE, LMU Munich, Munich, Germany; [5]Pettenkofer School of Public Health, Munich, Germany; [6]Clinical Pharmacy, S.Orsola-Malpighi University Hospital, Bologna, Italy

Background: The heterogeneity of data sources for biologic/biosimilar medicines, together with a lack of standardization for recording data, contribute to challenges in undertaking cross-national biologic/biosimilar utilization studies.

Objectives: We aim to produce an inventory of databases (DB) containing biologic/biosimilar information at a national and hospital level in European university hospitals including the University Hospital Alliance (EUHA), thus facilitating further cross-national drug utilization studies.

Methods: The characteristics of national DB containing biologic/biosimilar medicines will be identified through literature review. Specific questionnaires will be sent to university hospitals in order to identify and describe such sources. Characteristics of both national and hospital DB, including administrative and clinical databases/registries will be collected: type of drug data, accessibility, anonymized patient data, medicine-related data, population coverage, and the possibility of linkage with other data sources. The internal and external DB validity will also be assessed.

Results: The questionnaire has been piloted in two third-level university hospitals (Spain, Italy). Its main limitations were the duration of completion and the difficulty finding information about the population coverage, validity and clinical/drug registries. These issues have been resolved and a new contact with the responders was set up to facilitate the search for the information in question. Moreover, information on national databases has been collected for the countries included in the EUHA (Austria, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom). The project proposal has been sent to the EUHA and the questionnaire will be presented at the EuroDURG 2020 Conference.

Conclusions: This inventory is a first step to ease the process of undertaking cross-national biologic/biosimilar utilization studies in Europe at national and hospital levels through developing a network of European hospitals to enhance research activities involving these medicines.

4782 | The role of high-deductible health plans on the use of lenalidomide

Shelley A. Jazowski[1], Lauren Wilson[2], Stacie B. Dusetzina[3], Yousuf Zafar[4] and Leah L. Zullig[2]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Duke University School of Medicine, Durham, NC; [3]Vanderbilt University School of Medicine, Nashville, TN;[4]Duke Cancer Institute, Durham, NC

Background: High-deductible health plans (HDHPs) have become one of the preferred forms of coverage in the United States. However, significant upfront out-of-pocket costs have been associated with patients forgoing or delaying orally-administered anticancer therapy. The role of HDHP enrollment on lenalidomide use in patients with multiple myeloma remains unknown.

Objectives: To compare the use of and costs associated with lenalidomide between patients with multiple myeloma who are enrolled in HDHPs or non-HDHPs.

Methods: We used MarketScan Commercial Claims and Encounters data from 2013 to 2017 to identify two cohorts: patients who were either enrolled in HDHPs or non-HDHPs in every month of the calendar year. Eligible patients were adults (aged 18 to 64) diagnosed with multiple myeloma (International Classification of Diseases, version 9 [ICD-9] code 203.00; ICD-10 code C90.0); and who had continuous prescription coverage for the full calendar year in which diagnosis occurred. We used descriptive statistics and Cochran-Armitage tests to examine trends in the annual use of and costs (adjusted to 2017 dollars) associated with lenalidomide, and log-binomial regression models to evaluate the association between HDHP enrollment and use of and $0 out-of-pocket costs for lenalidomide in a calendar year.

Results: Among patients enrolled in HDHPs, the rate of lenalidomide use increased from 26.4% in 2013 to 38.8% in 2017 (p<0.001). Similarly, lenalidomide use increased from 28.8% in 2013 to 36.4% in 2017 (p<0.001) among non-HDHP enrollees. There was no significant association between HDHP enrollment and lenalidomide use in a calendar year (RR: 1.06, 95% CI: 1.00-1.12). Mean lenalidomide costs significantly increased among both HDHP and non-HDHP enrollees, with average spending equaling $114,556 (SD: $55,099) and $107,315 (SD: $60,675) in 2017, respectively. Mean out-of-pocket costs for lenalidomide increased from 2013 ($280, SD: $923) to 2014 ($367, SD: $1,002), but remained consistent through 2017 among non-HDHP enrollees (p=0.013). Compared to patients covered by non-HDHPs, HDHP enrollees were 44% more likely to have $0 out-of-pocket costs for lenalidomide in a calendar year (RR: 1.44, 95% CI: 1.34-1.55).

Conclusions: Lenalidomide use and mean costs significantly increased among HDHP and non-HDHP enrollees. However, HDHP enrollees were more likely to have $0 out-of-pocket costs, which indicates that enrollees reached their deductible and out-of-pocket maximum before initiating or in early treatment with lenalidomide.

4800 | Trends in the prevalence of polypharmacy and potentially inappropriate medication among people with type 2 diabetes

Monika P. Oktora[1], Sofa D. Alfian[2,3], Catharina C. M. Schuiling-Veninga[2], Jens H. J. Bos[2], Katja Taxis[2], Eelko Hak[2] and Petra Denig[1]

[1]University of Groningen, University Medical Center Groningen (UMCG), Groningen, Netherlands; [2]University of Groningen, Groningen, Netherlands; [3]Universitas Padjajaran, Jatinangor, Indonesia

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Although increasing trends in the prevalence of polypharmacy are of concern, not all polypharmacy is considered inappropriate. People with type 2 diabetes (T2D) often need at least 5 medications to treat multiple risk factors and prevent complications, but they may also receive potentially inappropriate medication (PIM).

Objectives: We aimed to assess trends in polypharmacy among T2D patients, stratified by age groups. Furthermore, we assessed trends in PIMs among elderly T2D patients with polypharmacy.

Methods: We conducted a repeated cross-sectional study over 5 years (2012-2016) using the Dutch University Groningen prescription database IADB.nl, with a study population of T2D patients aged ≥45 years. Polypharmacy was defined as the dispensing of ≥5 chronic drugs, and age was stratified in groups of 45-54 years, 55-64 years, and ≥65 years. PIMs were determined by applying the Beers Criteria for patients ≥65 years with polypharmacy. There were 24 PIMs criteria that could be defined in IADB database, including 11 at therapeutic class level and 13 individual drug substances. A sumscore of the number of PIMs per patient was calculated and linear-by-linear chi-square tests were conducted to explore trends in PIMs

Results: The prevalence of polypharmacy increased from 41.3% in 2012 to 43.7% in 2016, with a peak of 44.3% in 2015. The absolute increase over the study period was 1.3% in the 45-54 years old, 2.3% in the 55-64 years old, and 2.1% in the ≥65 years old. The highest prevalence in 2016 was seen in oldest age group (52.0%), whereas this was 34.6% (55-64 years) and 23.3% (45-54 years) in the younger age groups. In this oldest age group with polypharmacy, preliminary results show the highest prevalence of PIMs for benzodiazepines (13%), antidepressants (8%), and dipyridamole (6%). The percentage of older patients with at least 1 PIM decreased from 29.6% in 2012 to 27.5% in 2016. The decreasing trend in the number of PIMs per patient was statistically significant.

Conclusions: Polypharmacy is common in T2D patients with a slight increase in the study period, particularly in patients of 55 years and older. In older patients this increase may not be inappropriate, since the number of PIMs per patient slightly decreased in this period.

4814 | Prescribing patterns in patients with type 2 diabetes in slovenia: A nationwide pharmacoepidemiological study

Spela Zerovnik, Mitja Kos and Igor Locatelli
University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

Background: Metformin is recommended as a first-line therapy according to the national guidelines on type 2 diabetes management in Slovenia. Currently, it is not clear whether the initiation of antidiabetic therapy follows the guidelines and how it affects the management of diabetes.

Objectives: To explore prescribing patterns of antidiabetic medicines in patients with type 2 diabetes in Slovenia.

Methods: We performed a nationwide pharmacoepidemiological study using health claims data on prescription drugs from 2005 to 2018 obtained from the Health Insurance Institute of Slovenia. We evaluated the incidence of type 2 diabetes based on dispensed prescriptions for antidiabetic medicines. Incidence was calculated on the basis of patients, who received their first prescription for antidiabetic medicine over the period of 3 years, excluding patients under 45 years of age that received insulin as first-line therapy. Furthermore, we explored course of treatment in patients with type 2 diabetes who received first prescription for antidiabetic medicine in 2014. Patients were followed until the end of 2018. The risk for change in antidiabetic therapy (switch or add-on therapy) was evaluated using Cox regression model with age, sex, region and concomitant therapy as covariates.

Results: The incidence of type 2 diabetes was highest in 2009 (n=10,055) and lowest in 2018 (n=8,427). The majority of patients started treatment with metformin monotherapy; however, the percentage of those patients has increased over the years from 50% in 2008 to 66% in 2018. On the other hand, the percentage of patients who started treatment with sulphonylurea monotherapy has decreased over the years from 24% to 7%. The percentage of patients who started treatment with combination of metformin and sulphonylurea remained relatively constant over the years (around 14%). From a cohort of patients who initiated therapy with metformin or sulphonylurea in 2014, 27% discontinued and 31% changed their therapy during the follow-up period. When compared to metformin, sulphonylurea was associated with 29% higher risk for change in antidiabetic therapy [HR 1.29 (95% CI 1.21-1.49)]. Patients under 65 years of age were more likely to change their therapy [HR 1.31 (95% CI 1.16-1.48)] compared to patients aged 65 or more.

Conclusions: Initiation of diabetes treatment with metformin monotherapy is increasing, while initiation with sulphonylurea monotherapy is decreasing. Patients who initiated treatment with sulphonylurea were more likely to change their antidiabetic therapy compared to patients who initiated therapy with metformin.

4839 | Prescribing trends of antihypertensive drugs in the United Kingdom: A 30-year assessment

Julie Rouette[1,2], James M Brophy[1,3], Tibor Schuster[1] and Laurent Azoulay[1,2]
[1]McGill University, Montreal, QC, Canada; [2]Jewish General Hospital, Montreal, QC, Canada; [3]McGill University Health Centre Research Institute, Montreal, QC, Canada

Background: Antihypertensive drugs are among the oldest and most commonly prescribed drugs among adults. To date, however, few studies have described how these drugs are being prescribed in the natural setting of clinical practice.

Objectives: To describe the incidence and prevalence of antihypertensive drugs over a 30-year period in primary care practices in the United Kingdom (UK).

Methods: We used the UK Clinical Practice Research Datalink to identify all patients at least 18 years of age with ≥1 antihypertensive drug prescription between January 1, 1989 and December 31, 2018.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

These included thiazide diuretics, other diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta blockers, and other drugs (vasodilators, centrally acting agents, ganglion blockers, and renin inhibitors). We calculated annual incidence rates (IRs) of patients with any new antihypertensive drug prescription over the total number of person-time at risk for each calendar year. We also calculated the annual prevalence of use for each antihypertensive drug class.

Results: A total of 2.7 million patients were issued 287 million antihypertensive drug prescriptions over the 30-year period. The mean age of patients newly treated with an antihypertensive drug was 55.7 years (standard deviation: 17.1) and female patients were more prevalent (54.4%). In 1989, most patients initiated their antihypertensive treatment with thiazide diuretics (IR: 20 per 100 person-years), with a slight decline by 2018 (IR: 17 per 100 person-years). In contrast, between 1989 and 2018, initiation rates for ACE inhibitors rose from 7 to 42 per 100 person-years and represented the majority of antihypertensive drugs initiated in 2018. Patients initiating ARBs also rose over time, from 0.1 per 100 person-years in 1995 (when ARBs became available) to 18 per 100 person-years in 2018. CCBs initiation rates increased from 19 per 100 person-years in 1989 to 40 per 100 person-years in 2018. Finally, the initiation of beta-blockers remained relatively stable during the 30-year period, with initiation rates of 32 per 100 person-years in 1989 to 38 per 100 person-years in 2018. In terms of prevalence of use, thiazide diuretics have seen the largest decrease of all antihypertensive drugs during the 30-year period, from a prevalence of 16% in 1989 to 9% in 2018.

Conclusions: While the initiation of thiazide diuretics slightly decreased in the last thirty years, its prevalence of use has seen the largest decrease among all antihypertensive drugs. This is likely due to the increased utilization of ACE inhibitors and CCBs.

4866 | Using the web 2.0 to inform on drug utilisation worldwide

Alessandra Spanu[1], Roman Keller[1], Milo Alan Puhan[1], Antoine Flahault[2], Christian Lovis[3], Margot Muetsch[1] and Raphaelle Beau-Lejdstrom[1]

[1]University of Zurich, Zurich, Switzerland; [2]Université de Genève, Genève, Switzerland; [3]Université de Genève, Genève, Switzerland

Background: Real-world drug utilization is often difficult to assess through traditional data sources (e.g. drug sales, prescription volumes or Electronic Health Records EHR). The appropriate use of the web 2.0 or online user-generated content could provide an easier and timely access to information on medication's utilization.

Objectives: We aim to assess characteristics of studies comparing drug utilization extracted from the WEB 2.0 to other sources.

Methods: We searched Medline, Embase, Web of Science and Scopus until November 25th, 2019. All studies assessing the utilization of any medications, vaccines, vitamins, prescription drugs and nicotine alternatives using Google trends/Insight, Facebook, Twitter and Instagram and comparing it to other data sources on drug utilization were included.

Results: Of 6,563 deduplicated publications retrieved, 16 matched our inclusion criteria. A total of nine studies found significant correlations in drug utilization between web data and comparative data for all drugs investigated, whereas two studies found correlations only for some of the drugs included. The remaining five studies used other analysis methods to evaluate the association between the two sources. Vaccines (n=5) and antibiotics (n=3) represented the two most frequently investigated drug categories. Social media and websites targeted to retrieve drug utilization data comprised Google Trends (n=10), Twitter (n=3) and other Google Search services (n=3).

Conclusions: Our results indicate the emerging potential of web data used as an alternative method to collect drug utilization data in nearly real-time without requiring expensive and time-consuming investigations.

4882 | Discontinuation and switching rates among women of childbearing age taking oral hormonal contraceptives: A retrospective cohort study in the United States

Sebastian Jugl[1,2], Amie Goodin[1,2], Carl Henriksen[1], Almut G Winterstein[1,2] and Joshua Brown[1,2]

[1]University of Florida, Gainesville, FL; [2]Center for Drug Evaluation and Safety (CoDES), Gainesville, FL

Background: Women may discontinue or switch contraceptive methods because they are dissatisfied with the method, are concerned about potential side effects, or experience side effects. The resultant gap from discontinuation accounts for an estimated 20% of unintended pregnancies.

Objectives: The objective of this study was to describe discontinuation and switching rates for oral contraceptive products in women of childbearing age in the U.S.

Methods: This retrospective cohort study utilized IBM MarketScan commercial claims data from 2005 to 2018. New users of oral contraceptives aged 15-44 were included and 12-months enrollment prior to new contraceptive use was required. Index date was the first oral contraceptive dispensing date, and specific progestin components were noted. Women were followed from index date until they switched from the index contraceptive, discontinued the index contraceptive, 12 months following initiation if maintained use of index contraceptive, end of enrolment, or end of the study period. Switching was defined as: use of a different route of administration, different dose of estrogen, or a different progestin component product. Discontinuation was defined as first 30-day gap in contraceptive use. The combined unadjusted switching and discontinuation rate were compared between progestin products.

Results: During this period, nearly 3.2 million women started an oral contraceptive and met our inclusion/exclusion criteria. The average follow-up time was about 6-months and contributed over 1.6 million

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

person-years of follow-up time. The overall switch/discontinuation (S/D) rate was 1.35 per person-year. Progestin only products, containing levonorgestrel (4.67 per person-year) and norethindrone (1.98) had the highest overall S/D rate as well as the combination product containing an older estrogen component, mestranol+norethindrone (2.22 per person-year). Other combination products of ethinyl estradiol with varying progestin ingredients had rates ranging from 1.14-1.42 and were not significantly different from each other. Discontinuations made up the majority (~80%) of observed events for all products.

Conclusions: Progestin only products and an older generation combination product had higher switching and discontinuation rates while rates of switching and discontinuation between newer generation combination products did not significantly differ. Future work will identify risk factors associated with switching and discontinuation, such as additional medication information and patient characteristics.

4912 | Comparing drug expenditures in the Scandinavian capitals

Martin Erik Nyeland[1], Love Linner[2], Kristine Olsen[3], Espen Jimenez-Solem[1], Gustaf Befrits[2] and Björn Wettermark[4]

[1]Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark; [2]Region Stockholm, Stockholm, Sweden; [3]Norwegian Institute of Public Health, Oslo, Norway[4]Uppsala University, Uppsala, Sweden

Background: Pharmaceutical expenditure has been rising rapidly in most countries, partly attributed to the introduction of new expensive medicines. In recent years the drug market has changed with an increasing number of medicines introduced in the hospital setting. Cross national comparative studies on drug utilization are valuable tools to identify areas for improvement, few such studies have been conducted in the hospital setting.

Objectives: To compare drug expenditures between three Scandinavian capital regions in the hospital setting, to identify areas for improvement.

Methods: In this cross-sectional study, we compared the top substances (ATC4th and ATC5th level) by pharmaceutical expenditure 2017-2019 between the three Scandinavian capital regions of Copenhagen (1.8 million inhabitants), Oslo (0.7 million inhabitants) and Stockholm (2.4 million inhabitants). All analyses were based on sales data including all medicines used in hospitals and dispensed medicine in ambulatory care. Comparisons at 4th level ATC included refunds and rebates for all regions.

Results: In 2019, specialist medicines administered or prescribed in the hospital setting, dominated the top-15 medicines by expenditure in all three regions. However, there were differences in the rank and volume of most of these medicines. The specialist drugs accounting for the highest spending were aflibercept, coagulation factor VIII and adalimumab in Copenhagen, Oslo and Stockholm, respectively. Comparisons on the 4th ATC level revealed that Stockholm overall had higher relative net costs for TNF-inhibitors than the two other regions.

Conclusions: The drug market has changed with specialist medicines administered or prescribed in hospitals dominating expenditure in all the three Scandinavian capitals. However, there are substantial differences between regions in rank order and expenditure. Cross national comparative studies may therefore be used to identify areas for improvement.

4917 | Antidepressant use and adherence among breast cancer patients using tamoxifen

Sara Dejene, Jihye Park, Sophie E. Mayer, Alan Kinlaw, Hazel B. Nichols, Michele Jonsson-Funk, Virginia Pate, Eliza M. Park, Katherine E. Reeder-Hayes and Jennifer L. Lund

University of North Carolina Chapel Hill, Chapel Hill, NC

Background: Tamoxifen is a selective estrogen receptor modulator that is widely used for the treatment of early and advanced stage, ER- and PR-positive breast cancer. Antidepressants may also be prescribed to manage depressive or menopausal symptoms that arise after a breast cancer diagnosis or due to anti-neoplastic treatments, including tamoxifen. While results from existing literature are conflicting, some evidence suggests that certain antidepressants may inhibit CYP2D6, an enzyme involved in tamoxifen metabolic activation, thus reducing its effectiveness.

Objectives: To characterize use of antidepressants among tamoxifen users - particularly paroxetine, fluoxetine, and bupropion, which may inhibit metabolism of tamoxifen.

Methods: Using the IBM Watson Health MarketScan databases (2000-2018), we identified women ages 18-64 with ≥1 tamoxifen prescription fill followed by ≥1 fill of an antidepressant within the next 12 months. We further required ≥1 year of continuous enrollment before and after the first antidepressant fill date. We estimated the proportion of SSRI and CYP2D6-inhibitor use in this cohort. We estimated 1-year adherence to antidepressant medications by calculating proportion of days covered (PDC) by a prescription fill, where adherence was defined using a threshold of 80%. We examined prevalence of mental health diagnoses in the year prior to the index antidepressant fill.

Results: We identified a total of 13,240 antidepressant initiators with at least one tamoxifen fill in the prior year. Median age at antidepressant initiation was 51 years (IQR: 46-55). Overall, 25.6% had a diagnosis code for depressive, anxiety, or adjustment disorder in the year prior to antidepressant initiation. SSRIs were most common class used in this population, with 41.4% receiving ≥1 fill and 36.4% whose index antidepressant was an SSRI. The most common CYP2D6 inhibitor received was bupropion (7.3%), followed by paroxetine (5.7%) and fluoxetine (5.1%). In this population, 35.3% of patients had a 1-year PDC of ≥80% for their index antidepressant, with adherence fluctuating slightly over time (32.0% in 2001, 38.7% in 2012).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: In this large commercial claims analysis, a large proportion of tamoxifen users with an antidepressant prescription had ≥1 prescription fill for an SSRI, and 17% had ≥1 fill for a known strong or moderate CYP2D6 inhibitor. Approximately one-third of patients remained adherent to their antidepressant, but further work is needed to determine whether adherence to these medications is related to concomitant use of tamoxifen among users of certain antidepressants.

4936 | Off-label gabapentin utilization for psychiatric indications using the food and drug administration adverse event reporting system database from 1993-2019

Brianna Costales, Joshua D. Brown, Carl Henriksen and Amie J Goodin
University of Florida, Gainesville, FL

Background: Gabapentin was approved in 1993 and has two narrowly defined FDA-approved indications. However, off-label gabapentin utilization is rising for a variety of conditions, most prominently for pain and psychiatric disorders. There are case reports of suicidal behavior associated with off-label gabapentin use in psychiatric disorders, but comprehensive safety evidence is limited.
Objectives: This study aimed to quantify on- and off-label utilization of gabapentin, and to examine adverse drug events (ADEs) among off-label utilization for psychiatric indications.
Methods: Combined data from the Legacy Adverse Event Reporting System and FDA Adverse Event Reporting System (FAERS) were analyzed from 1993 to 2019 Q3. Generic and brand names (Neurontin, Horizant and Gralise) were used to extract cases in which gabapentin only (i.e. combination products excluded) was reported. Cases of on-label indications (postherpetic neuralgia and partial onset seizures) were aggregated in total using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. Cases of off-label indications were aggregated in total with MedDRA high level group terms, as were ADEs, with stratification by indication and ADE type.
Results: After de-duplication, there were 8,074,989 unique ADE cases for the study period, of which 21,874 cases identified gabapentin as the primary suspect drug. Of gabapentin-primary cases, 92.9% had an off-label indication, of which 6.8% (n=1,491) were for off-label treatment of a psychiatric disorder. The top three psychiatric indications were manic and bipolar mood disorders/disturbances (n=449), anxiety disorders/symptoms (n=299), and depressed mood disorders/disturbances (n=259). Across these psychiatric indications, the most frequent ADEs were suicidal and self-injurious behaviors (18.2%) followed by therapeutic and nontherapeutic responses (6.7%).
Conclusions: Most gabapentin-associated cases in FAERS were for off-label uses, and off-label treatment for psychiatric conditions accounted for more than 1 in 20 ADEs. Gabapentin use for the top three identified psychiatric indications are not supported by evidence; no clinical trials have demonstrated gabapentin's efficacy for bipolar disorder, anxiety disorders, or depressive disorders. The most frequent ADE of suicidal behaviors echoes concerns raised by case and media reports, which warrants further investigation into the association of off-label gabapentin use with suicidality outcomes in order to improve drug safety.

4980 | Identification of opioids use disorder related emergency department visits from recently collected data of the national hospital care survey, 2016

Adewumi Adegboye
US Food and Drug Administration, Silver Spring, MD

Background: Opioid use disorders (OUD), associated with both illegal and legal prescription drugs such as heroin, oxycodone, hydrocodone, and morphine, continue to be a significant problem in the United States (U.S.). Counting and studying ED visits provides a way to better understand the morbidity associated with the problem so that we can appropriately care for these patients and plan interventions. In 2018, it is estimated that 10.3 million people, aged 12 years or older, reported having misused opioids in the past year (2). Hospital ED treatment for OUD has increased. From 2005 to 2014, it is estimated that the national estimates of OUD ED visits increased by 99% (1). The National Hospital Care Survey (NHCS) provides the opportunity to study patients' episodes of care related to OUD in hospital settings. NHCS collects all ED visits from a sample of hospitals in the U.S. The data include information on diagnoses, services received, discharge status, and patient demographics. Additionally, NHCS collects patient identifiers, providing the opportunity to link patients' episodes of care across hospital settings and to additional data sources such as the National Death Index (NDI). Although, not nationally representative, NHCS yields large datasets that permit the in-depth study of OUD ED visits.
Objectives: To use the 2016 NHCS to examine OUD related ED visits and examine other diagnosis records on these OUD related visits.
Methods: Participating NHCS hospitals submit visit information from administrative claims (UB-04) or electronic health records (EHR). This study defines OUD as any-listed diagnosis of ICD-10-CM code F11.10 to F11.99. OUD ED encounters will be examined by age, sex, and associated characteristics (e.g., current smoking status, other substances involved in the visit, and mental health disorders).
Results: In 2016, 124 NHCS hospitals submitted ED data, comprising approximately 7 million ED encounters. Of these ED encounters, 21,422 (0.3%) were identified as relating to OUD. Approximately 47% of OUD encounters were patients between the ages of 16-34. Patients between the ages of 35-54 accounted for 38% of OUD encounters and 15% were patients aged 55 and over.
Conclusions: Although NHCS data are not nationally representative, they still contain a large volume of records, and can be used to demonstrate the analytic capacity to effectively identify OUD ED visits. In addition, these data contain patient identifiable information that provide the ability to identify multiple episodes of care for a unique patient and to link to other data sources such as the NDI.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4991 | Comparison of new oral anticoagulants use in atrial fibrillation patients from pivotal clinical trials vs southern Italian real-world setting

Ylenia Ingrasciotta[1], Andrea Fontana[2], Valentina Ientile[1], Maurizio Pastorello[3] and Gianluca Trifirò[1,4]

[1]*University of Messina, Messina, Italy;* [2]*Fondazione Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy;* [3]*Palermo Local Health Unit, Palermo, Italy;* [4]*A.O.U. Policlinico "G. Martino", Messina, Italy*

Background: Patients enrolled into pivotal randomized controlled trials (RCTs) may differ from real-world (RW) patients.

Objectives: To explore the generalizability of findings from NOACs pivotal RCTs to a RW setting with atrial fibrillation (AF) from Southern Italy.

Methods: Fully anonymized data were extracted from the claims database of Palermo Local Health Unit from 2013 to 2017. In line with RCTs, incident NOAC users (washout >1 year) with AF were grouped based on the dispensed NOAC (low/high dose dabigatran/edoxaban, any dose of apixaban/rivaroxaban). The baseline characteristics of enrolled patients in NOAC pivotal RCTs were identified from the original publications and compared with those of RW setting. Individual-level RW setting data were propensity score matched 1:1 on simulated RCT patients' data by age, sex and CHADS2 score. RCT pseudo-data were generated and matched 1,000 times on the basis of RCTs descriptive statistics. At each iteration, both effectiveness (e.g. stroke/myocardial infarction) and safety (e.g. major bleeding, including gastrointestinal (GI)/intracranial bleeding (ICH)) outcomes were assessed within the matched population setting (edoxaban users excluded).

Results: Overall, 42,336 NOAC users with AF were enrolled in the pivotal RCTs in 2005-2013 vs. 7,092 incident NOACs users with AF from the RW setting in 2013-2017. In RW setting, female-male ratio was in favor of females (1.1) and patients were older (mean age: 76.0 ±8.6 yrs) than RCT population (70.7±9.2 yrs); 34.2% of these were >80 years old. After the matching, 545 (68.6%), 458 (72.1%), 1,432 (47.3%) and 1,005 (47.6%) incident NOAC RW users of low- and high-dose dabigatran, rivaroxaban and apixaban, respectively, had overlapping characteristics with pivotal RCTs population. During the follow-up, rate of ischemic stroke (IS) events was lower in high-dose dabigatran users than in low-dose dabigatran users, both from RCTs/matched RW setting. In particular, compared to RCT population, rate of IS events was lower in RW users of high-dose dabigatran (0.1 vs. 0.9 per 100 PYs; P-value=0.010). As found in RCTs, rate of GI bleeding events was higher than rate of ICH events in RW setting. However, rates of GI bleeding events were lower in RW setting than those observed in RCT setting (P-value<0.001).

Conclusions: Characteristics of AF patients treated with NOAC in RW setting are substantially different from patients enrolled in pivotal trials (e.g. much higher proportion of very old patients and females). Heterogeneity of effectiveness and safety outcomes in the RW population was observed.

4997 | Ambulatory treatment of type 2 diabetes in the United States, 2013-2019

James Heyward[1], Sudipa Sarkar[2], Jacob Christopher[1], Rita Kalyani[2] and Caleb Alexander[1]

[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [2]*Johns Hopkins School of Medicine, Baltimore, MD*

Background: Type 2 diabetes afflicts more than 30 million U.S. adults and causes significant morbidity and mortality. The landscape of non-insulin antihyperglycemic therapy in the U.S. has transformed in recent years, but changes in prescribing patterns have not been studied.

Objectives: To examine trends in the pattern of non-insulin drug treatment of type 2 diabetes, including first- and second-line therapy, from 2013 to 2019.

Methods: We conducted a descriptive analysis of cross-sectional data using the IQVIA National Disease and Therapeutic Index (NDTI), a nationally representative audit of ambulatory physician practices in the U.S. We focused on visits for type 2 diabetes among patients age 35 and older in which one or more drugs were prescribed ("treatment visits"). We assessed both first- and second-line prescribing of non-insulin antihyperglycemic therapy for type 2 diabetes between September 2013 - March 2019.

Results: Ambulatory diabetes visits decreased from 33.5 million (M) treatment visits in 2014 to 31.8M treatment visits in 2018. Overall, metformin treatment visits declined from a total of 17.5M in 2014 to 16.1M in 2018; dipeptidyl peptidase 4 inhibitor (DPP-4i) visits declined from 6.0M to 5.1M; and sulfonylureas declined from 5.1M to 3.9M. During the same time period, use of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) increased from 1.5M to 3.9M treatment visits and use of glucagon-like peptide-1 receptor agonists (GLP1-RA) increased from 1.2M to 1.8M. Among treatment visits where a single drug was prescribed, use of metformin declined from 70.0% of monotherapy in 2013 to 61.3% of monotherapy in 2019, while during the same period the share of monotherapy by GLP-1-RA increased from 2.9% to 10.4% and the share by SGLT-2i increased from 3.1% to 10.2%. Among treatment visits where metformin plus another drug was prescribed, the share of second line therapy accounted for by DPP-4i decreased from 40.5% of treatment visits in 2013 to 36.6% of treatment visits in 2019; sulfonylurea use declined from 38.8% to 21.4%; and use of SGLT-2i increased from 2.9% to 28.7%, while use of GLP1-RA increased from 6.5% to 9.2%.

Conclusions: During the past seven years, significant changes in the landscape of ambulatory care for type 2 diabetes have taken place, including modest declines in metformin monotherapy, moderate declines in second-line sulfonylurea use, and large increases in GLP1-RA and SGLT-2i use. These changes underscore the dynamic nature of drug utilization for diabetes in the U.S., and reflect life-cycle drivers including emerging evidence, evolving clinical guidelines and regulatory and payment policies.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5000 | Trends in gabapentin utilization in the United States, 2004-2016

Abisola Olopoenia, Sean Fleming and Linda Simoni-Wastila
University of Maryland, Baltimore, MD

Background: Off label use of gabapentin within the United States is currently estimated to range from 83 to 95%. Little is known about the trends in gabapentin utilization, especially among those with pain and mental health conditions.

Objectives: Our goal was to characterize the utilization of gabapentin among US adults overall, and among specific demographic (age, insurance) and clinical (chronic pain [CP], non-chronic pain [NCP], mental health disorder [MHD], neuropathic pain and opioid/benzodiazepine users) subgroups.

Methods: We conducted a retrospective longitudinal analysis using 2004-2016 Medical Expenditure Panel Survey (MEPS) data. We included all adults aged 18 and older. Clinical conditions were defined based on a diagnosis of CP (back, neck, joint, head or chronic pain), MHD (anxiety, depression, substance use disorders, personality disorders, mood disorders, adjustment disorders, and attention deficit hyperactive disorders), NCP (sprains, strains, fractures, and other connective tissue disorders) and neuropathic pain. Opioid/benzodiazepine utilization was defined as ≥1 prescription for either medication in each calendar year. We compared the annual prevalence of gabapentin utilization overall, and among demographic and clinical subgroups. Logistic regression was used to test trends over time.

Results: The study included 305,130 adults between 2004 and 2016. The annual prevalence of gabapentin users increased over the study period. The percentage of individuals who utilized gabapentin increased from 0.02% (95%CI, 0.02-0.03) in 2004 to 0.26% (95%CI, 0.24-0.28) in 2016 (p <.0001), an increase of 915.4%. All subgroups experienced increased gabapentin utilization; however, the increase in gabapentin utilization was highest among adults ≥65 (0.05% to 0.59%), publicly-insured individuals (0.04% to 0.43%), and those with CP (0.30% to 0.71%), MHD (0.04% to 0.69%), NCP (0.03% to 0.68%) and opioid/benzodiazepine users (0.08% to 0.78%.) When compared to 2004, gabapentin users in 2016 were significantly more likely to be female, publicly-insured, and diagnosed with CP, NCP, and/or MHD (p<.0001).

Conclusions: Gabapentin utilization has increased significantly over the years, especially among individuals with pain and mental health conditions. Given emerging evidence concerning gabapentin's association with respiratory depression and overdose, it is essential we comprehensively examine its ongoing utilization, especially among those who may be potentially more vulnerable to these adverse effects

5007 | Investigation of opioid analgesic use in primary care

Ömer Ataç[1], Volkan Aydın[2] and Ahmet Akıcı[2]
[1]*Department of Public Health, School of Medicine, Istanbul Medipol University, Istanbul, Turkey*; [2]*Department of Medical Pharmacology, School of Medicine, Marmara University, Istanbul, Turkey*

Background: Opioid use has been consistently reported to increase in various countries. It could be a matter of concern when it involves potent opioids due to their potential harm for the community.

Objectives: We aimed to describe utilization of opioid analgesics in the prescriptions of primary care physicians.

Methods: We analyzed all opioid-containing prescriptions of family physicians selected by systematic sampling in Istanbul in 2016. The prescriptions were included only if they contained single diagnosis to assess appropriateness of the particular indication. Drug groups were further compared by age group and gender.

Results: We identified 7,063 opioid prescriptions, where women constituted 60.9% of patients and the mean age was 49.3 ± 17.2 years. Around one in five (20.1%) of the patients who received opioid was ≥65 years old. The most common indication (12.5%) for an opioid prescription was "M79-other soft tissue disorders", followed by "R52-unclassified pain" (9.3%) and "M54-dorsalgia" (7.3%). Hypertension and gastroesophageal reflux disease (GERD) were identified among the top ten frequent conditions for opioid prescriptions (4.0% and 2.5%, respectively). Opioids were detected to constitute 39.1% (n=7,244) of all 18,540 drugs in opioid prescriptions. At ATC-4 level, "natural opium alkaloids" were the most commonly prescribed medications (81.8%), followed by "other opioids" (14.8%) and "phenylpiperidine derivatives" (3.4%). The vast majority of the prescribed opioids was codeine combinations (80.8%), followed by tramadol (9.9%) and tramadol + paracetamol combination (4.9%). In 18-64-years' age group, women were more likely to receive natural opium alkaloids (86.0%) compared to men (82.9%, p=0.006). On the other hand, men were more likely to be prescribed tramadol than were their female counterparts (56.3% vs 47.0%, respectively; p=0.004).

Conclusions: Primary care physicians seem to prefer weak opioids with a slight tendency of increased tramadol use in young-middle aged male patients. Though mostly used for acute painful conditions as expected, presence of hypertension and GERD among the top indications in encounters implies irrational opioid prescribing behaviors of the primary care physicians.

5020 | Prevalence and trend of opioid use after total knee arthroplasty in electronic health records

Zhenna Huang[1], Deepak Krishnan[2], Chantal Holy[1], Julia Hwang[1] and John Wright[1]
[1]*Johnson and Johnson, New Brunswick, NJ*; [2]*Mu-sigma, Bangalore, India*

Background: The use of opioids in United States has had a significant impact on both patients and society. Americans consume 80% of the global opioid while only having 5% of the world's population. Opioids are commonly used to treat chronic pain due to osteoarthrosis.

Objectives: This study aims to describe the prevalence of opioid use prior to primary total knee arthroplasty (TKA) and estimate the opioids use trend following TKA.

Methods: The Pan-Therapeutic electronic health records (Panther EHR) from the Optum database (2007-2019) were used to identify

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TKA patients. The EHR data were available for a geographically diverse population of 80 million patients from more than 700 hospitals and 7,000 clinics. Preoperative and postoperative opioid use was measured by the number of opioid administration orders. Patients needed to have at least three-months baseline and one-year follow-up to be eligibly included. A multivariable logistic regression was developed to investigate the factors associated with opiate use 1-year post surgery.

Results: A total of 207,065 primary TKA were included in this study. Approximately 88.7% of the population had opioid administration three months prior to surgery. The mean number (± standard deviation) of opioid administration orders per patient had increased from 4.5±4.3 (median: 4) in 2007 to 8.8±4.8 (median: 9) in 2018. The percentage of patients who had opioids prior to surgery was 70% in 2007, 84% in 2012 and 93% in 2018. Around 10% of the cohort had opioid administration three months to six months after surgery (8% in 2007, mean: 0.58±3.01 orders, 10% in 2018, mean: 0.73±3.06 orders). Around 9% of the cohort had opioid administration nine months to twelve months after surgery (6% in 2007, mean: 0.44 ±3.35, 11% in 2018, mean: 0.73±2.80). Patients with higher functional comorbidity score, being current smoker and enrollment in Medicaid and Medicare insurance were associated with higher odds of consuming opiate nine months to twelve months after surgery.

Conclusions: Approximately 88% of TKA patients use opioids within the 3 months prior to surgery and this percentage has increased 23% during the study period. From 2007 to 2018, the mean number of opioid administration orders per patient has increased from 4.5 to 8.8 orders three months prior to surgery and 0.44 to 0.73 orders nine months to twelve months after surgery.

5021 | Trends and patient characteristics in concurrent use of opioids with high-risk medications among Arizona medicaid beneficiaries, 2011-2017

Ching-Yuan Chang[1], Juan M Hincapie-Castillo[1,2], Debbie L Wilson[1] and Jenny Lo-Ciganic[1,2]

[1]University of Florida, College of Pharmacy, Gainesville, FL; [2]University of Florida, College of Pharmacy, Gainesville, FL

Background: Concurrent use of opioids with benzodiazepines (BZDs), muscle relaxants, or gabapentinoids (GABs) is associated with an increased risk of opioid overdose. In response to the US opioid epidemic, states have enacted several policies to reduce high-risk opioid prescribing in the past few years. Little is known about recent trends and patient characteristics for concurrent use of opioids with high-risk medications.

Objectives: To examine the trends and patient characteristics of concurrent use of opioids with other high-risk medications in Arizona Medicaid from 2011 to 2017.

Methods: A cross-sectional study included Arizona Medicaid beneficiaries aged 18-64 with ≥1 opioid prescription. We included patients with opioid overdose, opioid use disorder, other substance use disorders, mental health disorders, musculoskeletal pain, HIV/AIDS, or hepatitis-C virus infection diagnoses. We examined patient characteristics and annual prevalence of concurrent use (defined as ≥30 overlapping days) of opioids with BZDs, muscle relaxants, and GABs. Cochran-Armitage tests were used to evaluate trend changes of concurrent use over time. A multivariable logistic regression model was used to identify the patient characteristics associated with the likelihood of concurrent use.

Results: Among 155,382 eligible beneficiaries in 2017 (mean age=40.1±12.7, 64.6% female), 19.0% had concurrent use of an opioid with any high-risk medication. The prevalence of concurrent use increased from 2011 to 2013, and then decreased by 2017 as follows: BZDs 11.6% to 22.7% and to 6.5%; muscle relaxants 11.9% to 26.7% and to 11.0%; GABs 8.0% to 14.7% and to 10.9 % (all P_{trend}<0.0001). Asians (OR=0.43, 95% CI=0.36-0.51), African Americans (OR=0.86, 95 %CI=0.82-0.90), Hispanics (OR=0.84, 95% CI=0.78-0.91), and Native Americans (OR=0.43, 95% CI=0.40-0.46) were associated with decreased odds of concurrent use of opioid with any high-risk medications compared to white beneficiaries. Characteristics significantly associated with concurrent use were married status (OR=1.62, 95% CI=1.56-1.75), being a native English speaker (OR=2.50, 95% CI=2.32-2.69), and higher Elixhauser comorbidity index (OR=1.21, 95% CI=1.20-1.21).

Conclusions: Concurrent use of opioids with other high-risk medications among Arizona Medicaid beneficiaries decreased from 2011 to 2017. However, at the end of the study period, one in five beneficiaries had concurrent use of opioids and other high-risk medications. Our findings suggest efforts to reduce high-risk opioid prescribing continue to be needed.

5023 | Melatonin use among children, adolescents and young adults: A Scandinavian drug utilization study

Rikke Wesselhoeft[1], Peter B. Jensen[1], Poul Jennum[2], Svetlana Skurtveit[3], Randi Selmer[3], Ingeborg Hartz[3], Lotte Rasmussen[1], Johan Reutfors[4], Lena Brandt[4], Lene A. Mølstrøm[5], Mette Bliddal[1] and Anton Pottegård[1]

[1]University of Southern Denmark, Odense C., Denmark; [2]University of Copenhagen, Copenhagen, Denmark; [3]Norwegian Institute of Public Health, Oslo, Norway; [4]Karolinska Institute, Stockholm, Sweden; [5]Mental Health Services in the Region of Southern Denmark, Odense C., Denmark

Background: The use of melatonin in children, adolescents and young adults is increasingly common, although there has been no licensed indication for Scandinavian children and adolescents until this year.

Objectives: We aimed to describe and compare the use of melatonin in the young Scandinavian population from 2012 to 2018.

Methods: Aggregate-level data on melatonin use (ATC code N05CH01) in Denmark, Norway and Sweden was extracted from publicly available data sources. Analyses considered annual prevalence and total use and were performed overall (age 5-24 years) and specified by age category (in 5-year intervals), sex and country. Information

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

about defined daily doses (DDDs) were only available for Denmark and Norway.

Results: The prevalence rates of melatonin use increased in the total Scandinavian population from 2012 (7 users/1,000 inhabitants) to 2018 (20 users/1,000 inhabitants) with no marked sex differences (females: from 6 to 20 users/1,000, and males: from 8 to 21 users/1,000, respectively). Sweden had an almost fourfold increase in prevalence rates (from 7 to 25 users/1,000), whereas prevalence rates doubled in both Denmark (from 6 to 12 users/1,000) and Norway (from 10 to 20 users/1,000). The increase in prevalent melatonin use from 2012 to 2018 was most pronounced for Scandinavian 15-19 year-olds (11 to 32 users/1,000) followed by 10-14-year-olds (9 to 23 users/1,000). Throughout the study period, the total annual amount of DDDs filled by children, adolescents and young adults in Norway and Denmark doubled (from 6.3 mill DDD in 2012 to 12.9 mill DDD in 2018). The intensity of melatonin treatment was higher in Norway compared to Denmark, with 2,860 and 5,520 DDDs/1,000 Norwegians in 2012 and 2018, respectively, compared to 1,936 and 4,114 DDDs/1,000 Danes in 2012 and 2018, respectively. Treatment intensity was highest for 10-14-year-olds in both countries with 8,062 DDDs/1,000 Norwegians and 6,135 DDDs/1,000 Danes in 2018, followed by 15-19-year-olds with 6,933 DDDs/1,000 Norwegians and 5,642 DDDs/1,000 Danes.

Conclusions: The number of young Scandinavian melatonin users (particularly 10-19-year-olds) increased rapidly in the last decade. Furthermore, overall treatment intensity increased and this finding was most pronounced for 10-14-year-olds. The utilization trends are concerning given the lack of licensed indications for melatonin use in children and adolescents and the limited knowledge of its long-term consequences.

5025 | A time series analysis of opioid use in Australian nursing homes from 2014 to 2019

Lisa G. Pont[1], Dung Chun (Lydia) Ko[1] and Gerard Stevens[2]
[1]*University of Technology Sydney, Sydney, Australia;* [2]*Webstercare, Sydney, Australia*

Background: Opioid use among older adults has more than doubled over the past decade globally. Nursing home residents are high medications users and at high risk of medication related harm, yet little is known about the trends in opioid use among nursing home populations.

Objectives: To explore trends in opioid use among Australian nursing home residents from 2014-2019.

Methods: A time series analysis using pharmacy individual resident supply data for residents of 35 Australian nursing homes between April 2014 and March 2019 was conducted. The data source included all medications, both prescribed and over the counter, for all residents of the 35 nursing homes. The rate of opioid use per 100 residents was calculated quarterly for use of any opioid, as well as for individual generic agents. A generalized additive model with polynomial smoothing was fitted to the data. Polynomials of increasing order were fitted, until the model fit (R^2) was maximised. The rate of change, averaged across the entire time period, was determined using linear regression.

Results: The study cohort included 4759 nursing home residents throughout the 5-year period. The average resident age was 81.2 years and 61% of residents in the cohort were female. Opioid use increased by 2.77 residents per 100 residents throughout the study period, increasing from 29.6% of residents in 2014, to 73.9% in 2019. The increasing use was driven primarily by increasing use of oxycodone and morphine.

Conclusions: Opioid use among nursing home residents increased considerably between 2014 and 2019 and appears primarily driven by increasing use of oxycodone and morphine. Future research to determine the appropriateness and harms associated with increasing opioid use in the vulnerable nursing home population is needed.

5036 | The utilization trends of analgesics and proton pump inhibitors in Turkey

Volkan Aydin, Caner Vizdiklar and Ahmet Akici
Marmara University School of Medicine, Istanbul, Turkey

Background: Widespread use of proton pump inhibitors (PPIs) and analgesics, particularly non-steroidal anti-inflammatory drugs (NSAIDs), raises debates about their potential excessive or irrational prescribing.

Objectives: This study aimed to examine utilization trends of analgesics and PPIs in Turkey.

Methods: We obtained nationwide consumption data of analgesics (NSAIDs, opioids, and others) and PPIs between years of 2014-2017 from IQVIA. Drug utilization was measured by DDD (defined daily dose)/1000 inhabitants/day (DID) unit.

Results: During the study period, analgesic utilization increased from 65.7 to 69.7 DID. Most of the consumption was through enteral route (96.2-96.4%) and in outpatient setting (97.9-98.1%). NSAIDs constituted 82.7-84.9% of all analgesic utilization while opioids ranged 1.4-1.7%, and the rest 13.5-15.9%. Consumption of NSAIDs (mean: 57.9 DID), increased by 7.4% (from 54.3 DID in 2014 to 58.4 DID in 2017), compared to a 0.2% reduction in all other analgesics. PPI utilization was found to regularly raise from 51.7 DID in 2014 to 69.9 DID in 2017. Only 0.8-0.9% of the PPIs were used parenterally and 1.3-1.5% in hospital setting. The most frequently consumed PPIs were lansoprazol (32.2%), pantoprazol (29.5%), and esomeprazol (25.7%) in 2014 compared to the reversing of the rank as esomeprazol (30.2%), pantoprazol (28.7%), and lansoprazol (28.3%) in 2017.

Conclusions: Utilization of examined drugs in Turkey exhibit an increasing trend for NSAIDs and a much higher (35%) increment for PPIs. Existing controversies about PPI overutilization occasionally signals excessive NSAID-PPI co-prescription in non-indicated conditions. Our findings might be explained by potential triggering effect of overuse of these drug groups on use of the other.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5041 | Rural variation of the impact of medicaid expansion on naloxone access

Yue Cheng[1], Patricia Freeman[1], Minji Sohn[2], Eugene Shin[1] and Chris Delcher[1]

[1]*University of Kentucky, Lexington, KY;* [2]*Ferris State University, Big Rapids, MI*

Background: The opioid epidemic is a major public health concern in the United States. Naloxone is a life-saving medication to prevent fatal opioid overdoses.

Objectives: This study evaluated the trends in access to naloxone by rural locations over the time as well as pre- and post- Medicaid expansion.

Methods: Naloxone dispensed, payer types, and the mean naloxone prescribing rate per 100,000 population in Medicaid expansion (32 states) and non-expansion states (19 states) over the study period by rurality were evaluated. 3-digit zip codes were classified into rural and non-rural areas. For rural areas, the percentage of the rural population was further stratified into quartiles. Cross-sectional analyses were conducted to describe the trend in naloxone dispensed pre- and post- Medicaid expansion in non-rural vs. rural areas.

Results: Naloxone dispensed in rural and non-rural areas increased notably (from 4.13 to 250.79 and from 4.90 to 468.42 in rural and non-rural areas respectively). The number of naloxone paid by cash decreased over 60% in both rural and non-rural areas, whereas other payers' share increased over time (paid by Medicaid increased by 16.74% and 29.49% in rural and non-rural areas, respectively). As rurality increased, the naloxone dispensing rate increased. The mean differences of naloxone dispensing rates ranged from 0.14 to 0.57 more in rural areas compared to non-rural areas and ranged from 0.69 to 1.79 more in more rural quartile compared to less rural quartile. Visual inspection suggested an immediate effect of Medicaid expansion in rural and non-rural areas. However, higher dispensing rates were sustained in rural areas whereas the rates converged in non-rural areas. The average rate of naloxone dispensed per 100,000 after Medicaid expansion increased more significantly in rural areas compare to non-rural areas.

Conclusions: Rates of naloxone dispensing increased over the study period with higher rates of naloxone dispensing in rural areas. Medicaid expansion may have increased naloxone access, especially in rural areas.

5056 | Methylphenidate adherence and loss to follow-up in ADHD children in a tertiary care psychiatric hospital

Nichaphat Kunacharoensuk[1], Tiwarat Kamjak[1], Nootjaree Kamduang[2] and Penkarn Kanjanarat[1]

[1]*Chiang Mai University, Chiang Mai, Thailand;* [2]*Rajanagarindra Institute of Child Development, Chiang Mai, Thailand*

Background: Methylphenidate is a common and effective medication treatment for ADHD in children. Little is known about long-term methylphenidate adherence and loss to follow up in this population.

Objectives: To determine the rates of methylphenidate adherence and loss-to-follow-up 3 years after the initiation of the treatment and factors associated with methylphenidate adherence.

Methods: We conducted a cross-sectional descriptive study using patient chart review. Children 6-12 years diagnosed with ADHD receiving methylphenidate treatment at a tertiary care psychiatric hospital in Thailand during January 2008-July 2012 were included. Methylphenidate was grouped by immediate-release or extended-release formulation. Adherence, using medication possession ratio (MPR), was measured using 80% cut-off in year 1 to 3. We collected data and tested whether age, gender, IQ, type of health insurance, distance from hospital, and care giver's relationship with the child, marital status, and education were associated with methylphenidate adherence using a binomial logistic regression model. Loss to follow-up of methylphenidate treatment was measured if no hospital visit over 6 months in one year was present.

Results: The study samples (n= 197) was male (84.3%) and diagnosed with ADHD at the age of 6-7 years (57.9%). Most patients were prescribed immediate-release methylphenidate (88.8%). First, second, and third year methylphenidate adherence rates (MPR≥80%) decreased over time (66.5%, 48.7%, and 45.2%, respectively). ADHD patients with care giver with higher education were more likely to adhere to methylphenidate than patients with care giver with less education (4.44, 95% CI, 1.02-19.34). Cumulative loss to follow-up rates were 21.8%, 24.4%, and 37.6% in 3 years.

Conclusions: Methylphenidate adherence in children was suboptimal and declined over 3 years after receiving the treatment. Care giver's education was associated with methylphenidate adherence in the first year of the treatment.

5087 | Opioid agonist therapy as treatment for opioid use disorder: Comparing duration, risks and frequency of healthcare encounters

Nima Tourchian and Mina Tadrous

University of Toronto, Toronto, ON, Canada

Background: Methadone and buprenorphine/naloxone (BUP) are considered first-line treatment options for opioid use disorder (OUD).

Objectives: The objective of this study is to compare duration of treatment, risks of overdose, and the frequency of interactions with healthcare professionals among people newly starting treatment with one of these medications.

Methods: We conducted a population-based propensity-score matched cohort study in Ontario among people newly initiating methadone or BUP between October 1, 2016 and September 30, 2017 using the Ontario Narcotics Monitoring System (NMS) database. The outcome was measured at 1-year follow-up, with reference to the cohort entry date. We excluded individuals under the age of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

18, individuals who had a methadone or BUP prescription in the 180 days prior to cohort entry, and those with missing unique identifiers. Individuals were assigned to two exposure groups; 1) Individuals newly initiating methadone, and 2) Individuals newly initiating buprenorphine/naloxone. We defined ongoing treatment on the basis of successive refills for the same medication within 30 days. The primary outcome was fatal or non-fatal opioid overdose using hospitalization visits and coronial records. Secondary outcomes included number of outpatient visits for OUD, and time to receipt of a 7-day take-home supply. We used Cox Proportional Hazards regression and Poisson models to compare outcomes between treatment groups.

Results: After 1 year, 45.6% of people initiating methadone and 29.6% of those initiating BUP continued treatment. Those initiating BUP had a similar risk of opioid overdose (adjusted Hazard Ratio (aHR) 0.85, 95% CI 0.62-1.17), but a lower risk of opioid overdose while on treatment (aHR 0.59, 95% CI 0.39-0.88). Compared to those starting methadone. Those treated with BUP also had a lower rate of outpatient visits for OUD (adjusted Rate Ratio 0.74, 95% CI 0.72-0.76) and were more likely to receive a weekly take-home dose over follow-up (aHR 2.63, 95% CI 2.43-2.85).

Conclusions: There are important differences in the risk of overdose and requirements for frequent healthcare encounters for people starting treatment with methadone and BUP, that can be explained by their differences pharmacologically, and in their models for delivery.

5098 | Dupilumab treatment trends among patients with atopic dermatitis

Maria Schneeweiss and Sebastian Schneeweiss
Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background: Dupilumab is the first systemic biologic immunomodulating agent specifically approved for the treatment of severe atopic dermatitis (AD) in the US. Its use pattern is unknown.

Objectives: This study sought to characterize systemic treatment patterns among patients with AD since the approval of dupilumab.

Methods: We used longitudinal claims data from commercially insured patients in the US, from January 2017 through July 2019. We identified patients of all ages diagnosed with AD, who escalate treatment to a systemic agent, *i.e.*, dupilumab, methotrexate, mycophenolate, cyclosporine or azathioprine. Cohort entry date was the first use of a systemic treatment for AD defined as not having used any systemic treatment during the 180 days before cohort entry. We excluded patients with the following: (1) less than 180 days of continuous enrollment before cohort entry, (2) less than at least 2 diagnoses of AD within 180 days prior to initiating systemic treatment or (3) a range of non-AD conditions that have an indication for treatment with the systemic agents of interest.

Results: We identified 690 patients with AD who were completely naïve to systemic treatment and started treatment to a systemic agent after March 1, 2017. 61% started on dupilumab, 16 % on methotrexate, 15% on cyclosporine, 5% on mycophenolate, 3% on azathioprine and 0.2% started on cyclosporine plus dupilumab. The first change from the initial systemic agent includes 97% stopped systemic treatment, 1% switched to dupilumab, 2% switched to dupilumab plus either cyclosporine, mycophenolate, or methotrexate. The second change includes 9% stopped systemic treatment, 28% switched to dupilumab, 39% to cyclosporine, 9 % to mycophenolate, 8% to azathioprine, and 6% to methotrexate. 3 months after initial treatment with a systemic treatment 25% of patient had discontinued treatment, 62% used dupilumab, 6% methotrexate, 3% cyclosporine, 2% mycophenolate, 1% azathioprine, 1% used dupilumab plus either cyclosporine, methotrexate, azathioprine, or mycophenolate. After 6 months, 49% of patients had discontinued treatment, 42% used dupilumab and after 1 year, 77% of patients had discontinued treatment, and 20% used dupilumab.

Conclusions: Among those patients with AD who started a systemic treatment the proportion of dupilumab initiators was surprisingly high shortly after its initial marketing. It was also the preferred 2nd and 3rd line treatment although absolute numbers are still small.

5104 | Secular trend and determinants of hydroxyurea use among commercially insured adults with sickle cell disease, 2005-2018

Motomori O. Lewis and Yu-Jung Jenny Wei
University of Florida, Gainesville, FL

Background: Hydroxyurea is the principal disease-modifying therapy to prevent vaso-occlusive crisis (VOC) and acute chest syndrome in patients with sickle cell disease (SCD). For adults with SCD, treatment is often stymied by the transition from childhood to adulthood, which introduces challenges in provider access, healthcare coverage, and disease severity. Though treatment patterns in children have been well studied, limited data exist on recent trends in hydroxyurea uptake in this vulnerable adult population.

Objectives: This study aims to determine the annual prevalence, trend, and determinants of hydroxyurea use among adults with SCD.

Methods: We conducted a multi-year, cross-sectional study using the 2005-2018 IBM MarketScan administrative claims database of a commercially insured US population. The study sample included adults aged 18 to 64 years who had 1) at least one inpatient visit, or 2 outpatient visits at least 30 days apart with an ICD-9/10 diagnosis for SCD; and 2) continuous enrollment in health and drug benefits 6 months before (baseline) and 6 months after (follow-up) the first SCD diagnosis in a given year. We excluded patients with sickle cell trait, malignant cancer, chemotherapy, bone marrow transplant, or solid organ transplant within the baseline period. Hydroxyurea use was measured by at least one prescription fill during follow-up. The trend in prevalence and determinants of hydroxyurea use were evaluated with a multivariable modified Poisson regression model.

Results: We identified 12,155 adults with SCD—62.1% were females and 36.2% were between 18-29 years of age. Of this sample, 14.3% received hydroxyurea. Use of hydroxyurea increased significantly between 2005 and 2018 (adjusted prevalence relative ratio (PRR)

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

= 1.39; 95% confidence interval (CI) = 1.19, 1.62). Females were less likely to receive hydroxyurea than males (PRR = 0.79; 95% CI = 0.73, 0.85). Individuals with at least one hospitalization for VOC in the baseline period were more likely to receive hydroxyurea than those without any hospitalizations for VOC (PRR = 1.99; 95% CI = 1.87, 2.11).

Conclusions: Among US commercially insured adults diagnosed with SCD, hydroxyurea uptake increased over time, but its prevalence remains low. Further studies are warranted to assess the impact of not having hydroxyurea in adults with SCD.

5137 | Prevalence, patterns, and risk factors of psychotropic polypharmacy among individuals with depressive disorder in Mainland China: A cross-sectional analysis based on a National Health Insurance database in 2015

Jingyuan Zhang, Guoxu Wei, Xiaodong Guan and Luwen Shi
Peking University, Beijing, China

Background: Psychotropic polypharmacy is reported common in the practice for individuals with depressive disorder, despite the limited supporting evidence and increased risk for adverse drug reactions and drug-drug interactions. The current status in China is largely unknown.

Objectives: To investigate the prevalence, patterns, and risk factors of psychotropic polypharmacy among individuals with depressive disorder in mainland China.

Methods: A cross-sectional analysis was conducted based on China's National Survey of Medical Service Utilization for Basic Medical Insurance Beneficiaries in 2015. Individual's demographic, diagnostic, and drug utilization information were extracted. International Classification of Diseases 10th Revision (ICD-10) was applied to identify persons with depressive disorder in 2015. According to the Anatomical Therapeutic Chemical classification system 4^{th} level, psychotropic polypharmacy was defined as the receipt of ≥2 psychotropic drugs from different classes in at least one medical encounter in 2015. Logistic regression was employed to determine the risk factors associated with psychotropic polypharmacy.

Results: 2337 (44.5%) out of 5240 individuals with depressive disorder were exposed to multiclass psychotropic polypharmacy in 2015. The most common psychotropic polypharmacy was selective serotonin reuptake inhibitors (SSRI) with benzodiazepines derivatives (21.1%), followed by SSRI with antipsychotics such as diazepines, oxazepines, thiazepines and oxepines (9.3%), other antidepressants with benzodiazepines derivatives (8.3%), and combinations of SSRI with other antidepressants (7.4%). Results of Logistic regression showed that adults (OR 3.61, 95%CI 1.73-7.83) and elderly patients (OR 3.01, 95%CI 1.44-6.57), individuals with inpatient encounters (OR 7.67, 95%CI 6.31-9.36), or those with more than three hospital visits (OR 3.39, 95%CI 2.99-3.85) were far more likely to receive psychotropic polypharmacy, while those who had a job (OR 0.42, 95%CI 0.33-0.53) or with somatic chronic conditions (OR 0.40, 95%CI 0.31-0.53) were less likely to be exposed to psychotropic polypharmacy.

Conclusions: Psychotropic polypharmacy among persons with depressive disorder is common in China, despite limited evidence of risks and benefits. Particular attention is required for adults with more intense, but not optimal medical utilization.

5147 | Utilization patterns of multiple sclerosis medications in Saudi Arabia: A cross-sectional retrospective study

Zakiyah Alkherb, Almaha Alfakhri, Maha Alrasheed and Tariq Alhawassi
College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Background: Multiple sclerosis (MS) is a chronic disease of the central nervous system. Although there is no cure for MS, several disease-modifying drugs (DMDs) are available. Data on the utilization patterns of DMDs among patients with MS in Saudi Arabia are limited.

Objectives: To describe treatment patterns in patients with MS in Saudi Arabia.

Methods: A cross-sectional retrospective study was conducted in a large tertiary university hospital in Riyadh, Saudi Arabia. Study data were derived from the hospital electronic information system during the period from June 9, 2019 to July 25, 2019. Patients age 18 years and older with a documented MS diagnosis who received at least one of the DMDs during the period from 2016 to 2018 were included. A number of demographic and clinical characteristics were evaluated. DMDs used as initial treatment were evaluated and medication discontinuation or switching were assessed. Comorbid conditions and the use of concomitant medications were identified. Categorical variables were summarized by frequency and percentage. Continuous variables were reported as mean and SD. All analysis was conducted using SPSS version 22.

Results: A total of 422 MS patients were included. The mean age was 34.4±9.40 years and 70.9% were females. The majority of patients (48.8%) had a diagnosis Relapsing-remitting MS subtype, however, 46.2% of patients with no subtype documentation. Interferon was the most commonly prescribed initial treatment in 77.49% of patients, followed by Fingolimod and Natalizumab with (11.84, 6.87%) respectively. More than half of the patients (59.72%) remained on their initial treatment and did not require treatment alteration and were less likely to have comorbid conditions (55.2%). The most common reasons for switching or stopping initial treatment were adverse drug reactions, followed by compliance issues, then disease progression, equally (34.7, 18.82 and 17.06%) respectively. Interferon initiators were more likely to remain on their medication (69.84%) and less likely (80.4%) to have comorbid conditions.

Conclusions: Most MS patients started on interferon and more likely required no treatment alteration. The practice is not based on local guidelines. Comorbidities were treated rather than the MS itself.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Geriatric Pharmacoepidemiology

55 | Oral anticoagulants and risk of acute liver injury in patients with nonvalvular atrial fibrillation: A propensity-weighted nationwide cohort study

Géric Maura[1], Marc Bardou[2], Cécile Billionnet[1], Alain Weill[3], Jérôme Drouin[3] and Anke Neumann[3]

[1]French National Health Insurance (Caisse Nationale de l'Assurance Maladie/Cnam), Paris, France; [2]Clinical Investigation Center, Clinical Epidemiology/Clinical Trials Unit, Dijon-Bourgogne University Hospital, Dijon, France; [3]EPI-PHARE Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM) and French National Health Insurance (Cnam), Saint-Denis, France

Background: Insufficient real-world data on acute liver injury (ALI) risk associated with oral anticoagulants (OACs) exist in patients with nonvalvular atrial fibrillation (NVAF), especially in patients with no prior liver disease (LD) and in those with a history of chronic alcoholism.

Objectives: To compare the 1-year risk of serious ALI between each non-vitamin K antagonist (VKA) oral anticoagulant (NOAC: dabigatran, rivaroxaban, apixaban) and VKAs.

Methods: Using data of the French national healthcare database (Régime Général, 54 million beneficiaries), a propensity-weighted nationwide cohort study was performed in NVAF patients initiating OACs from 2011 to 2016, considering three different populations: patients (i) with no prior LD as main population, (ii) with prior LD, (iii) with a history of chronic alcoholism. A Cox proportional hazards model was used to estimate the hazard ratio (HR) with 95% confidence interval (95%CI) of serious ALI (hospitalised ALI or liver transplantation) for each NOAC versus VKA.

Results: In patients with no prior LD (N=434,015), 218 experienced an ALI. Dabigatran and apixaban new users were not at increased risk of serious ALI compared to VKA initiation (adjusted HR: 1.17 [95%CI 0.79-1.75] and 0.82 [0.53-1.25], respectively) unlike rivaroxaban new users (1.41 [1.05-1.91]). This latter association was no longer observed in the sensitivity analyses (propensity score trimming, weight truncation) as it was mainly due to a very small number of patients treated contrary to the prediction. No increased risk was observed in patients with prior LD (N=12,961; 82 experienced an ALI). In patients with chronic alcoholism history (N=13,173; 68 experienced an ALI), only those initiating dabigatran were at increased risk of serious ALI compared to VKA (2.88 [1.74-4.76]). A control outcome (a proxy for elevation of transaminases) suggested that differential clinical follow-up between groups might partly explain this association (no regular blood monitoring needed for NOAC patients in contrast with VKA patients).

Conclusions: The results of this cohort study do not suggest an increased risk of ALI in NOAC versus VKA patients with NVAF during the first year of treatment.

61 | Population based prevalence of selected high priority prescribing cascades among patients with Alzheimers disease and related dementia

Sonal Singh[1], Noelle Cocoros[2], Kevin Haynes[3], Vinit Nair[4], Inna Dashevsky[5], Thomas Harkins[6], Paula Rochon[7], Richard Platt[8], Sybil Crawford[1], Kathleen Mazor[1], Kathryn Anzuoni[1], Sarah Bloomstone[1] and Jerry Gurwitz[1]

[1]University of Massachusetts Medical School & Meyers Primary Care Institute, Worcester, MA; [2]Harvard Medical School and Harvard Pilgrim Healthcare Institute, Boston, MA; [3]HealthCore, Wilmington, DE; [4]Humana Inc, Louisville, KY; [5]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [6]Humana Healthcare Research Inc, Miami, FL; [7]Women's College Research Institute University of Toronto, Toronto, ON, Canada; [8]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: Prescribing cascades (PCs) occur when a healthcare provider prescribes a second, potentially unnecessary drug therapy to address the side effect of a drug. Population based estimates of PCs among patients with Alzheimer's disease and related dementias (ADRD) are limited.

Objectives: We estimated the incidence of Calcium channel blocker-diuretic (CCB-diuretic) and antipsychotic/antiemetic-antiparkinsonism drug PC among older adults treated for ADRD in two large US health plans

Methods: We identified members aged 50+ who had been treated with an ADRD drug in the 365 days prior to or on Jan 1, 2017. Participants were enrolled in medical and pharmacy coverage for 1 year before and through cohort entry date, bridging enrollment gaps up to 45-days. We excluded participants with an institutional stay encounter and censored members based on first of: disenrollment from medical or pharmacy coverage, death, or end of data. We identified incident and prevalent CCB use and identified incident diuretic use separately among both incident and prevalent CCB users. Incident diuretic use was defined as diuretic use during day 8 through day 365 of CCB use after a washout period of 183 days. Similar methods were used to identify the antipsychotic/antiemetic-antiparkinsonism PC.

Results: There were 121,538 participants with ADRD eligible for inclusion. Approximately 62% were female, with a mean age of 79.5 (SD ± 8.6). Their Combined comorbidity index, a measure of comorbidity was 3 (SD ± 2.7). The mean number of generic drugs used was 9.2 (SD ± 4.9). Overall 2.1% of the ADRD cohort experienced the CCB-diuretic PC with 1586 incident diuretic users among 36,462 prevalent CCB users (4.3%) and 161 incident diuretic users among 3304 incident CCB users (4.8%). Overall 0.3 % of the ADRD cohort experienced the anti-psychotic/antiemetic-antiparkinsonism PC. There were 306 incident antiparkinsonism drug users among 20,746 prevalent antipsychotic/antiemetic drug users (1.4%); and 36 incident antiparkinsonism drugs users among 4534 incident antiparkinsonism/antiemetic users (0.8%).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Among two large nationally representative health plans in the United States, the burden of CCB-diuretic and anti-psychotic/antiemetic-antiparkinsonism PC was low. Administrative databases can be used to determine the burden of prescribing cascades.

131 | Potentially inappropriate use of non-steroidal anti-inflammatory drugs in the general older German population

Thi Ngoc Mai Nguyen[1,2], Dana Clarissa Laetsch[2] and Ben Schöttker[2,1]
[1]*Network Aging Research, University of Heidelberg, Heidelberg, Germany*; [2]*Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany*

Background: Non-steroidal Anti-inflammatory Drugs (NSAIDs) are listed as potentially inappropriate drugs (PIM) for adults aged 65 years and older in all frequently used PIM lists due to their negative risk-benefit profile in this population. However, these lists strongly differ in listed active substances and circumstances, in which NSAIDs could be indicated and thus should not be considered as PIM. So far, few studies compared different PIM lists, and none has focused on NSAIDs.
Objectives: The aims of this study were to compare the differences in the prevalences of NSAIDs - PIM use in a sample of the general older German population according to the recommendations of 5 PIM lists: Beers criteria, PRISCUS list, the EU(7)-PIM list, the STOPP criteria and the FORTA list and to identify the determinants of NSAIDs - PIM use.
Methods: We conducted a cross-sectional survey using the 14-year follow-up data from a population-based cohort study from Germany. Participants aged 65 years or older who reported the use of NSAIDs were included (n=287). Drug data were obtained according to the "brown bag method," which ensures the inclusion of over-the-counter preparations. To detect whether an NSAID is also a PIM, the 2019 Beers criteria, the 2015 STOPP criteria, the EU(7)-PIM list, the PRISCUS list, and the FORTA list were used. Multivariate logistic regression models were used to assess the determinants of NSAIDs-PIM use according to the 5 different PIM lists. Two-sided p-values < 0.05 were considered to be significant.
Results: Prevalence of NSAIDs -PIM use varied greatly among the PIM definitions used: STOPP criteria (54.7%), Beers criteria (45.6%), EU(7)-PIM list (29.6%), FORTA list (21.3%) and PRISCUS list (3.5%). 27% of all NSAIDs -PIM users would be only identified by one list, whereas none of them would be identified by all five lists. Determinants of NSAIDs -PIM use also varied by the PIM list used. For example, for the STOPP criteria, cardiovascular disease (CVD), chronic kidney disease (CKD), gout and peptic ulcer disease (PUD) were statistically significantly associated with the use of NSAIDs - PIM among NSAIDs users (Odds ratios [95% confidence intervals]: 4.91 [2.46, 10.24], 12.51 [5.28, 34.11], 2.22 [1.01, 5.04] and 5.46 [2.16, 15.47], respectively).
Conclusions: The recommendations of currently available PIM lists for NSAIDs highly vary and there is an urgent need for harmonization in order to provide better guidance to physicians for the prescription of NSAIDs for older adults.

2334 | Concomitant use of benzodiazepines and opioids and risk of fractures in older adults with chronic non-cancer pain in South Korea, 2011-2015: A nested case-control study

Ye-Jin Kang, Hyun-Ji Koo, Min-Taek Lee, Seung-Hun You, Myo-Song Kim, Ji-hye Seo and Sun-Young Jung
Chung-Ang University, Seoul, Republic of Korea

Background: Although benzodiazepines (BZDs) and opioids are each associated with an increased risk of fractures, the level of the risk associated with the combined use of these drugs is uncertain.
Objectives: To investigate the relationship between the combined use of BZDs and opioids with the risk of fractures in older patients with chronic non-cancer pain.
Methods: In this nested case-control study, we used the National Health Insurance Service-National Sample Cohort database of Korea from 2002 to 2015. Among osteoarthritis or low back pain patients (>64 years), cases were defined as the incident diagnosis of hip, humerus or forearm fracture between 2011 and 2015. For each case, up to four controls were matched using age (within 5 years), sex, and cohort entry date. We categorized BZDs exposure windows as current, recent and past use and defined current BZDs exposure as use within 30 days before index date, recent BZDs exposure as use within 31-90 days before index date and past BZDs exposure as use within 91-365 days before index date. We categorized each exposure to BZDs with and without opioids. We estimated adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of combined use of BZDs and opioids using conditional logistic regression analysis, adjusting for concomitant diseases and concomitant medications. We also performed subgroup analysis according to age groups, type of fracture, the presence of osteoporosis and an antidepressants prescription.
Results: We identified 3,487 cases and 12,350 controls. Among them, 81.8% of cases and 82.0% of controls were female, and mean ages were 75.2 (±6.5) and 74.7 (±6.0) years respectively. The aORs (95% CIs) for current use of BZDs + opioids and BZDs alone were 1.34 (1.15-1.57) and 1.04 (0.91-1.17), each compared to non-use. In subgroup analysis of hip fracture, aORs for current use of BZDs + opioids and only BZDs were 1.55 (1.16-2.06) and 1.04 (0.82-1.33) respectively. The aORs for current use of BZDs + opioids were 1.25 (1.03-1.51) in patients with osteoporosis, and 1.06 (0.89-1.25) in patients without osteoporosis. Finally, the aORs for current and past use of BZDs + opioids in patients had a prescription of antidepressants were each 1.44 (1.21-1.72) and 1.31 (1.05-1.64). There was no association with these outcomes in patients without a record of antidepressants.
Conclusions: Concomitant use of BZDs and opioids was associated with an increased risk of fractures in older adults with chronic non-cancer pain.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2414 | Nonselective beta-blocker eyedrops and the risk of fall-related injuries: A danish nationwide active comparator, new user propensity score matched cohort study

Sidsel Arnspang Pedersen[1], Mette Reilev[1], Lars Christian Lund[1], Daniel Henriksen[1], Bjarke Viberg[2] and Jesper Ryg[3]
[1]*University of Southern Denmark, Department of Clinical Pharmacology and Pharmacy, Odense, Denmark;* [2]*Lillebælt Hospital, Kolding, Denmark;* [3]*University of Southern Denmark, Department of Clinical Research, Odense, Denmark*

Background: Falls in older patients represent a major public health issue. Risk factors for falls are multifactorial and include the use of commonly prescribed medication such as betablockers. Timolol is a non-selective beta-blocking eye drop agent used in the treatment of glaucoma. Due to high systemic absorption, the use of timolol eye drops may cause alterations in heart rate and rhythm potentially increasing falls risk. However, this has not been investigated in older adults.

Objectives: To investigate the risk of injurious falls in older patients using topical non-selective betablockers compared to prostaglandin analogues.

Methods: We conducted an active comparator, new user cohort study using information on redeemed prescriptions and hospital discharge diagnoses from the Danish nationwide registries. We identified all patients ≥65 years, who initiated either timolol eye drops or topical prostaglandin analogues and matched them in a 1:1 ratio, based on a high-dimensional propensity score. The **primary outcome was injurious falls (defined as** contusion, wounds and fractures other than hand and feet**) within 90 days after a first prescription of either drug. Fall-related fractures was used as a secondary outcome.**

We obtained incidence rate ratios (IRR), incidence rate differences (IRD), and the number needed to treat to harm one additional patient (NNTH) for both unmatched and matched cohorts.

Results: In total, 40,420 older adults were identified as users of timolol and 55,754 as users of prostaglandin analogues. Of these, 43% were male and the median [IQR] age was 75 [70-80] years. For the unmatched cohort, the IRR of injurious falls was 1.20 (95% CI 0.98-1.49), IRD was 4 (0-8) cases per 1000 person years, and NNTH was 1,695 for one year of treatment with timolol compared to prostaglandin analogues. In the propensity score matched cohort we identified 28,431 first users of timolol eye drops and 28,431 users of prostaglandin analogues. The IRR of injurious falls was 0.96 (95%CI 0.73-1.27), IRD -1 (95% CI -6 to 5) per 1000 person years, and a number needed to treat for one year to prevent one additional case of 12,500. For fall-related fractures, the IRR was 1.30 (95% CI 0.96-1.76), IRD of 4 cases per 1000 person years and a NNTH of 252.

Conclusions: We found no increased risk of injurious falls after initiation of timolol eyedrops in an older Danish population.

2536 | Prescription drugs among dementia patients with behavioral disturbance

Wenjun Zhong, Xinyue Liu, Tiffini Voss, Sauzanne Khalilieh, Rezaul Karim Khandker1 Khandker, Edward Bortnichak and Kai-Li Liaw
Merck, North Wales, PA

Background: Behavioral disturbance (BD) in dementia patients is common and requires many healthcare resources, but there have been no FDA approved medications for this indication.

Objectives: This study examined real-world medication use in dementia patients with BD to inform future new drug investigational studies.

Methods: A cross-sectional study was conducted using Truven MarketScan Commercial and Medicare Supplemental database for outpatient medication use in Oct 2015-Dec 2018. Patients with two outpatient or one inpatient dementia diagnosis were identified through ICD-10-CM codes, and the first event of BD (including agitation, aggression, psychosis, delirium, and wandering) at or after the dementia diagnosis was identified through ICD-10-CM codes as the index BD. Medications prescribed before (days' supply should cover BD index date) and after BD index date (within 6 months) were identified through National Drug Code. All the medications used in this population were counted and the frequencies were reported both in therapeutic classes and in generic names.

Results: Among 232,921 patients with dementia during Oct 2015-Dec 2018, 83,024 (36%) had at least one BD event after dementia diagnosis during the same time period. Of these BD patients, the mean (standard deviation) age was 81 (13) years at the time of index BD (90% of the population were >=65 years, and 50% were >=85 years); about 60% were female. Among them, 85% (n=70,481) received prescriptions before or after the index BD event. Top 5 prescription classes were antidepressants (60%), antihyperlipidemic drugs (45%), beta blockers (40%), parasympathomimetic drugs (39%) and tranquilizers/antipsychotic drugs (37%). Top 5 drugs prescribed before BD index event were donepezil (20%), levothyroxine (18%), atorvastatin (16%), memantine (15%), and amlodipine (13%). Top 5 drugs prescribed after BD index event (within 6 months) were donepezil (27%), levothyroxine (21%), memantine (21%), atorvastatin (20%), and quetiapine (19%). Other central nervous system drugs (top 5 CNS) prescribed after BD index event were sertraline (13%), mirtazapine (12%), trazodone (12%), lorazepam (11%) and escitalopram (10%).

Conclusions: Patients with dementia and BD were an older population. A large proportion of them were exposed to prescription medications including CNS drugs such as antidepressants and antipsychotics. There is an unmet medical need in this population since this patient population is susceptible to the side effects of antidepressants and antipsychotics. This study provided real-world medication use data for future new drug investigational studies for dementia patients with BD.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2599 | Anticholinergic and sedative drug load among medicare beneficiaries

Shahar Shmuel[1], Virginia Pate[1], Marc J. Pepin[2], Janine C. Bailey[2], Laura C. Hanson[3,4], Til Stürmer[1], Rebecca B. Naumann[1,5], Yvonne M. Golightly[1,5,6,7], Danijela Gnjidic[8] and Jennifer L. Lund[1]

[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Durham Veteran Affairs (VA), Durham, NC; [3]Division of Geriatric Medicine & Palliative Care Program, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Injury Prevention Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [6]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [7]Division of Physical Therapy, University of North Carolina at Chapel Hill, Chapel Hill, NC; [8]Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

Background: Medications with anticholinergic and sedating properties are widely used among older adults despite strong evidence of their harm. The Drug Burden Index (DBI), a clinical screening tool that incorporates dose and cumulatively measures these properties across drug classes, may identify patients at high risk of physical and cognitive function-related adverse events. However, the DBI has been studied mainly outside the US, and not using US Medicare claims.

Objectives: We developed an updated US-based DBI drug list and operationalized the DBI for Medicare claims, and used this framework to (1) measure the monthly distribution based on mean daily DBI, (2) identify patient-level predictors of high mean daily DBI exposure, and (3) describe temporal trends in the prevalence of several DBI thresholds.

Methods: We screened medications for DBI properties and operationalized the DBI for Medicare claims. We then conducted a retrospective cohort study of a 20% random, nationwide sample of 4,137,384 fee-for-service Medicare beneficiaries aged 66+ years (134,757,039 person-months) from 2013 to 2016. We measured the monthly distribution based on mean daily DBI, categorized as (1) >0 vs. 0 (any use) and (2) 0, 0<DBI<=1, 1<DBI<=2, and DBI>2, and examined temporal trends. We described patient-level factors (e.g., demographics, healthcare use, and health status) associated with high (>2) versus low (0<DBI<=1) DBI exposure.

Results: The person-month distribution of the mean daily DBI was: 58.1% DBI=0, 29.0% 0<DBI<=1, 9.3% 1<DBI<=2, and 3.7% DBI>2. The estimated annual period prevalence of any (>0) DBI exposure decreased slightly over the study period, while the monthly point prevalence was stable. Predictors of high monthly DBI exposure (>2) included certain indicators of increased healthcare use (e.g., high number of drug claims), white race, younger age, low-income subsidy, frailty, and a psychosis diagnosis code.

Conclusions: This study operationalized the DBI in Medicare claims and described patterns of DBI exposure over time. The predictors of high monthly DBI exposure can be used to inform discussions between patients and providers about medication appropriateness and potential de-prescribing. Future studies should assess the association between the DBI and adverse events among Medicare patients.

2611 | The risk of fractures, acute myocardial infarction, atrial fibrillation and ventricular arrhythmia in geriatric patients exposed to promethazine

Maurizio Sessa, Dr[1], Annamaria Mascolo[2], Kim Dalhoff, Dr[3] and Morten Andersen, Dr[1]

[1]University of Copenhagen, Copenhagen, Denmark; [2]University of Campania "L. Vanvitelli", Napoli, Italy[3]Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark

Background: The risk of development of adverse drug reactions to first-generation anti-histamine receptors 1 (H1) is increased in the geriatric population due to physiological changes associated with aging and the age-associated high number of potentially interacting medications. From more than two decades, the American Geriatrics Society has recommended that first-generation anti-H1 with enhanced anticholinergic activity (i.e. promethazine) should be avoided in individuals aged 65 or more. However, to date, on an international perspective, evidence helpful for health policy-makers such as studies from routine clinical practice investigating the safety profile of promethazine in comparison to other therapeutic alternatives are scarce and needed. Additionally, it is unknown if the risk of experiencing these clinical outcomes is extended to all geriatric patients independently of their clinical and socio-demographic characteristics or if the risk is circumscribed to specific sub-populations (i.e. patients with a specific set of comorbidities).

Objectives: This study aimed to compare the risk of fractures, acute myocardial infarction, atrial fibrillation, and ventricular arrhythmia among Danish citizens aged ≥ 65 which were new users of promethazine or domperidone, triazolam, loratadine, and betahistine. Secondly, the study aimed to perform a risk stratification to identify the most relevant predictors for the study outcomes.

Methods: The study period was 01/01/2015 to 31/12/2016. The data sources were the Danish registers. Each patient was followed for 90 days. A logistic regression model was used to compute the unadjusted and adjusted odds ratios (OR), and a conditional inference tree was used to identify the most relevant predictors for the study outcomes.

Results: Promethazine had a higher risk of hospitalization for atrial fibrillation than loratadine and betahistine (OR 1.58; 95% CI 1.07-2.63 and OR 3.22; 95% CI 1.69-7.14, respectively). For fractures, acute myocardial infarction, and ventricular arrhythmia hospitalizations, no statistically significant differences were found among drugs under investigation. The medical history of cardiac arrhythmia (OR 4.14; 95% CI 2.94-5.78, p<0.0001) was the most relevant predictor for atrial fibrillation hospitalizations.

Conclusions: This study found an increased risk of atrial fibrillation hospitalization among promethazine users, and the risk was higher among patients with prior cardiac arrhythmia.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2612 | Metoprolol versus carvedilol in patients with heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and renal failure

Maurizio Sessa[1], Daniel B Rasmussen[2], Magnus T Jensen[3], Kristian Kragholm[4], Christian-Torp Pedersen[5] and Morten Andersen[1]
[1]*University of Copenhagen, Copenhagen, Denmark;* [2]*Naestved Hospital, Næstved, Denmark;* [3]*Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark;* [4]*Aalborg University Hospital, Aalborg, Denmark;* [5]*Nordsjaellands Hospital, Hillerød, Denmark*

Background: In heart failure patients, it is not uncommon to find patients with heart failure, chronic obstructive pulmonary disease, and diabetes mellitus, but currently, none of the most authoritative clinical practice guidelines provide recommendations on which β-blocker should be used. A recent study suggested that physicians prefer carvedilol to other β-blockers in this clinical scenario. However, evidence supporting this clinical practice is missing.

Objectives: This study aims to compare the survival and the risk of heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypoglycemia, and renal failure hospitalizations in geriatric patients with heart failure, chronic obstructive pulmonary disease, and diabetes mellitus exposed to carvedilol or metoprolol. Additionally, this study aims to identify the most import predictors for these study outcomes by using an artificial intelligence technique and to evaluate subpopulations of interest such as patients with concurrent lipid disorder or chronic kidney disease.

Methods: Data sources were Danish administrative registers. Patients aged ≥65 and having heart failure, chronic obstructive pulmonary disease, and diabetes mellitus were followed for 1 year from the first β-blocker prescription redemption. Patients' characteristics were used to 1:1 propensity score match carvedilol and metoprolol users. A Cox regression model was used to compute the hazard ratio (HR) of study outcomes. For statistically significant associations, a conditional inference tree was used to assess predictors most associated with the outcome.

Results: In total, 1,424 patients were included. No statistically significant differences were observed for survival (HR 0.86; 95% confidence interval [CI] 0.67 to 1.11, p = 0.240) between carvedilol/metoprolol users. The same applied to chronic obstructive pulmonary disease (HR 0.88; 95% CI 0.75 to 1.05, p = 0.177), diabetes mellitus (HR 0.95; 95% CI 0.82 to 1.10, p = 0.485), hypoglycemia (HR 0.88; 95% CI 0.47 to 1.67, p = 0.707), and RF (HR 1.25; 95% CI 0.93 to 1.69, p = 0.142) hospitalizations. Carvedilol users had a 38% higher hazard then metoprolol users of heart failure hospitalization during the follow-up period (HR 1.38; 95% CI 1.19 to 1.60, p <0.001). Artificial intelligence identified carvedilol exposure as the most important predictor for heart failure hospitalization.

Conclusions: This study found an increased risk of heart failure hospitalization for carvedilol users compared with metoprolol users with this triad of diseases.

2652 | Identifying frequent drug combinations associated with delirium in older adults: Application of association rules method to a case-time-control design

Prasad Nishtala[1] and Te-yuan Chyou[2]
[1]*University of Bath, Bath, United Kingdom;* [2]*University of Otago, Dunedin, New Zealand*

Background: Older adults are at an increased risk of delirium because of age, polypharmacy, multiple comorbidities and acute illness.

Objectives: The aim of this case-time-control study was to apply association rule analysis to ascertain drug combinations contributing to the risk of delirium in adults aged 65 years and older.

Methods: We sourced a nationwide representative sample of New Zealander's aged ≥65 years from the pharmaceutical collections and hospital discharge information. Prescription records (2005-2015) were obtained from New Zealand pharmaceutical collections (Pharms). Medication exposures were coded as binary variables at the individual drug level. All medications, including antimicrobials, antihistamines, diuretics, opioids, non-steroidal anti-inflammatory medications were considered as drugs of interest. The first-time coded diagnosis of delirium was extracted from the National Minimal Dataset (NMDS). A unique patient identifier linked the prescription dataset to the event dataset, to set up a case-time-control cohort, indexed at the first delirium event. Association rules were then applied to identify frequent drug combinations in the case and the control periods (l-day with a 35-day washout period) that are statistically associated with delirium, and the association was tested by computing a time-trend adjusted matched odds-ratio (MOR) and its 95% confidence interval (CI).

Results: We identified 26343 individuals (mean age 84.3) from 2005 to 2015 with incident delirium and exposed to at least one prescription record. Our combined association rule and case-time-control analysis identified several drug classes including antipsychotics, benzodiazepines and opioids, that are associated with delirium. Our analysis also identified frequently used drug combinations that are associated with delirium. Examples include quetiapine and furosemide (MOR=6.17; 95%CI= [2.05-18.54]), haloperidol (MOR=4.81; 95%CI= [3.16-6.69]), furosemide plus omeprazole plus lorazepam (MOR=3.94; 95%CI= [3.03-5.10]), and fentanyl (MOR=3.46; 95%CI [2.05-9.21]).

Conclusions: Association rules uncovered previously implicated drug classes such as antipsychotics, benzodiazepines and opioids that increase the risk of delirium in older adults. The application of association rule method to a case-time-control design is a novel method to identify chronic effects of medication exposures during the time at risk of an adverse drug event.

3708 | Three strategies to measure frailty and/or complex health needs in real world data: An analysis of UK primary care and hospital linked data

Leena Elhussein, Ying H. E., Danielle E. Robinson, Antonella Delmestri, Victoria Y. Strauss and Daniel Prieto-Alhambra

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

Background: Complex health needs and frailty are key confounders in geriatric pharmaco-epidemiology. Although a number of definitions exist, none are formally accepted or adopted in geriatric pharmacoepidemiology. Recent NICE guidelines recommend using primary care electronic health records to identify markers of frailty, including the electronic Frailty Index (eFI). Others have advocated for the measurement of polypharmacy and/or healthcare resource use as alternative methods for the identification of frail patients in routine data.

Objectives: We tested the use of three definitions of frailty, and assessed the overlap between the resulting three cohorts. Sociodemographics, co-morbidity, and common drug/s use were then characterised in the three cohorts.

Methods: All participants aged 65 or older on 1 Jan 2009, registered for 1 year or above were identified from CPRD GOLD, a primary care database including >10 million UK people. Those registered in practices with no linkage to Hospital Episode Statistics (HES) data were excluded. Three cohorts were identified based on the top quintile of three indices measured in the previous year: 1.healthcare resource use defined as the number of unplanned hospital admissions [cohort1], 2.score in electronic frailty index (eFI) [cohort2], and 3.polypharmacy estimated as the number of different drugs prescribed in GP records [cohort3]. Baseline characteristics and overlap between the cohorts were described.

Results: 464,886 participants were eligible for the study, of whom 73,724, 104,885, and 100,965 constituted Cohorts 1, 2 and 3 respectively. 20,741 (4.5%) patients were included in all three cohorts. Mean age (SD) was very similar for all three cohorts (77.0 (7.7), 77.6 (7.4) and 77.2 (7.3) respectively). Cohort 3 had the lowest proportion of males: 38.8% vs. 43.2% in cohort 1 and 41.0% in cohort 2. Preventative medicines, such as, bisphosphonates, statins and diuretics were prescribed to a higher proportion of patients in the three cohorts compared with the background (non-frail) population in the year prior to start (e.g. statins were prescribed to 47.8% in cohort 1 vs. 38.9% in the background population).

Conclusions: All three strategies are feasible for the identification of elderly frail patients in UK data, but the overlap between all three is small. Further research is needed on the best strategy/ies to measure frailty in real world data.

3768 | Negative association between dementia and gout or gout medications using national health insurance service claim database

Kyung Hyun Min, Sang Oh Kang, Ha Rim Yeon and Kyung Eun Lee
Chungbuk National University, Chungchungbugdo, Cheonjusi, Republic of Korea

Background: Uric acid is known to have neuroprotective effect. Gout which is caused by hyperuricemia might have association with dementia.

Objectives: To find out how gout or gout medications affect dementia incidents (overall dementia, Alzheimer's, vascular and others) in elderly Korean patients (≥ 60 years of age).

Methods: We conducted retrospective population-based cohort study using Elderly Cohort from 2002 to 2013 provided by Korean National Health Insurance service (NHIS) claims data. In NHIS-Elderly Cohort, patients with gout were selected as exposure group. In this process, we selected patients with at least two times of gout diagnosis (KCD7 code 'M10') and minimum of 180 days of lag-time between gout and dementia. Index data was assigned as the first date of gout diagnosis. To define as new patients, patients with index date in 2002 were excluded. Non-exposure group was formed by conducting 1 on 5 matching by age and sex. In non-exposure group, index date was assigned randomly between January 1st, 2002 and first diagnosis of dementia or death or end of study. We conducted statistics using cox proportional hazard model. Hazard ratio were adjusted for age, sex, hypertension, diabetes mellitus (type 1&2), dyslipidemia, cardiovascular diseases and Parkinson's disease. To describe the effects of medication (allopurinol, febuxostat and colchicine) regardless of gout itself, we conducted nested case-control study. Dementia patients were selected as case group and 1 on 4 matched non-dementia patients were selected as control group. For statistics, we used multivariate logistic regression. Covariates from analysis above were used for odds ratio adjustment. Primary outcome of this study was adjusted hazard ratio of dementia according to gout status. Secondary outcome was the odds ratio of dementia according to gout medication. All data processing steps and statistics were done using SAS Enterprise Guide 7.1.

Results: Among 558,147 patients registered in NHIS-Senior cohort, 22,718 patients had gout incidents. 20,821 patients out of total 136,308 study population developed any dementia. 2,557 patients (11.26%) and 18,264 patients (16.08%) had dementia incidents for exposure and non-exposure group, respectively. Hazard ratio adjusted by covariates was 0.63 (CI: 0.60-0.66, p<0.0001). Similar tendency is shown for each type of dementia. 7,394 out of 12,784 gout patients (57.8%) were prescribed of gout medication and adjusted odds ratio for dementia was 0.93 (CI: 0.85-1.02, p=0.95).

Conclusions: Gout seems to have negative association with dementia considering covariates.

3784 | The effect of low-dose oral glucocorticoid therapy on osteoporotic fracture risk in patients with rheumatoid arthritis

The Clinical Practice Research Datalink Gold

Frank de Vries[1,2], Annemariek Driessen[1], Andrea Burden[1,3], Patrick Souverein[4], Tjeerd van Staa[2], Joop van den Bergh[5,6] and Shahab Abtahi[1]
[1]*Maastricht University Medical Centre+, Maastricht, Netherlands;* [2]*Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands;* [3]*Institute of Pharmaceutical Sciences, Zurich, Switzerland;* [4]*Utrecht*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Institute for Pharmaceutical Sciences, Utrecht, Netherlands; [5]Maastricht University Medical Centre+, Maastricht, Netherlands; [6]VieCuri Medical Centre, Venlo, Netherlands

Background: Randomized clinical trials (RCTs) showed that low-dose glucocorticoid (GC) therapy in patients with rheumatoid arthritis (RA) was associated with less bone mineral density (BMD) loss in hand or hip. However, the effect on osteoporotic fractures is not yet clear and observational studies mostly reported contrasting results compared to the BMD studies.

Objectives: To investigate the use of low-dose oral GCs on osteoporotic fracture risk among patients with RA in the UK.

Methods: This was a cohort study including all RA patients aged 50+ from Clinical Practice Research Datalink (CPRD) between 1997-2017. Exposure to oral GCs was stratified into current (<6 months), recent (7-12 months), and past use (>1 year), based on the time since the most recent prescription. Current use was further stratified by average daily and cumulative doses. Time-dependent Cox proportional-hazards models estimated risk of osteoporotic fracture (included hip, vertebrae, humerus, forearm, pelvis, or ribs) in RA patients with current use of low-dose oral GCs (average daily dose ≤7.5mg prednisolone equivalent dose [PED]/d) versus past use. The analyses were statistically adjusted for life-style parameters, comorbidities and co-medications.

Results: Among 15,123 patients with RA (mean age 68.8 years, 68% females), 1,640 osteoporotic fractures occurred. Low-dose oral GC therapy (≤7.5mg PED/d) in RA patients was associated with no increased risk of OP fractures compared with past GC use (adjusted [adj.] hazard ratio (HR) 1.1, 95%CI 0.98-1.3). Only clinical vertebral fractures were associated with low-dose GC therapy (adj. HR 1.6. 95%CI 1.1-2.3). Cumulative GC use ≥1g PED in current users was associated with an increased OP fracture risk (adj. HR 1.2, 95% CI 1.0-1.5). However, low-dose oral GC use (≤7.5mg PED/d) was not associated with an increased risk, regardless of the cumulative dose.

Conclusions: Low-dose GC therapy did not increase the OP fracture risk in RA patients compared with past GC use. Our results are in line with findings from RCTs reporting a similar effect of low-dose GC use on BMD in various anatomical sites. These data does not support additional assessment for OP fracture sites other those of the clinical vertebrae when a RA patient is receiving GCs in low daily doses (≤7.5mg PED/d).

3926 | Potentially inappropriate medication in older adults attended in the emergency department (ED) and their association with ED visits

Marcela Jirón[1], Matías F. Martínez[1] and Luis Herrada[2]

[1]University of Chile, Santiago, Chile; [2]Clinical Hospital at University of Chile, Santiago, Chile

Background: Potentially Inappropriate Medications (PIM) increase the risk of adverse outcomes in older adults. Little is known of the prevalence of PIM according to the 2019 Beers Criteria in older adults attended in the Emergency Department (ED) and their association with ED visits.

Objectives: To determine the prevalence of PIM among older adults attended in the ED and their association with ED visits.

Methods: We conducted a cross-sectional study in a database of randomly selected sample of older adults in an ED at a teaching hospital in Chile from 2015 to 2016. Patients included were aged ≥60 years with a signed informed consent form. Patients with cognitive impairment or severe illness unable to provide informed consent were included only if a caregiver responsible was able to sign in on behalf of the patient. Prevalence of patients with at least one PIM at the admission, during, and at discharge of the ED visit were estimated. An independent pharmacist and an emergency physician assessed potential Adverse Drug Events (ADE) as a cause of ED visit by direct observation. They collected sociodemographic characteristics, clinical and pharmacotherapy profiles of each patient. PIM was defined according to the 2019 Beers Criteria. We identified the association between PIM and ED visits using multiple logistic regression in STATA 15.1.

Results: A total of 298 patients were included. The mean ± SD age was 72.1 ± 8.9 years, 63.8% (n=190) were women, and 45.0% (n=134) of patients were using 5 or more medications (mean 4.6 ± 3.0 drugs/patient). The prevalence of older adults with at least one PIM at the admission, during, and at discharge of the ED visits were 73.2% (95% CI: 68.1-78.2), 51.1% (95%CI: 44.7 - 57.4), and 40.9% (95% CI :33.0 - 48.9), respectively. A 22.6% (95%CI: 21.5 - 30.8) of patients studied were admitted at the ED as a cause of an ADE. PIM according to 2019 Beers Criteria were independently associated with ED visits as a cause of an ADE (adjusted OR 2.2; 95%CI: 1.01 - 4.94; $p<0.05$), controlling by age, sex and number of medications.

Conclusions: PIM is highly prevalent among older adults attended in the studied ED. PIM according to 2019 Beers Criteria are independently associated with ED visits related to an ADR. There is a potential to optimize the older patients' drug safety, and health care utilization by preventing avoidable ADEs.

3951 | Evaluation and comparison of potential over-treatment rates among older adults with type-2 Diabetes in Manitoba using prescription vs dispensation databases

139.1.1. | Sai Krishna Gudi[1], Shawn Bugden[2], Kevin Friesen[1] and Jamie Falk[1]

[1]University of Manitoba, Winnipeg, MB, Canada; [2]Memorial University of Newfoundland, St. John's, NL, Canada

Background: Diabetes is highly prevalent among older adults and significant concerns exist regarding potential over-treatment. Currently, the extent of overtreatment in older adults with type-2 diabetes in Manitoba has not been addressed.

Objectives: To evaluate and compare potential over-treatment related to intensity of glycemic control among older adults with type-2 diabetes across Manitoba using prescription & dispensation data.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: An observational cohort study was conducted using data from Manitoba, Canada from 2010-2017. A cohort extracted from the Manitoba Primary Care Research Network (MaPCReN, a dataset of prescriptions by primary care providers) was linked with corresponding Manitoba Centre for Health Policy (MCHP, a dataset of dispensations of prescriptions by all prescribers) data in order to assess and compare potential over-treatment rates. Patients aged ≥65 years with type-2 diabetes defined by the Canadian Primary Care Sentinel Surveillance Network validated case definition with at least one HbA1c measurement were included. Intensity of glycemic control was assessed in two cross-sectional years (2012, 2016). Over-treatment was defined as an index HbA1c (first recorded HbA1c of the year) of <7% and dispensation of any anti-diabetic medication other than metformin within 3 months before and after index HbA1c. The secondary outcome was contribution of prescriber-type towards the prescription of over-treatment medications in the MCHP database. SAS Version 9.4 was used for all data analyses.

Results: A cohort of 3376 patients (51.8% females, mean age 76.6 years) was identified. Overall rates of potential over-treatment were 10.7% (2012) and 11.1% (2016) (p = 0.67 [95% CI -1.47 to 2.20]), and 20.4% (2012) and 21.5% (2016) (p = 0.37 [95% CI -1.32 to 3.47]), using prescription and dispensation data, respectively. Among potentially over-treated patients, 19.8% in 2012 and 21.5% in 2016 (p = 0.16 [95% CI -0.70 to 4.05]) of over-treatment medications were prescribed by non-general practitioners (i.e., specialists like endocrinologists), using MCHP data.

Conclusions: Rates of potential over-treatment among older adults with type-2 diabetes were found to be remarkably higher in the province of Manitoba using dispensation data (MCHP) compared to provincial primary care prescription data (MaPCReN), with no evidence of rates decreasing over time. Non-GPs contributed to approximately 20% of over-treatment prescriptions which may account for some, of the difference between over-treatment rates between the MCHP and MaPCReN cohorts.

4002 | Systematic review and meta-analysis on the associations of polypharmacy and potentially inappropriate medication with adverse outcomes in older cancer patients

Li-Ju Chen[1,2], Kira Trares[1,2], Dana Clarissa Laetsch[1], Thi Ngoc Mai Nguyen[1,2], Hermann Brenner[1,2] and Ben Schöttker[1,2]

[1]German Cancer Research Center, Heidelberg, Germany; [2]University of Heidelberg, Heidelberg, Germany

Background: Polypharmacy and potentially inappropriate medication (PIM) intake are prevailing in older cancer patients. However, the current evidence regarding their associations with adverse outcomes in older cancer patients has not been summarized.

Objectives: To systematically search, review, appraise, and meta-analyze the currently available evidence from observational studies about associations of polypharmacy and PIM use with all-cause mortality, hospitalization, prolongation of hospitalization, treatment-related toxicity, and postoperative complications.

Methods: A systematic review and a meta-analysis of observational studies reporting associations of polypharmacy or PIM with at least 1 out of 5 pre-defined adverse outcomes in older cancer patients (≥ 60 years) were conducted. PubMed and Web of Science were used to search for relevant studies published between January 1991 and February 2019. Data were pooled by adopting a random-effects model.

Results: 27 publications were included in the systematic review. Meta-analyses could be performed on 23 studies about polypharmacy and 10 studies about PIM. Polypharmacy was found to be significantly associated with all-cause mortality (risk ratio [95% confidence interval]: 1.36 [1.19-1.55]), hospitalization (1.59 [1.18-2.15]), and postoperative complications (1.73 [1.36-2.20]). Associations of polypharmacy with prolongation of hospitalization (1.62 [0.98-2.66]) and treatment-related toxicity (1.25 [0.96-1.64]) were close to statistical significance. In contrast, no statistical significance was found between PIM and any assessed adverse outcome.

Conclusions: Polypharmacy was found to be associated with several adverse outcomes in older cancer patients. However, these results should be interpreted with caution because two-thirds of the studies identified for polypharmacy did not adjust for comorbidity. For PIM, no significant associations were noticed. However, 7 out of 8 included studies applied a prevalent user design and were therefore susceptible to the healthy-user/sick-stopper bias. Further well-designed studies are needed.

4014 | Updated data on potentially inappropriate medications use in older adults in France: A population-based study

Barbara Roux[1,2,3], Pernelle Noize[1,3], Julien Bezin[1,3], Camille Morival[1,3] and Marie-Laure Laroche[2,4]

[1]Bordeaux Population Health Research Center, Team Pharmacoepidemiology, UMR 1219, University of Bordeaux, Bordeaux, France; [2]INSERM UMR 1248, Faculty of Medicine, University of Limoges, Limoges, France; [3]Service de Pharmacologie Médicale, Pôle de Santé Publique, CHU de Bordeaux, Bordeaux, France; [4]Centre of Pharmacovigilance and Pharmacoepidemiology, Department of Pharmacology-Toxicology and Centre of Pharmacovigilance, University Hospital of Limoges, Limoges, France

Background: The use of potentially inappropriate medications (PIM) in the older population remains a public health concern in several countries. Few recently population-based data exists on PIM use in community-dwelling older people in France. Yet their use may be associated with preventable adverse events and significant health costs.

Objectives: To estimate the prevalence and incidence of potentially inappropriate medications (PIM) use in community-dwelling older adults ≥ 65 years in France.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: A cross-sectional study was conducted using data from a 1/97th random sample of the French national healthcare reimbursement system (covering 90% of the entire population). Individuals aged ≥ 65 years who were insured between January and December 2016 were included for the estimation of the prevalence of PIM use. Among this population, individuals without PIM dispensing in the previous year were identified for the estimation of the incidence of PIM use. PIM were defined using a revised version of the French Laroche list including medications that should be generally avoided in older adults or that should be avoided depending on dose or duration.

Results: Around half of the 98,568 older adults included (48.4%) were dispensed at least one PIM in 2016. Of these, 60.0% were women, mean age was 76.3 years (SD 8.2) and 82.8% used ≥10 different medications yearly. The most prevalent PIM were proton-pump inhibitors >8 weeks (22.3%), long-acting benzodiazepines (9.2%), anxiolytic benzodiazepines >12 weeks (7.0%), first-generation antihistamines (5.6%), anticholinergic antiemetics (5.1%) and hypnotic benzodiazepines >4 weeks (4.8%). In 2016, 8,743 individuals initiated at least one PIM (8.9% of the total population); 58.1% were women, mean age was 74.4 years (SD 7.6) and 73.5% used ≥10 different medications yearly. The PIM most frequently initiated were proton-pump inhibitors >8 weeks (4.2%), anticholinergic antiemetics (4.0%), first-generation antihistamines (3.4%), loperamide (3.0%), long-acting benzodiazepines (2.7%) and antitussives anticholinergics (2.1%).

Conclusions: PIM use remains common in community-dwelling older adults in France. Effective targeted-interventions should be implemented particularly to prevent PIM initiation and also to promote their deprescribing.

4032 | The epidemiology of polypharmacy in a large cohort with linked health records over 5 years of follow-up in Scotland

Mina Khezrian, Phyo Myint, Chris McNeil, Marjorie Johnston and Alison Murray

University of Aberdeen, Aberdeen, United Kingdom

Background: Most of the outcomes associated with polypharmacy, concomitant use of several drugs, are independently associated with pre-existing multimorbidity. Therefore, our understanding of the potential harm of taking multiple medications in older, multi-morbid populations is limited.

Objectives: We aimed to measure the prevalence of polypharmacy and to model the association of polypharmacy and hospitalization in a large cohort with linked health data over 5 years of follow-up.

Methods: This was a prospective observational cohort study using linked administrative data. Prescription and hospital admission records of the Aberdeen Children of the 1950s Cohort were extracted from the National Health Services Scotland database and linked from 2011-2016. We estimated polypharmacy by measuring monthly drug exposure for 1) total number of prescribed medications and 2) total number of defined daily doses (DDDs). Cox proportional hazard models (adjusted for demographics, socioeconomic circumstances and health conditions) were used to examine the association of polypharmacy and hospitalization.

Results: Prescription records were successfully linked for 8,735 participants. Mean age at baseline was 58.5 years (SD=1.5) and 50% were female. The proportion of cohort with polypharmacy (taking 5+ medications; taking 5+ DDDs) at baseline was 20.9% for counting medications (female=21.4% vs male=20.3%, P=0.179), and 21.9% for counting DDDs (female=20.6% vs male=23.1%, P=0.007). The prevalence of excessive polypharmacy (taking 10+ medications; taking 10+ DDDs) was 6.3% for counting medications (female=6.7% vs male= 6.0%, P=0.219), and 8.6% for counting DDDs (female= 7.9% vs male=9.3%, P=0.030). After adjustment for confounders, the hazard ratio for hospitalization was 1.40 (95 % CI 1.31-1.51) for polypharmacy measured by number of medications and 1.35 (95 % CI 1.26-1.45) for polypharmacy estimated by number of DDDs. Hazard ratios for excessive polypharmacy was 1.54 (95 % CI 1.38-1.71) for count of medications and 1.37 (95 % CI 1.24-1.50) for count of DDDs.

Conclusions: The prevalence of polypharmacy varies in male and female depending on the method used to estimate it in this cohort. Polypharmacy and excessive polypharmacy are independently associated with hospitalization. The extent to which polypharmacy is the proximate cause of poor outcome rather than a marker of the increased risk needs to be confirmed further. More studies are needed to generate evidence-based information for future policy and health services to improve polypharmacy measurement and management.

4052 | Anticholinergic burden and fractures in older adults: Results from a methodological systematic review

Jonas Reinold[1], Wiebke Schäfer[1], Lara Christianson[2], Francesco Barone-Adesi[3], Oliver Riedel[1] and Federica Edith Pisa[1]

[1]Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany; [2]Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany; [3]University of Eastern Piedmont, Novara, Italy

Background: Medications with anticholinergic activity (MACs) are used to treat many diseases common in older adults. Evidence on the association between high anticholinergic burden and increased risk of fractures is inconsistent.

Objectives: To conduct a systematic review of observational studies addressing the association of anticholinergic burden with fractures and to provide a methodological appraisal.

Methods: We searched MEDLINE, EMBASE, the Science Citation Index, CENTRAL and grey literature combining the terms "anticholinergic" and "fractures" from database inception to 2018. The eligibility criteria were: observational design (excluding cross-sectional studies), anticholinergic burden exposure measured through a scale, fracture of any type as outcome, and reported crude or adjusted measures of effect. No restrictions related to time, language or type of data were applied. The risk of bias was assessed using the Newcastle-Ottawa Quality Assessment Scale and RTI Item Bank.

Results: We included 9 studies with a total population of 610,862 persons, 74% (n=452,659) of which were women, mainly drawn from

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

North America (n=363,723; 60%) and East Asia (n=175,686; 29%). Study participants were mostly older adults aged ≥65 years (N=5 studies). The most commonly used tool to assess exposure was the Anticholinergic Risk Scale (ARS) (N=5 studies). No study used a new-user design. Only (N=3) studies included a longitudinal assessment of exposure. The most common outcome were any fractures (N=4), and hip fractures (N=3). The majority of studies had a low risk of bias. Baseline prevalence of MAC ranged from 8% to 85%; 7 studies reported an increased risk of fractures associated with anticholinergic burden. In studies using the ARS, the adjusted risk of fractures was increased by 2-61% for an ARS score of 1, by 0-97% for an ARS of 2, by 19-84% for an ARS of 3, and by 56-96% for an ARS of ≥4; in two studies the ARS was aggregated with a risk increased by 39% for ARS of 1-2 and by 17% for ARS 2-3, respectively. In the other two studies the risk was no longer increased when factors related to health status and risk factors for fractures were adjusted for.

Conclusions: This systematic review suggests that an increased risk of fractures is associated with anticholinergic burden with possible dose-exposure gradient in studies using the ARS. The low number of studies and heterogeneity of the employed methods calls for the conduct of more studies using consistent methodology.

4060 | Longitudinal trajectories of frailty in older populations: Latent curve models and mortality

Victoria Y. Strauss, Danielle E. Robinson, Antonella Delmestri, Daniel Prieto-Alhambra and Alan Silman

Botnar Research Centre, NDORMS, University of Oxford, Oxford, United Kingdom

Background: A validated frailty index (eFI) based on cumulative deficits in the electronic primary care record has been implemented in the UK NHS primary care. eFI scores categorise people into fit, mild, moderate and severely frail, whilst ignoring transitions between stages.

Objectives: To identify clusters of frailty trajectories over five years; and to examine their association with subsequent mortality.

Methods: A cohort of 270,908 older people, aged 65+ in 2009 and alive in 2013, were identified from UK primary care records (CPRD GOLD) linked to hospital inpatient and mortality data. Each calendar year, eFI index was applied to calculate the cumulative number of deficits. These deficit counts were modelled with latent class growth analyses to identify clusters of people with differential frailty trajectories. Bayesian information criterion (BIC) was used to select the optimal number of clusters and distribution. To illustrate transition between stages over five years, the emerging clusters were retro fitted to predefined frailty stages at each year. Follow up after classification in frailty trajectories went from 1/1/2014 until end of 2018, death, or loss to follow-up, and Cox models used to estimate relative risk of death according to frailty trajectory clusters, adjusted for age and gender.

Results: Overall, mean (SD) eFI changed from 0.11(0.08) to 1.48 (0.09), indicating slow worsening frailty. Five-cluster Poisson models of frailty trajectories had the smallest BIC. Two clusters (C5, 6%, C4, 20%) included fit people remaining fit with zero deficit throughout the 5-year period, and with slowly onset frailty (increasing from 0 to up to 2 deficits over the 5-year period), respectively. One cluster (C3, 37%) could be classified as slow frailty progression from pre to mild frail. Patients in C2 (29%) and C1 (8%) experienced slow accelerating rates of mild and moderate frailty respectively. Patients with slowly onset frailty cluster, C4, and slow frailty progression cluster, C3, were 24% (95% CI: 1.17, 1.31) and 53% (1.46, 1.61), respectively, more likely to die in 5 years compared to C5. The death risk increased to twice for patients in the two clusters of slow acceleration of mild (C2) and moderate (C1) frailty.

Conclusions: Five distinct frailty trajectories are identified in older patients including one cluster experiencing transitions from fit to mild frailty and over 50% higher risk of mortality. Further research is needed, including the validation of the identified clusters in external datasets.

4166 | Associations between patterns of antipsychotic use and mortality among older adults with late-life psychotic disorders

Soham Rej[1] and Dallas Seitz[2]

[1]*McGill University, Montreal, QC, Canada;* [2]*University of Calgary, Calgary, AB, Canada*

Background: Antipsychotic medications (AP) are important in management of individuals with schizophrenia and related psychotic disorders. Concerns about the safety of AP in older adults have been raised largely from studies of individuals with dementia where an increased risk of mortality has been observed. There is little know about whether there is an increased risk of death associated with the use of AP in older adults with late-life psychosis (LLP).

Objectives: 1.) To evaluate the associations between use of APs in older adults with LLP and the subsequent risk of mortality in this population.

Methods: We identified all adults aged 66 years and older who met criteria for a psychotic disorder (schizophrenia or schizoaffective disorder) in Ontario, Canada between 2008 and 2016. A validated algorithm was used to identify individuals with LLP using outpatient physician visits and hospitalization data. AP exposure was assessed in the 5 years preceding and 5 years following cohort entry. Cumulative AP doses were recorded using defined daily doses for both oral and long-acting injectable AP and AP was categorized as atypical monotherapy, typical monotherapy, AP polypharmacy, and by relative different doses of AP based on Olanzapine equivalents. Cox proportional hazards models were used to determine the associations between patterns of cumulative AP exposure and mortality.

Results: A total of 6,498 individuals were included in the study cohort. At baseline, 28% of individuals did not receive any AP in the 120 days preceding cohort entry, 42% received atypical AP monotherapy, 8% received typical AP monotherapy, and 22% received antipsychotic polypharmacy. When compared to no use of AP, there was a reduced risk of mortality in association with exposure to an atypical AP

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

monotherapy (HR: 0.60, 95% CI: 0.52 - 0.69), typical AP monotherapy (HR: 0.71, 95% CI: 0.55 - 0.93), and AP polypharmacy (HR: 0.65, 95% CI: 0.54 - 0.79). These results were consistent in subgroups with and without dementia, after adjustment for baseline differences between AP exposure groups, and in an sensitivity analysis incorporating a grace period for definition of AP discontinuation dates.

Conclusions: In this large population-based cohort study, AP use was associated with a reduced risk of mortality among older adults with LLP, even among those with comorbid dementia. Clinicians should be aware of the specific benefits and risks of AP in older adults which may be different for those with late-life psychosis when compared to other populations of older adults.

4171 | Patterns of rate control, rhythm control and anticoagulant medication use before and after nursing home admission among residents with dysrhythmias

Qiaoxi Chen, Kate Lapane and Matthew Alcusky
University of Massachusetts Medical School, Worcester, MA

Background: Management of dysrhythmias typically includes use of one or more rate control, rhythm control, and anticoagulant medications to address symptoms and reduce the risk of life-threatening cardiac and cerebrovascular events.

Objectives: To describe rate control, rhythm control, and anticoagulant medication use before and after nursing home admission among residents with dysrhythmias.

Methods: Newly admitted long-stay nursing home residents between April 1st, 2011 and September 30th, 2016 were studied using the Minimum Data Set (MDS). The prevalence of atrial fibrillation or other dysrhythmias (MDS item: I0300) was estimated at admission. Use of oral rate-control, rhythm-control, and anticoagulant medications was studied in the 3 months before and 3 months after the admission using Part D claims among those with a diagnosis of dysrhythmia and continuous Medicare fee-for-service enrollment (n=107,769). Rate-control medications were further sub-classified as non-selective beta-blocking agents (BBAs), BBAs indicated for heart failure, other cardio-selective BBAs, calcium channel blockers with cardiac effects, dihydropyridine calcium channel blockers, and cardiac glycosides. Rhythm-control medications included class I and III antiarrhythmic agents. Residents were classified as non-users, discontinuers, initiators, and continuous users of each medication class based on the presence/absence of $\geq$1 claim for a medication in the class before and after admission.

Results: Among 3.4 million newly admitted nursing home residents, 18.9% had a diagnosis of dysrhythmia. The average age of residents with dysrhythmia was 89.5 years; 14.5% had a history of stroke and 34% had heart failure. Use of rate-control (79.0% before vs. 76.9% after), rhythm-control (20.4% before vs. 21.0% after), and anticoagulant medications (44.8% before vs. 43.3% after) was largely consistent after nursing home admission. Before admission, 11.3% used none of these medications and 12.5% used none afterwards. Although 11.4% of anticoagulant users discontinued after admission, 6.6% of non-users initiated anticoagulants. Among residents with heart failure, less than half (46.9%) used BBAs indicated for heart failure after nursing home admission; 19.9% used other cardio-selective and 4.0% used non-selective beta blockers.

Conclusions: Our findings suggest the large majority of newly admitted residents with dysrhythmia continue their outpatient medication regimen in the nursing home setting.

4174 | Barriers and enablers of deprescribing preventive cardiovascular/diabetes medication health care professionals' perspective

Jamila Abou
Amsterdam UMC, Amsterdam, Netherlands

Background: Both the benefits and risks of preventive medication change over time for ageing patients. Not much is known about barriers and enablers for deintensifying preventive medication from the perspective of healthcare professionals (HCPs) in the Netherlands.

Objectives: The aim of this study was to identify barriers to and enablers of deprescribing preventive cardiovascular and diabetes medicines from the perspective of HCP and to explore the role of the pharmacist in deprescribing.

Methods: Three focus groups with in total 5 general practitioners, 8 pharmacists, 3 nurse assistants, 2 geriatricians, 2 elder care physicians were conducted in 3 cities in the Netherlands. Interviews were recorded and transcribed verbatim. Directed content analysis was performed on the basis of the Theoretical Domains Framework (TDF). Two researchers separately coded the data.

Results: Most HCPs agreed that deprescribing in this area is relevant but that barriers include poor communication between the various prescribers, insufficient reimbursement, and lack of knowledge on the subject. Some HCPs feared the deterioration of their patients' health after discontinuation their cardiovascular or diabetes medicines. All HCP stated that adequate patient communication and addressing the patients' priorities enables deprescribing. A guideline could enable the process of deprescribing such medication in elderly patients. Several HCPs stated that pharmacists could enable deprescribing by conducting medication reviews or advising about side effects and drug interactions.

Conclusions: HCPs recognize the importance of deprescribing cardiovascular and diabetes medication as a medical decision that must be well grounded. A multidisciplinary approach including the pharmacist could support deprescribing.

4185 | The association between polypharmacy and frailty in older adults

Deng-Chi Yang[1], Chien-Chou Su[2] and Yea-Huei Kao Yang[2]
[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Institute of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background: Polypharmacy and frailty are well-known geriatric syndromes, and both are common in older adults. Although polypharmacy and frailty often coexist and have been researched individually and extensively, the association between polypharmacy and frailty still remains unclear.

Objectives: The objective of this study was to investigate the association between the polypharmacy and frailty in older adults.

Methods: We conducted a cross-sectional study by using the database of Taiwan Longitudinal Study on Aging (TLSA). A total of 2,468 older adults (age ≥65 years) were recruited. Polypharmacy was defined as taking≥5 kinds of medication, and frailty was defined as modified Fried criteria. The geriatric syndromes included a depressive disorder, cognitive impairment, impaired activities of daily living, impaired instrumental activities of daily living, urine incontinence, pain, fall, and polypharmacy. Other characteristics were age, gender, marital status, educational level, self-rated health, and chronic diseases. Univariate analysis and multinominal logistic regression will be performed to explore the relationship between polypharmacy and frailty.

Results: Among 2,468 older adults, there were 1,229 individuals without frailty, 1,078 individuals with pre-frailty, and 161 individuals with frailty. Univariate analysis demonstrated that age, sex, education, marriage, self-rated health, depressive disorder, impaired cognition, dependence in activities of daily living, fall, urine incontinence, pain, and polypharmacy were associated with pre-frailty and frailty. In multinominal logistic regression, there was an increased risk in association between frailty and polypharmacy, but it was not statistically significant.

Conclusions: Our results showed an increased risk in association between frailty and polypharmacy although it was not significant. Owing to the cross-sectional study design, the factor of temporal relationship between polypharmacy and frailty in the older adults was not evaluated. Further longitudinal studies are needed to confirm this relationship.

4224 | Inflammatory bowel disease medication use among community-dwelling persons with and without Alzheimer´s disease

Tuulia Heikkilä, Anna-Maija Tolppanen, Marjaana Koponen, Sirpa Hartikainen and Miia Tiihonen
University of Eastern Finland, Kuopio, Finland

Background: The incidence of inflammatory bowel disease (IBD) has been increasing in western societies and therefore the prevalence is increasing in older population. We hypothesize that more and more people with IBD will get dementia in the future.

Objectives: To determine the prevalence of IBD medications use among community-dwelling IBD persons with and without Alzheimer's disease (AD).

Methods: This study was a part of the nationwide register-based MEDALZ (MEDication use and ALZheimer's disease) study. MEDALZ-data includes all community-dwelling residents of Finland diagnosed with AD during 2005-2011 (n=70 718). For each person with AD, one age-, sex- and region of residence matched comparison person without AD were identified. Persons with AD and IBD were identified from the Special Reimbursement Register. Altogether 416 (0.6%) in the AD and 426 (0.6%) in the non-AD cohort had IBD three years before the index date (date of AD diagnosis). Data on the purchases of IBD medications were obtained from the Prescription Register. Descriptive statistics were carried out using means, standard deviations (SD) and percentages.

Results: The prevalence of IBD medications use was similar in IBD persons with and without AD at the index date. Among persons with IBD 60.3% in AD and 63.6% in non-AD cohort used at least one IBD medication at the index date. The most commonly used IBD medications were mesalazine, corticosteroids, sulfasalazine, azathioprine and methotrexate.

Conclusions: Persons with and without AD used IBD medications in the same frequency and there were no changes before and after the AD diagnosis.

4237 | "I Simply Don't Know Because I Don't Know Which Drugs I Get": A qualitative study of perspectives on deprescribing among nursing home residents and their relatives

Carina Lundby[1], Trine Graabæk[1], Jesper Ryg[1], Jens Søndergaard[2], Anton Pottegård[1] and Dorthe Susanne Nielsen[1]
[1]*Odense University Hospital, Odense C, Denmark;* [2]*University of Southern Denmark, Odense C, Denmark*

Background: Use of medication with questionable benefit is common among nursing home residents. This makes deprescribing particularly relevant. To effectively carry out deprescribing in this population, it is important to understand the perspectives of both residents and relatives.

Objectives: To explore perspectives on deprescribing among nursing home residents and their relatives.

Methods: We conducted a qualitative study using semi-structured face-to-face interviews. Participants were Danish nursing home residents, deemed cognitively able to participate by nursing home staff, and relatives pointed out by the residents themselves. Interviews were audio recorded and transcribed verbatim. Analysis was conducted using systematic text condensation.

Results: Ten nursing home residents (aged 72-96 years; six women) and nine relatives (aged 45-82 years; five women) were interviewed. Three main themes reflecting their perspectives on deprescribing were identified: 1) Wishes and attitudes towards medication, 2) Knowledge and experiences with medication, and 3) Relationship with health care professionals regarding medication.

Medication was generally perceived as a necessity by the residents; however, the majority did not know which drugs they took and why, and would not notice if their medication was changed. Most participants, including both residents and relatives, had not considered the possibility of taking less medication but were open towards

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

deprescribing if proposed by the physician. Despite this, most residents did not find their medication challenging to take, regardless of their daily number of medications. Both residents and relatives generally considered the physician or the nursing home staff as being responsible for the medication; however, they would also like to be involved in or informed about medication decisions to some degree. Lastly, they generally had faith in health care professionals despite limited contact.

Conclusions: Our study suggests that many factors may affect deprescribing in the nursing home population; however, as a starting point, the willingness of nursing home residents and their relatives to try deprescribing is considerable if supported by the physician. To facilitate more deprescribing in this population, it seems that health care professionals need to initiate more discussions about the possibility of taking less medication.

4294 | Identification of dementia diseases in health claims data - Results from the German Pharmacoepidemiological Research database

Oliver Riedel, Malte Braitmaier and Ingo Langner
Leibniz Institute for Prevention Research and Epidemiology, Bremen, Germany

Background: Dementia ranks highest among neurodegenerative diseases in the elderly, and it has been estimated that Alzheimer's disease (AD) accounts for approximately 70% of all dementia cases, followed by vascular dementia (VD) with 15%. While the epidemiology of dementia in general has been well investigated, most reported estimates relate to dementia as a group of diseases. Thus, it is unclear how single entities such as AD or VD can be reliably identified in health claims data.

Objectives: To assess the plausibility of different case definitions for detecting AD, VD and other dementia (oD) in health claims data.

Methods: Using data of the year 2016 from the German Pharmacoepidemiological Research Database (GePaRD; health claims of ~17% of the German population), insurants were categorized as having AD, VD or oD based on five algorithms: at least one inpatient/outpatient AD, VD or oD diagnosis (alg. 1); at least one inpatient diagnosis or one outpatient diagnosis by a neurologist (alg. 2) and at least one prescription of antidementives (alg. 3); at least one inpatient/outpatient AD, VD or oD diagnosis and conduct of liquor diagnostics (alg. 4) or at least one inpatient AD, VD or oD diagnosis and conduct of imaging procedures (alg. 5). For algorithms 2-5, the events had to occur within a time frame of 183 days. For each algorithm, the number of detected cases and the proportions of AD/VD/oD among these cases were calculated.

Results: Overall, 215,676 cases with dementia were identified by algorithm 1, of which 23.5% had AD, 23.2% had VD and 53.3% had oD, respectively. Similar proportions were found by algorithm 2 (N=199,033, AD=23.2%, VD=22.9%, oD=53.9%), algorithm 4 (N=3,080, AD=26.3%, VD=20.2%, oD=53.5%), and algorithm 5 (N=3,154, AD=26.1%, VD=19.9%, oD=54.0%). Algorithm 3 identified 48,741 dementia patients with higher proportions of AD (45.0%) and lower proportions of VD (12.1%).

Conclusions: None of the algorithms estimated the expected proportion of 70% of AD cases among all insurants with dementia. Prescriptions and supportive diagnostics were of limited use for the algorithms, since they were rarely carried out in our study sample. Further exploration on how to improve identification of AD in health claims data is needed.

4312 | Incidence and predictors of potentially inappropriate medication use (PIMU) in the elderly population

Ramesh Madhan, Anna George Fenn Archa, Penumarthi Krishna Sai, Johny Rosangkima, Rithika V. R and Sri Harsha Chalasani
JSS College of Pharmacy, Mysuru, India

Background: Aging is an inevitable and irreversible process. With complex medical problems and polypharmacy, elderly are at a higher risk for experiencing drug related problems in hospitals and ambulatory settings.

Objectives: The study aimed to assess the prescribing pattern of drugs, incidence and predictors of Potentially Inappropriate Medication Use (PIMU).

Methods: A prospective observational study was conducted for a period of six months. All the elderly patients admitted to Departments of General Medicine and Surgery were reviewed intensively. All those patients who met the eligibility criteria were enrolled into the study and the collected data were screened to assess the prescribing pattern of drugs. PIMU were assessed by using Beers' Criteria 2015. Bivariate analysis and subsequent Multivariate logistic regression was used to assess the predictors of PIMU.

Results: Of the 656 patients, male [359 (54.72%)] predominance was observed. 75.6% of patients had $\leq$ 3 comorbid conditions and the average length of hospital stay was 6 days. Circulatory system disorders [526 (80.18%)] was commonly observed. The total medications and doses received were 5296 and 5,866 respectively. The alimentary tract and metabolism drugs [1444 (27.26%)] were most commonly used. A total of 266 drug related problems (DRPs) were identified and the most common was drug interactions [124 (46.61%)]. Further, 216 PIMU were identified from 187 patients with a prevalence was 28.5%. Drugs of nervous system [110 (50.92%)] were most frequently implicated in PIMU. Predictors of PIMU were found to be significant for patients having 3 co-morbidities, prescription with more than 8 drugs, duration of hospital stay of 6-10 days and administration of more than 100 doses during hospital stay.

Conclusions: Incidence of PIMU was high among elderly hospitalized patients. Pharmacists can play an important role in detection and prevention of PIMU in elderly patients.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4349 | Polypharmacy as a risk factor for all-cause mortality among older people in England

Yun-Ting Huang[1], Andrew Steptoe[2], Li Wei[3] and Paola Zaninotto[1]
[1]University College London, London, United Kingdom; [2]University College London, London, United Kingdom; [3]University College London, London, United Kingdom

Background: Polypharmacy is a prevalent phenomenon in older people. Both positive and negative outcomes of polypharmacy have been reported, making the role of polypharmacy somewhat uncertain. Most previous studies have found polypharmacy is associated with increased mortality in older people, but the definition of polypharmacy varies widely. Therefore, we tested this relationship by using the most common definition of polypharmacy.

Objectives: To investigate the association between polypharmacy and all-cause mortality among older people.

Methods: Participants were from the English Longitudinal Study of Ageing (ELSA), a nationally representative sample of people aged 50 and older. In 2012/2013, 7729 people participated in the nurse visits, of these, 7727 were followed up for mortality until March 2018. Complete data were available from 6757 people. Polypharmacy was defined as taking five to nine long-term medications a day for chronic diseases or chronic symptoms, while using ten or more medications was categorised as heightened polypharmacy. The presence of illness was defined as either self-reporting conditions or taking specific medications for the condition. Cox proportional hazards model was used in this study.

Results: The age- and sex-adjusted hazard ratios of polypharmacy and heightened polypharmacy were 2.35 and 4.24, respectively, and these effects on all-cause mortality were primarily attenuated when adjusting for chronic conditions such as diabetes, coronary heart diseases, lung diseases and cancer. The effects of polypharmacy and heightened polypharmacy on mortality were further attenuated after adjusting for disability and health behaviours but remained significant. After adjusting for demographics, existing chronic diseases, disability, health behaviours, cognitive function and high-risk medications, people reporting polypharmacy (n=1357) had 1.51 times higher risk of death (95% CI 1.05, 2.19) compared with people not taking any medications (n=1924). People reporting heightened polypharmacy (n=162) also had 2.12 times higher risk of death (95% CI 1.29, 3.50), by contrast, people taking one to four drugs no longer showed a higher risk of death after adjustments.

Conclusions: People reporting polypharmacy and heightened polypharmacy had a higher risk of mortality than people who did not take any medications. The results imply the presence of polypharmacy or heightened polypharmacy could be an indicator of mortality for older people, highlighting the need to ensure the appropriateness of multiple medications.

4381 | Proton pump inhibitors following strongly anticholinergic medications: A novel prescribing cascade

Shanna C. Trenaman[1], Susan K. Bowles[2], Susan Kirkland[3] and Melissa K. Andrew[4]
[1]Dalhousie University, Halifax, NS, Canada; [2]Nova Scotia Health Authority, Halifax, NS, Canada; [3]Dalhousie University, Halifax, NS, Canada; [4]Dalhousie University, Halifax, NS, Canada

Background: Anticholinergic medications are associated with gastrointestinal symptoms such as dry mouth and reflux. These symptoms may be treated with proton pump inhibitors (PPI). Use of anticholinergic medications in older adults with dementia may lead to a prescribing cascade as PPI are initiated to manage adverse drug events.

Objectives: To determine prevalence and factors associated with anticholinergic medication leading to PPI prescribing cascade in older adults with dementia.

Methods: This is a retrospective cohort study using administrative claims for Nova Scotia Seniors' Pharmacare Beneficiaries with dementia (NSSPBD). The cohort included beneficiaries who received a diagnosis of dementia according to ICD-9/10 codes from physician billings between April 1, 2008 and March 30, 2015. All NSSPBD prescription claims for medications receiving a score of 3 on the anticholinergic cognitive burden scale and PPI (ATC code A02BC) were collected from April 1, 2009 to March 30, 2015. This allowed a look-back period of 1 year prior to the period of study (April 1, 2010 to March 30, 2015) to ensure PPI did not precede the anticholinergic medication. The prescribing cascade was identified when PPI prescription followed anticholinergic medication prescription by <180 days. To test robustness of the association we reduced the interval to <90, 60 and 30 days. Multivariable logistic regression was used to identify risk factors associated with the prescribing cascade.

Results: The cohort of NSSPBD included 30,703 subjects over the period of study. 9,325 NSSPBD (30.4%) received at least one prescription for an anticholinergic medication (mean age 80.6 years). 10,657 NSSPBD (34.7%) received at least one prescription for a PPI (mean age 80.9 years). 795 cases of the prescribing cascade were identified (2.6%) where the PPI was initiated within 180 days of the anticholinergic medication. Altering the window for the prescribing cascade to 90 days reduced the number of identified cases to 569 (1.9%). At 60 days the number of cases fell to 458 (1.5%). At 30 days the number of cases fell to 313 (1.0%). Logistic regression suggested that younger age (OR -0.021; 95% CI[-0.030, -0.012]) and female sex (OR -0.49; 95% CI[-0.65, -0.32]) were significant risk factors for the prescribing cascade.

Conclusions: Prescription of anticholinergic medications leading to PPI prescription in a population of older adults with dementia represents a novel prescribing cascade. Younger age and female sex was associated with the prescribing cascade. Further investigation of this prescribing cascade in populations without dementia is warranted.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4470 | Identifying fractures in medicare claims before and after the ICD-9-CM to ICD-10-CM transition

Shahar Shmuel[1], Virginia Pate[1], Yvonne Golightly[1,2,3,4], Laura Hanson[5,6], Rebecca B. Naumann[7,2], Til Stürmer[1], Marc Pepin[8], Janine C. Bailey[8], Danijela Gnjidic[9] and Jennifer L. Lund[1]

[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Injury Prevention Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Division of Physical Therapy, University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Division of Geriatric Medicine & Palliative Care Program, University of North Carolina at Chapel Hill, Chapel Hill, NC; [6]Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC; [7]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Carrboro, NC; [8]Durham VA Geriatric Research Education and Clinical Center (GRECC), Durham, NC; [9]Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

Background: Fractures are common, severe physical complications among older adults (aged 65 years+) that often result from unintentional falls and can lead to reduced long-term mobility. Since the Centers for Medicaid and Medicare Services (CMS) transitioned from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to the Tenth Revision, Clinical Modification (ICD-10-CM) coding on October 1, 2015, the ICD-9-CM codes used for fracture identification need to be mapped so that trends of this adverse health outcome can be studied in the ICD-10-CM era.

Objectives: We mapped and evaluated the consistency in assessing fracture diagnosis and procedure code frequency before and after the coding transition.

Methods: We graphically compared trends in the monthly prevalence and incidence of fracture diagnoses and procedures from the end of the ICD-9-CM era (January 2013 - October 2015) to the start of the ICD-10-CM era (October 2015 - December 2016) using a 1% nationwide, random sample of US Medicare claims data. Validated ICD-9-CM diagnosis and procedure codes from the algorithm developed by Ray and colleagues were mapped using the CMS General Equivalence Mappings and a forward-backward mapping (FBM) approach. We examined each fracture site (hip, radius/ulna, humerus, rib/sternum, pelvis/sacrum/coccyx, ankle, femoral shaft, hand, tibia/fibula, skull/face, foot, clavicle/scapula, and patella) individually and also a composite outcome of all non-vertebral fracture sites.

Results: The incidence and prevalence of the fracture site diagnosis codes did not have consistent trends in the two eras. For all fracture sites (other than skull/face) and the composite outcome, both measures were lower after the coding transition. For example, hip fracture incidence in December 2013 and 2016 was 0.09% and 0.02%, respectively. Whereas for the skull/face fracture diagnoses, both prevalence and incidence were higher in the ICD-10-CM era (i.e., incidence was 0.04% and 0.08% in December 2013 and 2016, respectively). The incidence and prevalence of the fracture procedure codes across eras were consistent for the humerus, skull/face, and tibia/fibula, but inconsistent for all other sites.

Conclusions: The automated mapping performance was poor for most fracture sites. Careful, manual review is needed to ensure that the relevant codes are captured after mapping.

4516 | Opioid prescribing among medicare part D providers before and after the introduction of national prescribing guidelines in the United States

Mary C. Figgatt, Kristin Y. Shiue and Yvonne M. Golightly

University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC

Background: Opioid therapy is a common pain management strategy in the United States, but prescription opioids are involved in over one-third of all opioid overdose deaths. To date, there is limited evidence of the impact of the 2016 *CDC Guideline for Prescribing Opioids for Chronic Pain* on national prescribing patterns, especially among older adults, This patient group is of particular interest because of a recent increase in opioid overdose rates among older adults and the link of opioid use with an increased risk of falls.

Objectives: To describe temporal trends in opioid prescribing among Medicare Part D providers, overall, by prescriber specialty, and by state.

Methods: Descriptive analyses were conducted using data from the Medicare Part D Prescriber Public Use Files for 2015-2017 (n=1300319 unique providers). Opioid prescribers, defined as providers with >10 claims for any opioids, were evaluated as a percent of all Part D providers. Mean days supply was calculated as the sum of all days supply divided by the total count of opioid claims.

Results: From 2015-2017, the percent of Part D providers prescribing opioids declined from 74% to 71%, representing a decrease of over 4 million claims per year. Nearly all providers (>95%) in pain management, maxillofacial surgery, orthopedic surgery, rheumatology, and emergency medicine were opioid prescribers, though there was a slight decline observed in rheumatologists (2015: 97%, 2017: 94%). The most commonly represented specialties were internal medicine (13%), dentistry (13%), family medicine (12%), emergency medicine (6%), and obstetrics/gynecology (3%). Within these top specialties, the reduction in opioid prescribing was the greatest in obstetrics/gynecology (-5%) and dentistry (-4%), while across all specialties, the greatest absolute decline occurred in cardiology (-12%). By state[GY1] [SKY2], opioid prescribing decreased most notably in the Northeast (-7% to -4%), including New Hampshire, Massachusetts, New York, Maine, Pennsylvania, New Jersey, Vermont, and Connecticut. There were no meaningful changes in mean days supply from 2015-2017 (22 days per claim).

Conclusions: Although we observed slight decreases in the proportion of providers prescribing opioids, the overall mean days supply remained relatively constant[GY1] despite recommendations for

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

clinicians to limit prescriptions for acute pain to ≤7 days. Further research should examine provider prescribing behaviors in relation to existing guidelines, in addition to opioid prescribing trends among populations not served by Medicare Part D.

4557 | Impact of polypharmacy on risk of mortality among older people who received home care: A retrospective longitudinal cohort study

Shih-Tsung Huang[1], Liang-Kung Chen[2] and Fei-Yuan Hsiao[1]
[1]*College of Medicine, National Taiwan University, Taipei, Taiwan;*
[2]*National Yang-Ming University School of Medicine, Taipei, Taiwan*

Background: Older people who need home care are usually characterized by very old age, severe disability, multimorbidity as well as polypharmacy. Although polypharmacy has been identified as one of the modifiable factors to these people, conflicting data has been reported to the association between polypharmacy and clinical adverse events. These discrepancies in previous studies may result from different methodological limitations of existing studies, including small sample size or one-time measurement of polypharmacy status.
Objectives: This study aims to examine the association between polypharmacy and the risk of mortality in older people who need home care by adopting the time-varying (quarterly) measures of polypharmacy status.
Methods: People aged 65 years or older who were newly received home care service between 2008 to 2010 were identified from Taiwan's National Health Insurance Research Database. To prevent protopathic bias and guarantee that the identified participants' prescription records can be fully assessed for the first quarter, patients who died in the first quarter have been excluded. Polypharmacy status were collected on a quarterly basis during the 5 years follow-up period. The chronic use of 0 to 4 medications was consider as non-polypharmacy, 5 to 9 medications as polypharmacy, and 10 medications or more as excessive polypharmacy. All deaths occurring during the 5-year follow up period were identified. Generalized estimating equation model was used to examine the association between distinct polypharmacy status and risk of 1-, 3- and 5-years mortality.
Results: The mean age of 50,210 eligible subjects were 80.5 years, with 52.3% of women, and 78.9% of them have the Charlson's comorbidity index (CCI) scored to 2 and above. The mean follow-up period was 31.2 months. We categorized our study subjects into non-polypharmacy (n=14,198, 28.3%), polypharmacy (n=25,489, 50.8%) and excessive polypharmacy group (n=10,523, 21.0%) according their first quarter of polypharmacy status. After adjustment for age, sex, CCI, and other comorbidities, the GEE models indicated that polypharmacy and excessive polypharmacy group had lower risk of 5-year all-cause mortality than non-polypharmacy group (polypharmacy: adjusted odds ratio [aOR] =0.76, 95% CI=0.74-0.78; excessive polypharmacy: aOR=0.73, 95% CI=0.71-0.76). Similar results were observed at 1- and 3- years of follow-up.
Conclusions: Polypharmacy did not appear to significantly increase the risk of short- and long-tern mortality among home care patients, which deserves further prospective study to clarify.

4589 | Antipsychotics and mortality risk in patients with dementia and comorbidities

Ane Nørgaard Christensen[1], Theresa Wimberley[2], Thomas M. Laursen[3], Kazi Isthiak Ahmed[4,5], Jesper Hastrup Svendsen[6], Christina El-Ali Jensen-Dahm[1], Gunhild Waldemar[1] and Christiane Gasse[4]
[1]*Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;*
[2]*Aarhus University, Aarhus, Denmark;* [3]*Aarhus University, Aarhus, Denmark;* [4]*Aarhus University Hospital Psychiatry, Aarhus University, Aarhus, Denmark;* [5]*University of Copenhagen, Copenhagen, Denmark;*
[6]*Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Background: Antipsychotic drugs are commonly used to treat behavioral and psychological symptoms in patients with dementia. Antipsychotics are associated with increased risks of adverse events and death, which may vary in patients with comorbid conditions.
Objectives: To investigate whether cardiovascular and metabolic comorbidities affect the mortality risk associated with the initiation of antipsychotic treatment in patients with dementia.
Methods: We conducted a population-based matched cohort study using nationwide Danish registry data. The study population included all residents aged 65-95 with dementia in 2009-2014. Dementia was identified at a first-time dementia diagnosis registered in the Danish Hospital Registers and/or a first-time prescription for anti-dementia medication. Patients exposed to antipsychotics after dementia diagnosis were matched with up to three unexposed patients on sex, and age at and calendar year of the first-time dementia diagnosis. Patients were followed from the date of the first prescription for an antipsychotic (index date) until death, emigration, or Dec 31, 2015, whichever came first. We estimated hazard ratios (HR) with 95% confidence intervals (CI) using Cox proportional hazards analyses comparing mortality rates within 180 days after the index date in antipsychotic users and non-users. We adjusted for potential confounders, including living status, Charlson Comorbidity Index, psychiatric comorbidity, antidepressant or benzodiazepine use, tested for interactions, and stratified the analyses by diabetes, heart disease, and cerebrovascular disease.
Results: The study cohort included 8,244 exposed patients and 24,730 unexposed patients who were followed for 14,285.6 person-years (PYs). During the first 180 days of follow-up, 5,938 patients died (41.6/100 PYs). Patients exposed to antipsychotics had a crude mortality rate of 56/100 PYs, and a significantly higher risk of death (adjusted HR: 1.35, 95% CI: 1.27-1.43) than unexposed patients. Patients with heart disease and diabetes had overall higher mortality rates/100 PYs compared with patients without, particularly when using antipsychotics (heart disease: 78.2/100PYs (72.9-83.9), diabetes 69.5/100 PYs (62.7-77.0)). HRs within strata were not statistically different from the overall adjusted HRs.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: This study adds to the evidence that antipsychotic treatment is associated with an increased mortality. Caution in prescribing antipsychotics should be taken for all patients but most importantly for patients with prior comorbid disease related to the cardiovascular and metabolic systems.

4607 | Incident antiepileptic use and risk of hip fracture among persons with Alzheimer's disease

Federica Pisa[1,2,3], Jonas Reinold[4,2], Piia Lavikainen[5], Marjaana Koponen[5,6], Heidi Taipale[5,7,8], Antti Tanskanen[7,8,9], Jari Tiihonen[7,8,10], Sirpa Hartikainen[5] and Anna-Maija Tolppanen[2]

[1]UCB Pharma, Brussels, Belgium; [2]University of Eastern Finland, Kuopio, Finland; [3]Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany; [4]Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany; [5]University of Eastern Finland, Kuopio, Finland; [6]Monash University, Melbourne, Australia; [7]Karolinska Institutet, Stockholm, Sweden; [8]Niuvanniemi Hospital, University of Eastern Finland, Kuopio, Finland; [9]National Institute for Health and Welfare, Helsinki, Finland; [10]Center for Psychiatry Research, Stockholm City Council, Stockholm, Sweden

Background: Antiepileptic drugs (AEDs) have been associated with increased risk of hip fractures in adults with epilepsy, but the evidence for older adults with Alzheimer´s disease (AD) is limited.

Objectives: We conducted a matched cohort study to determine the risk of hip fracture in persons with AD who initiated AEDs.

Methods: In the Medication use and AD (MEDALZ) cohort of 70,718 Finnish community dwellers with clinically verified AD diagnosis in 2005-2011, we identified all incident users of AEDs using national Prescription register. Incident users were persons with a first AED dispensation after AD diagnosis without any AED use within 1 year before. AEDs were classified as older (valproate, carbamazepine, clonazepam, phenytoin, levetiracetam, primidone) or newer (pregabalin, gabapentin, oxcarbazepine, lamotrigine, topiramate). We matched each user to 2 non-users by sex, age (±1 year), and time since AD diagnosis (± 183 days) using incidence density sampling without replacement. Incident hip fractures until 2015 were identified from Care register for health care. We calculated age- and sex- adjusted incidence rates (aIRs) of hip fracture and inverse probability of treatment weighted hazard ratio (IPTW HR), using Cox regression.

Results: 5,522 incident users were identified and matched to 11,044 non-users (in both groups, women: 65%; median age: 81 years). 53.3% of users initiated with newer AEDs (pregabalin 79.8%, gabapentin 10.2%) while 46.7% initiated with older AEDs (valproate 67.6%, carbamazepine 13.0%). aIR of hip fracture (/100 person-years) was 1.6 (95% CI 1.5-1.8) in non-users and 1.9 (1.7-2.2) in users. IPTW HR was 1.17 (1.05-1.30) in users compared with non-users; it was 1.28 (1.10-1.49) for short (<14 weeks) and 1.42 (1.22-1.66) for medium (14 to <64 weeks) duration of use, compared with duration ≥64 weeks. Older AEDs had HR of 0.96 (0.77-1.19) compared with newer AEDs.

Conclusions: Higher risk of hip fracture in AED users prompts careful consideration before prescribing AEDs to persons with AD and monitoring of those who need to be treated.

4678 | Network analysis of interacting medication use in elderly persons in Norway

Mohsen Askar and Kristian Svendsen

UiT - The Arctic University of Norway, Tromso, Norway

Background: Co-use of medications is common amongst patients and especially elderly who have more morbidities. This use is often beneficial but it also carries increased risks of drug-drug interactions (DDI) and adverse drug reactions

Objectives: Using network analysis to map and study the comedication of interacting medications in the elderly Norwegian population.

Methods: We used data from the Norwegian Prescription Database (NorPD) from 2012-2014 of dispensed medications among persons 65 years or older. The total population was 765,383 persons with over 62 million prescriptions. Of these our study population consisted of 669,683 persons having at least one prescription dispensed covering the index date of 1.1.2013. The covered days was calculated for each prescription using number of Defined Daily Doses dispensed. Treatment episodes were constructed using Proportion of Days Covered (PDC) and allowing for 80% adherence and a 14 days gap period. Any treatment episodes covering the index date was included and used to create co-medication patterns. Drug-drug interactions (DDI) were found using the National Prescription support database (FEST) from the Norwegian Medicines Agency. Only severe interactions that should be fully avoided was used in this study. This consisted of 57,151 severe interactions in 1699 different drugs. Prescription data from the NorPD was merged with DDI data from FEST using ATC codes and visualized as a network using Gephi 0.9.2

Results: Combining the interaction data with drug utilisation data provided 229 drugs with 662 interactions used by the study population. The data has been visualised as a network to see the pattern of use. Simvastatin in combination with atorvastatin was the most commonly co-used interacting medications with 2320 users representing 0.35% of elderly medication users. Other interesting interactions within the top 10 most used DDI combinations are esomeprazole and clopidogrel, simvastatin and carbamazepine, metoprolol and paroxetine (pharmacokinetic) and metoprolol and verapamil (pharmacodynamic). All of these with a prevalence of between 0.12 and 0.06% of the study population. The network showing all interactions where the medications included has at least 900 (0.13%) users can be seen online here: https://www.dropbox.com/s/8rv782gdh48ro5t

Conclusions: There are many severe interactions occurring in the elderly Norwegian population. None of them are very common, but our results will allow for further research into the use of medications with severe interactions and could be used in research into the role DDIs have in outcomes such as hospital admissions and death.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4718 | The association between medication and alcohol use and the incidence of frailty among older adults: An international retrospective cohort study

Janja Jazbar, Igor Locatelli and Mitja Kos
University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

Background: Frailty as an age related syndrome is considered one of the most pressing public health challenges as the population is aging worldwide. Understanding potentially modifiable factors that influence the risk of frailty is one of the key concerns in managing frailty.
Objectives: To evaluate the association between medication and alcohol use and the incidence of frailty among older adults.
Methods: This study was a retrospective cohort study on older adult outpatients (≥ 65 years) using the data from the longitudinal Survey of Health, Ageing and Retirement in Europe (SHARE survey, 27 European countries). Data from 2013 (wave 5) and 2015 (wave 6) were used for the analysis. The exposures were medication and alcohol use measured at baseline (in 2013). Medication use was measured as number of concomitant medication classes. Exposure to alcohol was assessed with two variables, namely alcohol use (AUDIT-C) and excessive drinking problems in the past. The outcome measure was the incidence of frailty after two years (in 2015), defined by frailty index. Multiple logistic regression model was used to evaluate the association with adjustment for several potential confounding factors.
Results: Of the 17,489 nonfrail participants at baseline, 2,104 (12.0%) developed frailty syndrome in two years. Participants with more medication classes at baseline had higher incidence of frailty (4.6% in the population without chronic medication compared to 30.7% in the population with 5 or more medication classes). The adjusted odds ratios (95% CI) for the incidence of frailty when taking 1-2, 3-4 and ≥5 concomitant medication classes compared to no medications were 1.74 (1.44-2.09), 2.89 (2.34-3.57), and 4.67 (3.51-6.21), respectively. The adjusted odds ratios (95% CI) of frailty in non-hazardous and hazardous alcohol users compared to no alcohol users were 0.67 (0.59-0.75) and 0.78 (0.67-0.90), respectively. Participants with excessive drinking problem in the past had higher odds ratio for frailty compared to participants with no drinking problem in the past (adjusted OR, 95% CI: 2.20, 1.62-2.99; incidence: 16.4% vs. 10.1%).
Conclusions: The use of higher number of concomitant medication classes is associated with higher incidence of frailty. Hazardous and non-hazardous alcohol use are associated with decreased incidence of frailty compared to no alcohol use, which may be due to reversed causality. Excessive drinking problem in the past is associated with increased incidence of frailty, which supports the literature on harmful effects of alcohol use on frailty syndrome.

4735 | Discharge prescribing in older adults with type 2 diabetes hospitalised for diabetes-related complications

Stephen Wood[1], J. Simon Bell[1,2], Dianna Magliano[3,2] and Jenni Ilomäki[4,2]
[1]Monash University, Melbourne, Australia; [2]Monash University, Melbourne, Australia; [3]Baker Heart and Diabetes Institute, Melbourne, Australia; [4]Monash University, Parkville, Australia

Background: Intensive therapy is often required for the treatment of Type 2 Diabetes (T2D) in order to achieve glycated haemoglobin (HbA_{1C}) targets as the disease progresses. However, this must be balanced against the need to avoid aggressive treatment in vulnerable populations such as older or frail individuals and those with dementia, since stringent glycated haemoglobin targets confer no known benefits to these people.
Objectives: To determine whether age, frailty or dementia are associated with the intensity of anti-hyperglycaemic therapies prescribed for hospitalised patients at discharge.
Methods: A cross-sectional study was completed using discharge prescribing data from Melbourne's Eastern Health (EH) hospital network. We identified 3,067 patients aged 65-99 years with T2D, at least one diabetes related complication and an index discharge between 2012 and 2016. Multinomial Logistic Regression was used to estimate Odds Ratios (ORs) with 95% confidence intervals (CI) for being prescribed insulin, non-insulin anti-hyperglycaemics or a combination of those two compared to no anti-hyperglycaemics. T2D, relevant co-morbidities, diabetes complications, level of frailty and number of co-morbidities, indicated by the Charlson Comorbidities Index (CCI), were identified using International Classification of Diseases-10 (ICD-10) codes. Medications were identified Anatomical Therapeutic Chemical (ATC) codes: insulins (A10A) and non-insulin anti-hyperglycaemics (A10B).
Results: No T2D therapy, insulin, non-insulin T2D therapy, and combinations of insulin and non-insulin therapy respectively, made up 23%, 19%, 39%, 20% of the cohort. People aged >80 were less likely than people aged 65-80 to be discharged with insulin (OR 0.53; 95%CI [0.42-0.68]), non-insulin T2D therapy (OR 0.67; 95%CI [0.55-0.81]), or combinations of these two (OR 0.37; 95%CI [0.30-0.47]), compared to no T2D therapy. Frailty was associated with lower odds of being prescribed insulin (OR 0.64; 95%CI [0.43-0.94]) or non-insulin T2D therapy (OR 0.64; 95% CI [0.46-0.89]), compared to no T2D therapy. People with dementia were less likely to be discharged with insulin and non-insulin combinations (OR 0.56; 95%CI [0.34-0.92]) compared to no T2D medication.
Conclusions: Prescribers are aware that people >80 years and frail individuals require less aggressive treatment targets in T2D compared to older people aged 65-80 years and those who are not frail. People with dementia are also less likely to be prescribed combinations of insulin and non-insulin anti-hyperglycaemics compared to those without dementia.

4749 | Prescription gabapentinoid use and opioid-related adverse events in medicare older adults

Cheng Chen, Almut G. Winterstein, Wei-Hsuan Jenny Lo-Ciganic, Patrick J. Tighe and Yu-Jung Jenny Wei
University of Florida, Gainesville, FL

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Use of prescription gabapentinoids (i.e., gabapentin and pregabalin) in older adults has increased 3-fold from 2002 to 2015. Gabapentinoid use is suspected as a contributor to the rising rates of hospitalizations due to opioid use disorder (OUD) and overdose in this population.

Objectives: To examine the association between gabapentinoid use and opioid-related adverse events among older adults.

Methods: In a case-crossover study using 5% Medicare claims data (2011-2015), we included fee-for-service beneficiaries aged ≥65 years newly diagnosed with an opioid-related adverse event (i.e., OUD or overdose) in the inpatient or outpatient settings. New cases were defined as having no diagnosis of opioid-related adverse events during the 180 days before the first OUD or overdose event (i.e., index event). We excluded beneficiaries who were not continuously enrolled, did not use prescription opioids, had a cancer diagnosis, or used hospice or palliative care services in the 180-day pre-index period. Within each patient, we compared the exposure to gabapentinoids during a 30-day hazard period (i.e., the 1-30 days before the index event) with the exposure during two 30-day control periods (i.e., the 61-90 and 121-150 days before the index event). Conditional logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of gabapentinoid exposure, adjusting for concurrent prescription opioid use and dose and other medication use. To address temporal trends in pain management, we conducted a case-time-control analysis by estimating the OR of gabapentinoid use in a control group without opioid-related adverse events. A trend-adjusted OR was calculated as the ratio of ORs in the cases and controls.

Results: We identified 11,481 older adults newly diagnosed with an opioid-related adverse event (mean age=74±7; female=70%; White=86%). The prevalence of gabapentinoid use during the hazard period (30%) was slightly higher than in the two control periods (28% and 26%). The main analysis showed a positive association between gabapentinoid use and opioid-related adverse events (OR=1.62, 95% CI=1.46-1.80). Case-time-control analysis yielded similar results (trend-adjusted OR=1.37, 95% CI=1.08-1.74). We observed associations in both gabapentin-only (OR=1.69, 95% CI=1.50-1.90) and pregabalin-only users (OR=1.31, 95% CI=1.01-1.70).

Conclusions: Medicare older adults who had an opioid-related adverse event were more likely to have prescription gabapentinoid in the immediate 30 days before the event than in more distant historical control periods.

5043 | The use of preventative treatments (statins, bisphosphates and anti-hypertensives) in older patients with complex health needs: An analysis of UK primary care and linked hospital data

Ying He, Leena Elhussein, Antonella Delmestri, Danielle Robinson, Victoria Y Strauss and Daniel Prieto-Alhambra

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

Background: With an increasing ageing population, the UK NHS is under pressure to provide large amounts of long-term treatments for the prevention of cardiovascular disease and fragility fractures.

Objectives: We aim to characterise the population-level use of key preventative therapies (statins, bisphosphonates and anti-hypertensives) in three cohorts of older patients with complex health needs based on healthcare resource use, frailty (electronic frailty index (eFI) score) and polypharmacy respectively.

Methods: All participants aged 65 or older on 1 Jan 2009, registered to an up-to-standard practice for at least 1 year were identified from a UK primary care database (CPRD GOLD) and linked to Hospital Episode Statistics (HES) and The Office for National Statistics mortality register. Patients were followed up until the earliest of practice last collection date, patient transfer-out date, death date or data download date. Three cohorts were identified based on the top quintile of 1) number of unplanned hospital admissions in HES (cohort1), 2) eFI score (cohort2), and 3) number of different medications prescribed (cohort3), in the previous year. We estimated the point prevalence (PP) at study start date. Incident use was defined as new use after start date without use in the month prior to or on this date. Incidence rates (IR) of each drug group was calculated using Poisson regression model.

Results: A total of 73,724, 100,485 and 100,965 participants were identified in cohorts 1-3 respectively. The PP at start date for statins was 31.7%, 38.7% and 43.6%; for bisphosphates 7.0%, 7.3% and 9.8%; and for anti-hypertensives 50.1%, 59.8% and 66.1% in cohorts 1-3, respectively. The average follow-up time for the three cohort patients was 4.99, 5.06 and 5.18 years respectively. The overall IRs for statins in cohorts 1-3 were 5.31 (95%CI 5.23, 5.38), 5.29 (95%CI 5.23, 5.35) and 5.24 (95%CI 5.18, 5.30) per 100 person-years, respectively. The IRs were lower for bisphosphonates: 2.77 (95%CI 2.71, 2.82), 2.71 (95%CI 2.67, 2.76) and 2.98 (95%CI 2.94, 3.03) in cohorts 1-3 respectively; whereas the IRs of anti-hypertensives were slightly higher or similar compared to the IRs of statins: 6.11 (95%CI 6.03, 6.19), 5.60 (95%CI 5.53, 5.66) and 5.07 (95%CI 5.01, 5.13) in cohorts 1-3.

Conclusions: Statins, bisphosphonates, and anti-hypertensives are commonly prescribed among older patients with complex health needs. Further research is needed on the effectiveness and safety of preventative medications for these patients.

5113 | Predicting fall risks in older adults with atrial fibrillation

Kueiyu Joshua Lin[1,2], Ajinkya Pawar[1], Nileesa Gautam[1] and Dae Hyun Kim[1,3]

[1]*Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA;* [2]*Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA;* [3]*Hebrew Rehabilitation Center, Harvard Medical School, Boston, MA*

Background: High risk of falling is one of the leading reasons for withholding anticoagulation in patients with Atrial fibrillation (AF) when it

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

is recommended by clinical guidelines. However, such risk is often assessed arbitrarily and there is no objective fall assessment developed for this particular population.

Objectives: To externally test the performance of a claims-based fall risk prediction score developed by Homer et al. in the general population and optimize it in older adults taking oral anticoagulant (OAC) for non-valvular AF by incorporating additional relevant predictors.

Methods: We used the US Medicare claims data to identify new initiators aged ≥ 65 years of OAC (warfarin, dabigatran, rivaroxaban, or apixaban) with a diagnosis for non-valvular AF in the preceding 180 days from 2010/10 to 2014/12. We held out patients from the Midwestern US as the validation set and used patients from all other US regions as the training set for the model development. We used Lasso regression with 5-fold cross-validation to select among the component variables in the previously developed 39-variable Homer score (Am J Med 2017) and 174 additional predictors based on literature, predicting 1-year risk of fall requiring hospitalization. We compared Homer score vs. new AF fall risk score in terms of Area under ROC curve (AUC) and reclassification, which measures performance of different scores in classifying patients into multiple risk groups. We defined the risk category as low (less than the average risk), intermediate (1 to <2 times average risk), or high (≥2 times average risk).

Results: Our study cohort included a total of 154,158 (mean age 76.4 years and female 52.8 %) patients (107,924 in training and 46,234 in validation set). Based on 3,332 fall events (3.1%) in the training set, the new AF fall risk score included 19 variables and has an AUC of 0.67 in the training and 0.67 in the validation set (superior to the corresponding Homer's AUC of 0.63 and 0.64, respectively, $p>0.001$). In the validation set, stratifying patients based on the predicted risk of our AF fall risk score, the actual fall risk in patients in the top decile was 8.2 times that in the lowest decile (6.3 vs. 0.8 %). In the validation set, our AF fall risk score reclassified 22.3, 35.8, and 48.6% of low, intermediate, and high-risk patients determined by Homer score with a net reclassification improvement of 5.4% ($P<0.001$).

Conclusions: When comparing effects of oral anticoagulants in patients with non-valvular AF, our claims-based AF fall risk score can be helpful in both clinical (to aid prescribing decisions) and research (to stratify patients for treatment effect heterogeneity assessment) contexts.

5139 | Impact of central nervous system depressant burden on the relationship between new opioid use and fracture risk

Qi Guan[1], David Juurlink[1], Siyu Men[2], Susan Bronskill[2], Hannah Wunsch[1], Pat Messner[3], Marie McMillan[3] and Tara Gomes[1]
[1]*University of Toronto, Toronto, ON, Canada;* [2]*ICES, Toronto, ON, Canada;* [3]*Ontario Drug Policy Research Network, Toronto, ON, Canada*

Background: Central nervous system (CNS) depressants are known to increase the risk of falling. This is particularly dangerous for older adults because falls are a leading cause of injury-related hospitalization and death in this population. However, CNS polypharmacy remains common due to the high prevalence of comorbidities in older adults.

Objectives: This study aims to assess whether additional CNS depressant burden modifies the relationship between new opioid therapy and the risk of falls/fractures.

Methods: Using administrative data from ICES, Canada, we are conducting a cohort study on adults >65 years old who started prescription analgesic therapy (opioid or non-steroidal anti-inflammatory drug [NSAID]) from 2008-2018. Individuals are stratified based on CNS depressant burden (none, low, high), measured by the number of concurrent non-opioid CNS depressant drug classes used (0, 1-2, ≥3). Within each group, opioid and NSAID users are balanced using inverse probability treatment weighting and compared using marginal Cox models to determine risk of wrist/hip fractures in the 14 days following opioid/NSAID therapy. Pairwise comparisons of outcome risk between burden groups are conducted using z-tests.

Results: Of the 1,048,330 individuals included in our study, 884,341 (84.4%) had no CNS depressant burden, 157,441 (15.0%) had low burden, and 6,528 (0.6%) had high burden. Opioid and NSAID use was almost evenly split among those with no CNS burden (N=474,813 [53.7%] for opioids and N=409,528 [46.3%] for NSAIDs) while almost 2/3 of the low and high CNS depressant burden groups consisted of opioid users (N=95,926; 60.9% and N=4,079; 62.5%, respectively). Groups experiencing more CNS depressant burden tended to have more females (range: 65.4%-67.5%) and reside in lower income neighbourhoods. While event rates were low, opioid users experienced fractures more than NSAID users (N=449, 0.09% vs N=140, 0.03% for no burden; N=166, 0.17% vs N=41, 0.07% for low burden; high burden values censored).

Conclusions: Based on crude values, opioids had more effect on falling than NSAIDs when individuals were free of CNS depressant burden. This may be attributed to lack of tolerance to CNS depressants or increased mobility due to fewer comorbidities but will be explored further with statistical modelling.

Health Economics/Outcomes Research

60 | Trial participants vs real-world users of medicines: How different are they really and does it matter?

Anton Pottegård[1], Olaf Klungel[2], Daniel Morales[3], Mehdi Najafzadeh[4]
[1]*University of Southern Denmark, Odense, Denmark;* [2]*Utrecth University, Utrecth, Denmark;* [3]*University of Dundee, Dundee, United Kingdom;* [4]*Harvard University, Boston, MA*

Background: Differences between trial participants and real-world users of medicines are often considered one of the main reasons for generating 'real-world evidence'. However, few studies have systematically explored these potential differences and their impact on study results.

Objectives: This symposium will address the following issues:

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(i) Does current evidence suggest a systematic difference between trial participants and real-world users?
(ii) To what extent are real-world users different from trial participants when considering patient characteristics and trial eligibility?
(iii) How do differences between real-world users and trial participants affect estimates of treatment effectiveness and safety?
(iv) How do differences in measurement of risk factors and outcomes affect perceived differences between trial evidence and real-world evidence?
The symposium will target any pharmacoepidemiologist working within the 'real-world evidence' space.

Description: The symposium will be initiated by prof. Anton Pottegård. The common perception that the difference between trial participants and real-world users is a well-documented fact will be challenged, followed by selected examples of real-world efficacy estimates (compared to trial findings) to set the scene for the subsequent presentations.
Prof. Olaf Klungel will review the extent of exclusion of elderly from pivotal trials on therapeutic indications typically present among elderly. Further, examples of the impact of differences in patient characteristics between trial participants and real-world users on effectiveness and safety of medicines (direct oral anticoagulants for atrial fibrillation and chemotherapy for non-small cell lung cancer) will be discussed. Daniel Morales, will review how exclusion rates vary by trial setting, funding source and over time. Examples demonstrating how differences between trial participants and real-world users impact how we quantify the safety and effectiveness of medicines (ACE inhibitors for renal disease and antiplatelets for stroke) will be discussed. Mehdi Najafzadeh, will review the difference in how outcomes and risk factors are captured in trials versus in databases. He will discuss how this impact on findings from different studies and propose potential solutions for addressing such differences in the future. The symposium will end with a panel discussion. Selected literature references will be prepared in advance for participants to easily access them.

100 | Readmissions and postoperative mortality of coronary artery revascularization in people with and without Alzheimer's disease: A nationwide cohort study

Mai Vu[1,2], Marjaana Koponen[1,3,2], Heidi Taipale[1,4,5,2], Raimo Kettunen[6], Sirpa Hartikainen[1,2] and Anna-Maija Tolppanen[1,2]
[1]University of Eastern Finland, Kuopio, Finland; [2]University of Eastern Finland, Kuopio, Finland; [3]Monash University, Parkville, Australia; [4]Karolinska Institutet, Stockholm, Sweden; [5]Niuvanniemi Hospital, Kuopio, Finland; [6]University of Eastern Finland, Kuopio, Finland

Background: Coronary artery disease is common in older persons, and one of the management strategies is revascularization procedure (coronary artery bypass grafting and percutaneous coronary intervention). However, effectiveness as well as survival rate in persons with Alzheimer's disease (AD) after these procedures have not been investigated before.

Objectives: To compare the incidence of coronary artery revascularization, readmission, and mortality after procedure among persons with and without AD.

Methods: Our study is based on a retrospective register-based Medication Use and Alzheimer's disease (MEDALZ) cohort which includes all community dwellers with a clinically verified AD diagnosis during 2005 - 2011 in Finland (N=70 719). For each incident revascularized persons with AD, four comparison persons without AD were was matched by age, sex, and hospital district. The follow-up for this study began on the date of AD diagnosis (matching date for comparison persons). Altogether 448 persons with AD and 5999 without AD underwent revascularization during the follow-up. The outcomes were 30-day and 90-day re-admission rate after discharge, and all-cause 1-year and 3-year mortality. Analyses were conducted with Cox proportional hazard models adjusted with age, sex, comorbidities, and statin use.

Results: Revascularization were less often performed in persons with AD (adjusted hazard ratio HR = 0.23, 95% CI 0.21 - 0.26). Persons with AD tended to have lower risk of 30-day readmission (adjusted HR: 0.77, 95% CI 0.57 - 1.03), and 90-days readmissions (adjusted HR: 0.87, 95% CI 0.70 - 1.08). Higher proportion of persons with AD (7.4%) died in the operative unit compared with persons without AD (4.8%) There was no difference in 1-year mortality (adjusted HR:1.20, 95%CI 0.89 - 1.62) but people with AD had higher 3-year mortality (adjusted HR: 1.73, 95%CI 1.48 - 2.01).

Conclusions: The higher three-year mortality in people with AD after revascularization is in line with the overall increase in risk of death in persons with AD. Persons with AD had higher in-hospital mortality but there were no differences in the short-term outcomes regarding rehospitalizations or death. Lower rate of revascularization, especially given the higher prevalence of ischaemic heart disease in people with AD raises questions about possible undertreatment as this group also needs these operations to improve functioning and quality of life.

2457 | Drug use variability by community sampling place and setting for rural women

Carl Leukefeld, Megan Dickson, Christopher J. McLouth, Matt Webster and Michele Staton
University of Kentucky, Lexington, KY

Background: Rural drug use across the US has increased, as has the number of studies examining those increases. However, there is a paucity of studies focused specifically on rural women.

Objectives: This study examines self-reported drug use in two rural county settings among women on public assistance (Welfare to Work) and in community confinement (jails) to: 1) determine how drug use

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patterns compare across sampling place, and 2) describe how county setting relates to self-reported drug use. It was hypothesized that rural women in jails would report more drug-involvement than those in Welfare to Work settings, but that there would also be differences related to county of recruitment.

Methods: The current study design includes data from two datasets of drug-using rural women who were consented during the same time period (between December 2012 and August 2015), in the same two rural Appalachian Kentucky counties. The first dataset includes random selection and interviews with 279 women recruited from two county jails. The second dataset is 254 low-income women on Welfare to Work (public assistance). The current study includes baseline measures from both datasets such as self-reported lifetime drug use from the Addiction Severity Index. Participation rates exceeded 80% in the both samples. Logistic regressions controlling for demographic differences and county were used to compare drug use patterns across samples.

Results: Women recruited from jail were significantly older ($p<.001$), more likely to be white ($p=.022$), married ($p=.010$), and have less than a high school education ($p=.011$). When controlling for recruitment county and demographic differences, women recruited from jail were more likely to self-report having used of 8 of the 9 drugs examined, as well as injecting (AOR=12.66; $p<.001$) and multiple drug use (AOR=14.31; $p<.001$). Examining individual samples across county sites found similarities in drug use patterns by county of recruitment. Specifically the prevalence of methamphetamine use was significantly higher ($p<.001$) in both samples from the same site, while illicit methadone use was significantly lower ($p<.05$).

Conclusions: Results support study hypotheses, suggesting that although jail participants are more drug-involved, drug use patterns may also be associated with county of recruitment. Implications include the need to: 1) consider both the community sampling place and setting when selecting subjects, 2) screen rural women for treatment needs and refer to interventions or treatment, as appropriate, and 3) improve service availability for rural women to reduce the likelihood of future drug use and related behaviors.

2461 | Real-world outcomes of patients with locally advanced or metastatic epithelioid sarcoma

Mrinal M Gounder[1], Priscilla Merriam[2], Ravin Ratan[3], Shreyaskumar R Patel[3], Rashmi Chugh[4], Victor M Villalobos[5], Mark Thornton[6], Brian A Van Tine[7], Amr H Abdelhamid[2], Preeti Joshi[8], Jennifer Whalen[8], Jay Yang[8], Anand Rajarethinam[8], Mei Sheng Duh[9], Priyanka J Bobbili[9], Lynn Huynh[9], Todor I Totev[9], Angela K Lax[9] and George D Demetri[2,10]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana Farber Cancer Institute and Harvard Medical School, Boston, MA; [3]The University of Texas M.D. Anderson Cancer Center, Houston, TX; [4]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; [5]University of Colorado Cancer Center, University of Colorado, Aurora, CO; [6]Sarcoma Foundation of America, Damascus, MD; [7] Washington University School of Medicine, St. Louis, MO; [8]Epizyme, Inc., Cambridge, MA; [9]Analysis Group, Inc., Boston, MA; [10]Ludwig Center at Harvard, Boston, MA

Background: Epithelioid sarcoma (ES) is an ultra-rare and aggressive subtype of sarcoma that typically affects young adults. Limited data are available on effectiveness and safety of conventional systemic therapies for treatment of advanced (unresectable and/or metastatic) ES.

Objectives: This study aimed to collect real-world (rw) data on outcomes of ES patients receiving at least first-line (1L) or 2 or more lines (2L+) of systemic therapies.

Methods: Retrospective chart review was conducted in patients with advanced ES who initiated systemic therapy between 2000-2017 at 5 US cancer centers. RECIST assessment was not performed in clinical practice, thus rw overall response rate (rwORR), duration of response (rwDOR), disease control rate (rwDCR; stable disease ≥32 weeks or response of any duration) and progression-free survival (rwPFS) were assessed by review of radiology reports. Overall survival (OS), rwDOR and rwPFS were estimated from start of therapy by Kaplan-Meier method. Endpoints were compared among patients treated with monotherapy vs combination therapy. Adverse events (AEs) resulting in treatment modification, discontinuation, hospitalization, permanent sequelae or death, were abstracted from medical records.

Results: Of 74 eligible patients, 53 (72%) were male, and 63 (85%) had metastatic ES. INI-1/BAF47 was undetectable in 90% of 41 tumors tested. Median (range) age at diagnosis was 33 years (11-76), and number of lines of therapy received was 2 (1-7). Anthracycline-based (54%) and gemcitabine-based (24%) regimens were used most often in 1L. 1L rwORR was 15%, rwDCR was 20%, median rwDOR was 3.3 months, median rwPFS was 2.5 months, and median OS was 15.2 months. Among 46 (62%) patients with evaluable data in 2L+, rwORR was 9%, rwDCR, was 20%, median rwDOR was 4.5 months, median rwPFS was 6.0 months, and median OS was 10.0 months. In 1L, the 20 (27%) patients who received monotherapy had a lower rwORR (5% vs 19%) and rwDCR (16% vs 22%) compared with patients who received combination therapy; a similar trend was observed in 2L+. Over 50% of patients had at least one AE; most frequently febrile neutropenia (14%), pain (9%), anemia, dyspnea, fever, thrombocytopenia and transaminitis (5% each).

Conclusions: Cytotoxic chemotherapies and tyrosine kinase inhibitors have limited efficacy in advanced ES and are associated with standard toxicities. This US-based rw study provides benchmarking treatment efficacy and safety data to understand the medical need of patients with advanced ES.

2476 | High pollen levels increase the likelihood of asthma-related inpatient admissions and emergency department visits in children with asthma: A matched case control study using patient-level claims and linked weather data

Elizabeth R. Packnett, Nicole M. Zimmerman, Caroline Hendriques and Debra E. Irwin

IBM Watson Health, Bethesda, MD

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Asthma is a common, chronic respiratory condition that affects about 6 million children in the United States. Previous ecologic studies showed increased asthma-related healthcare use when pollen levels are high.

Objectives: This study's objective was to describe the association between pollen levels and likelihood of asthma-related inpatient (IP) admissions or emergency department (ED) visits in children with asthma.

Methods: Children with asthma were identified from the MarketScan Commercial Database linked to pollen data in the IBM MarketScan Weather Database between March and October 2016. Those with an asthma-related IP admission or ED visit were cases; date of the IP/ED visit was the index date. Controls had no asthma-related IP/ED utilization during 2016 and the index date was the date of first asthma-related outpatient encounter in 2016. Cases were matched to controls at a 1:1 ratio on index month. Pollen levels (none, low, moderate, high) were assigned using the maximum pollen value in the five days before the index date. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression to describe the likelihood of asthma-related IP/ED visits while controlling for baseline patient demographic and clinical characteristics related to asthma severity.

Results: 11,502 cases and controls were matched at 1:1 ratio; 63% were male. Likelihood of asthma-related IP/ED use was significantly higher when the maximum pollen level was high for both grass pollen (OR: 1.25; 95% CI: 1.09,1.43) and ragweed pollen (OR: 1.18; 95% CI: 1.02,1.38) vs. none. Moderate grass pollen levels were also associated with higher likelihood of asthma-related IP/ER visits (OR: 1.17; 95% CI: 1.09, 1.43).

Conclusions: Probability of an asthma-related IP/ER visit in children with asthma was significantly increased when grass or ragweed pollen levels were high after controlling for patient baseline demographic characteristics and clinical characteristics related to asthma severity. Further research is necessary to evaluate the role of seasonal variation in pollen type on the effectiveness of asthma medications and asthma-related healthcare utilization.

2478 | Clinical outcomes in the first year of life among infants of mothers with preeclampsia or gestational diabetes: An analysis of linked maternal and infant claims

Elizabeth R. Packnett, Helen V. Varker, Kristin A. Evans and Debra. E Irwin
IBM Watson Health, Bethesda, MD

Background: Preeclampsia and gestational diabetes mellitus (GDM) are common complications of pregnancy and are associated with infant morbidity. Rates of both conditions have increased in incidence in the US over the past two decades.

Objectives: This study's objective was to compare infant outcomes by maternal preeclampsia and GDM status in a cohort of infants linked to their mothers using claims data.

Methods: Women aged 15-50 with a singleton delivery between 1/1/2010 and 9/30/2015 and at least 12 months of continuous enrollment before and after the delivery date were identified in the MarketScan Commercial Database. Infants were linked to their mothers and required to be continuously enrolled for at least 12 months following their birthdate. Maternal preeclampsia and GDM were identified if a diagnosis of preeclampsia or GDM was present prior to delivery. Infant outcomes were assessed in 12 months following birth and stratified based on presence of maternal preeclampsia or GDM.

Results: 557,481 mother:infant pairs were identified (10,371 with maternal preeclampsia and 547,110 without preeclampsia; 49,202 with maternal GDM and 508,279 without GDM). Rates of cesarean section (Preeclampsia vs. no preeclampsia: 55.9% vs. 36.6%; GDM vs. no GDM: 47.1% vs. 36.0%), preterm delivery (Preeclampsia: 15.3% vs. 5.4%; GDM: 7.6% vs. 5.4%), low birthweight (Preeclampsia: 18.9% vs. 5.0%; GDM: 7.1% vs 5.1%), feeding problems (Preeclampsia: 38.3% vs. 32.3%; GDM: 33.9% vs. 32.3%), and delayed developmental milestones (Preeclampsia 1.3% vs. 0.6%; GDM: 1.4% vs. 1.2%) were significantly higher among infants with vs. without preeclampsia or GDM ($p<0.001$ for all). The proportion of infants with at least one inpatient admission (Preeclampsia: 42.5% vs. 26.5%; GDM: 29.6% vs. 26.9%) or emergency room visit (Preeclampsia: 29.9% vs. 23.8%; GDM: 25.9% vs. 23.7%) during follow-up were also significantly higher in infants with maternal preeclampsia or GDM ($p<0.001$ for all).

Conclusions: It is feasible to link mothers with their newborns to evaluate infant health outcomes based on maternal comorbidities. Infants with maternal preeclampsia or GDM have higher rates of events indicative of worse outcomes during their first year of life which were more pronounced among infants with maternal preeclampsia than infants with maternal GDM.

2515 | Using electronic data to validate acute pancreatitis diagnoses

Gregory A. Nichols[1], Anouk Deruaz-Luyet[2], Hristo Iliev[2] and Kimberly G. Brodovicz[3]
[1]Kaiser Permanente Northwest, Portland, OR; [2]Boehrniger Ingelheim GmbH, Ingelheim am Rheim, Germany; [3]Boehrniger Ingelheim Pharmaceuticals, Ridgefield, CT

Background: Recorded diagnoses of acute pancreatitis (AP) using ICD9/ICD10 codes only are often inaccurate in the United States resulting in limited utility for case identification.

Objectives: To validate ICD9/ICD10 diagnoses of AP recorded in the electronic medical record (EMR) of an integrated health system and to determine whether other recorded data could be included as covariates in an algorithm to more accurately identify cases of AP in common US EMR and claims data.

Methods: We identified random samples of potential cases of AP from inpatient diagnoses (any position) and from outpatient or emergency department diagnoses immediately preceding a hospitalization for any reason, and from hospitalizations for differential diagnoses (cholangitis and cholecystitis) in 2012-2018. We conducted an EMR

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

review to confirm cases meeting the Atlanta Classification or cases with a clinician recorded note of AP. Using confirmed cases as the "gold standard", we used logistic regression to develop EMR-based and claims-based algorithms using variables typically available in these data sources for identifying cases of acute pancreatitis. Algorithm performance was assessed with the C statistic, sensitivity, specificity, and positive and negative predictive value.

Results: Of the 550 patients with an AP diagnosis from any source, 467 (84.9%) met the gold standard as did 5 of 150 patients (3.3%) with a differential diagnosis. An AP diagnosis from any source had high sensitivity (98.9%), modest specificity (63.6%), and a reasonably good C statistic (0.813). A simple EMR-based model attained a C-statistic of 0.913 using an AP diagnosis (from any source), body mass index > 30 kg/m^2, serum lipase > 3 times upper limit of normal (ULN), and presence of diabetes. A simple claims-based model attained a C-statistic of 0.892 using an AP diagnosis (from any source) and dichotomous variables for whether a serum lipase test was performed and whether an abdominal ultrasound was performed; sensitivity was 89.8%, specificity 79.4%, and positive and negative predictive values of 90% and 79%, respectively. Use of ICD10 vs. ICD9 diagnoses appeared to only slightly improve case identification.

Conclusions: Consistent with available studies, we found diagnoses of AP do not accurately identify confirmed cases in US data sources. Our results suggest that the addition of a few variables typically available in existing data sources can increase accurate identification of AP cases, producing an area-under-the-curve (C statistic) of approximately 0.90 with high levels of sensitivity and specificity, and positive and negative predictive value.

2589 | Scale-up of amoxicillin dispersible tablet in the management of uncomplicated childhood pneumonia in Nigeria: A cost-benefit analysis

Charles E. Okafor[1], Obinna I. Ekwunife[2] and Sabina O. Nduaguba[3]
[1]*Griffith University, Nathan, Brisbane, Australia;* [2]*Nnamdi Azikiwe University, Awka, Nigeria;* [3]*University of Florida, Gainesville, FL*

Background: In Nigeria, about 19% of children under five die of pneumonia every year. The World Health Organisation (WHO) recommends the use of oral amoxicillin dispersible tablet (DT) as the first-line agent in its management. Some parents may be unable to procure the medication for a full treatment course due to other competing needs. In pursuant of SDG-3 and the African Union Agenda, 2063, there is need for external support.

Objectives: The principal objective of this study is to evaluate the cost and benefit of implementing amoxicillin DT in management of childhood pneumonia in Nigeria and to determine if scale-up of treatment will be worthwhile.

Methods: The study was a cost-benefit analysis using simulation-based decision-analytic Markov model for the Nigerian setting and a sample size of 34.6 million children at risk of having pneumonia. The study used retrospective data and cost analysis was from the payer's perspective. Amoxicillin DT was the intervention used in the study. Health outcome was expressed in terms of disability adjusted life years (DALY) averted and converted to monetary terms (benefits). Both cost and benefit were expressed in US dollars. Data was analysed using Microsoft excel 2007. Distribution appropriate to each parameter was used in the analysis.

Results: The mean cost of management of pneumonia was $0.47 while the mean DALYs averted was 0.006. With a 2018 GNI per capita of $1960, the Benefit-cost ratio (BCR) obtained is 31. The annual benefit of scale-up of amoxicillin DT will be $153 million per annum.

Conclusions: There is a significant benefit with amoxicillin DT in the management of pneumonia in a high prevalent country like Nigeria. Scale-up of treatment has the potential to generate high returns on investment and should be considered especially in far-to-reach areas in Nigeria.

2668 | Cost of illness studies using the clinical practice research datalink: A review of costing methodologies

Preveina Mahadevan[1], Elaine Stamp[1], Cormac Sammon[1] and Robert Carroll[2]
[1]*PHMR, London, United Kingdom;* [2]*BMS, London, United Kingdom*

Background: The linked Clinical Practice Research Datalink (CPRD)-Hospital Episode Statistics (HES) dataset is increasingly being used to investigate resource utilisation and costs associated with specific patient groups. In order to ensure this work produces reliable and comparable findings it is important that they use appropriate and consistent methods.

Objectives: To review methodologies used to estimate costs of resource utilisation from the CPRD.

Methods: The Ovid MEDLINE(R) database was searched for keywords relating to studies that investigated cost of illness (COI) using CPRD data. All COI studies published between 2017 to 2019 were identified and screened. Information on the source of cost data and the methodology used to attribute costs to episodes of healthcare resource use were extracted and reviewed. All data extraction was performed by two independent reviewers and all decisions were reached by consensus with an additional third reviewer.

Results: A total of 30 COI studies were identified. Of the 27 studies that costed GP visits, 26 (96%) used *Personalised Social Services Resources Unit (PSSRU)*. Of 25 studies that included GP prescription costs, 10 studies (40%) used the *Prescription Cost Analysis (PCA)*, 11 (44%) used the *British National Formulary (BNF)*, 3 (12%) used *NHS Drug Tariff*, one study used the *RESIP Gem- script Code Dictionary* and one study used the *Dictionary of Medicines and Devices browser*. One study used *PCA* and *BNF data* and one used *PCA* and *NHS Drug Tariff data*. Studies which were non-specific regarding the source of cost data included one for GP data and two for prescriptions. Of 26 studies that costed inpatient admissions, 17 (65%) used *NHS reference costs*,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

7 (27%) used the *National Tariff* and 2 (8%) used both these sources. Amongst these, 20 (77%) stated they additionally used the *Healthcare Resource Grouper (HRG) software*. Of only 18 studies that costed outpatient visits, 16 (89%) used *NHS reference costs* where 9 studies (56%) defined the cost by speciality, 2 (11%) used *National tariff* and one study used *PSSRU*.

Conclusions: While there is some consistency in the methodologies used to attach costs to resource utilisation data from the CPRD, variation in the choice of sources of unit cost data and their application was observed. Incomplete reporting of methodologies also limited the extent to which the consistency of approaches could be determined. A more standardised and transparent approach to calculating total and relative costs using the CPRD-HES database is needed, this will allow for comparison of results and effective evaluation of methodologies.

3765 | Psychometric assessment of Urdu version of WHOQOL HIV BREF among Pakistani HIV infected patients

Ali Ahmed and Juman Dujaili
Monash University Malaysia, Jalan Lagoon Selatan, Malaysia

Background: The assessment of the health-related quality of life (HRQoL) in people living with HIV (PLHIV) has become crucial to evidence-based practice

Objectives: The current analysis was aimed to translate and examine the psychometric properties of the Urdu version of WHOQOL HIV BREF among HIV patients in Pakistan.

Methods: The standard forward-backward translation technique was used for Urdu translation of the WHOQOL HIV BREF. Based on the principle of 5 subjects minimally for each item, a sample of 182 patients were recruited by employing a universal random sampling technique. Data were analyzed to measure reliability, internal consistency, known-group, and multiple linear regression.

Results: High internal consistency was found for all WHOQOL HIV BREF facets scales as demonstrated by higher reliability coefficients (Sum scale: α = 0.93, Physical Health: 0.931; Psychological Health: 0.93; Level of Independence: 0.93; Social Relationships: 0.93; Environment Health: 0.93; Spiritual Health: 0.93). The test-retest reliability revealed a statistically significant interclass correlation coefficient ranged from 0.88-0.98 ($p<0.001$). In known group validity, subjects with lower CD4 counts had lower scores for all six domains ($p<0.001$). In similar, symptomatic participants had significantly lower scores than asymptomatic participants on the physical, psychological, social relationship and independence domains ($p<0.05$). Spearman's correlation tests indicated a significant inverse correlation ($P<0.001$) between HIV stages and all six domains of HIV-BREF scale, explaining higher stages associated with poor quality of life. Results also revealed a statistically significant positive correlation of all six domains with CD4 count ($P<0.001$), exhibiting patients with higher CD4 count will have higher mean scores of all six domains. When all domains were assessed together via Multiple linear regression analysis; only physical, psychological health and environment health domains were found significantly associated with higher CD4 count (Beta= 0.121, $P<0.001$, Beta=0.103, $P=0.002$, and Beta= 0.032, $P=0.032$).

Conclusions: The findings offer promising support for the use of the Urdu version of the WHOQOL HIV Bref among Pakistani HIV patients as a reliable and valid instrument.

3783 | Policy options for improving insulin affordability

Stacie B Dusetzina[1], Laura Keohane[1], Haiden Huskamp[2] and Nancy Keating[2]
[1]*Vanderbilt University School of Medicine, Nashville, TN;*[2]*Harvard Medical School, Boston, MA*

Background: Insulin affordability is a major concern in the United States. Several policy options are currently being debated to reduce out-of-pocket spending by older adults on the Medicare Part D program.

Objectives: We sought to summarize Medicare Part D plan design for insulin in 2019 and estimate expected Medicare beneficiary out-of-pocket spending on long-acting insulin under Part D's current benefit and under a proposed Part D redesign that eliminates the coverage gap and extends the initial coverage phase to an out-of-pocket spending limit of $2,000.

Methods: We used formulary files for all Medicare Part D plans available in 2019. We calculated expected out-of-pocket spending for 12 fills of long-acting insulin using median point-of-sale prices and cost-sharing arrangements used by Part D plans in 2019. We applied the 2020 Part D spending limits to determine when beneficiaries would move from the initial coverage phase to the coverage gap, where out-of-pocket spending changed from flat copayments to coinsurance (paying a percentage of the drug's price). We re-estimated out-of-pocket spending on insulin under two simplified designs: copayment only and coinsurance only.

Results: In 2019, most plans offered insulin using flat copayments for beneficiary cost sharing in the initial coverage phase, switching to coinsurance in the coverage gap. Based on an average per-fill point-of-sale price of $615 (across all long-acting insulin products), beneficiaries would expect to spend $1,115 out-of-pocket in 2020 for 12 fills of long-acting insulin based on the most common plan cost-sharing structure in 2019. With no coverage gap and an extension of the initial coverage phase to an out-of-pocket limit of $2,000, beneficiaries needing insulin would save $611 per year relative to the status quo if plans elected to use a flat copayment for cost-sharing. However, beneficiaries would pay $730 more under these proposed reforms if plans switch to coinsurance for the initial coverage phase.

Conclusions: Recent federal proposals to modify Medicare Part D could result in higher out-of-pocket spending for beneficiaries

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

needing insulin if plans elect to use coinsurance instead of flat-fee copayments in the revised benefit. This could have a negative impact on insulin access and adherence. As policymakers Medicare Part D, they should aim to provide affordable cost sharing for high-value, chronic use medications such as insulin.

3785 | Medicare part D plan coverage of brand-name drugs when generics are available

Stacie B Dusetzina[1], Juliette Cubanski[2], Leonce Nshuti[1], Sarah True[2], Jack Hoadley[3], Andrew Roberts[4] and Tricia Neuman[2]
[1]*Vanderbilt University School of Medicine, Nashville, TN;* [2]*KFF, Washington, DC;* [3]*Georgetown, Washington, DC;*[4]*Kansas University Medical Center, Kansas City, KS*

Background: Medicare Part D provides prescription drug coverage for older adults in the United States. There have been recent concerns that Part D plans might prefer branded drugs over generics, driving up spending for beneficiaries and taxpayers.
Objectives: To quantify how often Medicare Part D plans offer preferred formulary placement of brand drugs over their generic equivalents. We also evaluate cost implications for Medicare and beneficiaries when plans favor brand drugs to generics.
Methods: We evaluated Medicare Part D formulary coverage of generic and brand-name drugs from 2012 to 2019. We identified exact brand-generic pairs based on the RxNorm product description in each year. We determined the relative frequency of formulary coverage patterns of the brand-generic pairs: only brand covered, only generic covered, and both covered. The unit of analysis is "plan-product combination," where each observation represents the coverage status of one product for one plan. We also estimated differences in product prices and out-of-pocket costs when both brands and generics were offered on a formulary.
Results: Only 0.9% of observations (of 4,176,772 plan-product observations) correspond to brands covered and generics excluded. Conversely, 84% of observations correspond to generics included and brands excluded, while 15% of observations correspond to both generics and brands covered by the same plan. For the 15% of product-plan combinations where both branded and generic versions of the same drug product were covered on the same plan formulary, we found that 1% of brands were placed in lower cost-sharing tiers than their generic equivalents; 40% of generics were placed on a lower cost-sharing tier than brands; and 59% of brands and generics were placed on the same tier. When brands and generics were on the same tier, mean list prices were $349 (SD:1,350) for brands and $197 (SD:$666) for generics. In such settings, beneficiary cost sharing took the form of copayments instead of coinsurance in 80 percent of observations resulting in no difference in out-of-pocket costs for consumers.
Conclusions: Despite recent reports, we find little evidence of Part D plan preference for brands over generics. While preferential formulary placement of brands and/or exclusion of generic drugs was not common, we found that a small number of brand drugs were indeed subject to higher rates of preferential treatment on Part D plan formularies. Better inclusion and coverage of these generic drugs, and all excluded or non-preferred generic drugs on Part D formularies, could present an opportunity for cost savings to the Medicare program as well as its beneficiaries.

3836 | Disease severity, comorbid conditions, treatment patterns, and flares in adults with systemic lupus erythematosus in the United Kingdom: A real-world observational retrospective cohort analysis

Julia Langham[1], Volkan Barut[2], Mihail Samnaliev[1], Sue Langham[1], Sharada Weir[1], Xia Wang[3], Barnabas Desta[3] and Edward R Hammond[3]
[1]*Maverex Limited, Manchester, United Kingdom;* [2]*BioPharmaceuticals Medical, AstraZeneca, Cambridge, United Kingdom;* [3]*BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD*

Background: There is limited real-world evidence describing the presentation and treatment patterns of systemic lupus erythematosus (SLE) in the United Kingdom (UK).
Objectives: To characterize disease severity, comorbid conditions, treatment patterns, and flares in a longitudinal cohort of adults with SLE in the UK.
Methods: Patients aged ≥18 years with SLE were identified in the Clinical Practice Research Datalink - Hospital Episode Statistics database from January 1, 2005, to December 31, 2017. Patients were required to have ≥12 months of data before and after index date (date of earliest SLE diagnosis available). SLE disease severity and flares were classified as mild, moderate, or severe using adapted claims-based algorithms that use SLE-related conditions (eg, end-stage renal disease), medications (eg, antimalarials, immunosuppressants, and corticosteroids), and health service use (eg, hospitalizations and emergency department visits).
Results: Of 802 patients with SLE, 369 (46.0%) had mild, 345 (43.0%) had moderate, and 88 (11.0%) had severe SLE at baseline. In total, 692 (86.3%) patients were treated with SLE medications in the first year after SLE diagnosis. Among the total population (802), 557 (69.5%) patients received antimalarials, 203 (25.3%) received immunosuppressants, and 416 (51.9%) received corticosteroids (prednisolone); patients may have received ≥1 type of drug. Information on biologic use in hospitals is unavailable in these data. The mean (standard deviation [SD]) time to initiating any medication from index date was 177 (385.3) days. The median time to first flare from index date was 63 days (95% confidence interval 57-71). A majority of patients (750/802, 93.5%) experienced ≥1 flare during follow-up; the first flare was mild for 73.2% of patients (549/750), moderate for 15.5% (116/750), and severe for 11.3% (85/750). The mean (SD) annual overall flare rate in the first year after index date was 3.5 (2.5) (mild flares: 2.6 [2.5]; moderate flares: 0.7 [1.5]; severe flares: 0.2 [0.6]). A shorter median

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

time to first flare was significantly associated with moderate or severe disease (P<0.001) and the presence of comorbid conditions (P<0.001).

Conclusions: Our findings suggest some delay in SLE treatment initiation in the UK. Most patients with SLE experience flares within 2 months from diagnosis. Early treatment may delay or reduce the severity of the first SLE flare after diagnosis and may translate to slower disease progression, lower organ damage accrual, and better outcomes.

3860 | Health care utilization and costs in adults with systemic lupus erythematosus in the United Kingdom: A real-world observational retrospective cohort study

Mihail Samnaliev[1], Volkan Barut[2], Sharada Weir[1], Julia Langham[1], Sue Langham[1], Xia Wang[3], Barnabas Desta[3] and Edward R. Hammond[3]
[1]Maverex Limited, Manchester, United Kingdom; [2]BioPharmaceuticals Medical, AstraZeneca, Cambridge, United Kingdom; [3]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD

Background: There is limited real-world evidence demonstrating the long-term direct costs associated with systemic lupus erythematosus (SLE) in the United Kingdom (UK).

Objectives: To describe health care resource utilization and costs in adults with SLE in the UK over time and document costs by disease severity and type of encounter, including primary care, hospitalizations, outpatient visits, and prescription drugs.

Methods: Patients aged ≥18 years with SLE were identified in the linked Clinical Practice Research Datalink - Hospital Episode Statistics database from January 1, 2005, to December 31, 2017. Patients were required to have data from ≥12 months before and after the index date, defined as the date of earliest diagnosis available in the data set. Patients were classified as having mild, moderate, or severe disease using an adapted claims-based algorithm. Costs were calculated in 2017 UK pounds from the UK national health care system perspective. We estimated all-cause health care costs and incremental costs associated with each year of follow-up compared with a baseline year (3 years before index) using each patient as his or her own control and adjusting for age, sex, disease severity, and comorbid conditions.

Results: Of the 802 patients identified, 369 (46.0%) had mild SLE, 345 (43.0%) had moderate SLE, and 88 (11.0%) had severe SLE. The mean all-cause cost increased in the 3 years before diagnosis and, in the first year after diagnosis, amounted to £7532 (standard deviation [SD] £9634). This cost varied by disease severity: mild SLE, £5221 (£8064); moderate SLE, £8323 (£9846); and severe SLE, £14,125 (£11,267). Adjusted total mean annual increase in costs per patient in the overall study population was £4476 (95% confidence interval £3809-5143) greater in the year of diagnosis compared with the baseline year (P<0.0001), adjusted for age, sex, disease severity, and comorbid conditions. Primary care utilization was the leading component of costs during the first year after diagnosis, followed by prescriptions, outpatient care, and inpatient care. Information on biologic use in hospitals is unavailable in these data.

Conclusions: The direct costs of health care for patients with SLE in the UK are substantial and persist over the years after diagnosis. Patients with moderate or severe SLE have higher all-cause costs over time compared with patients with mild SLE. Earlier diagnosis and treatment may reduce disease severity and occurrence of comorbidities, and the associated high health care costs.

3863 | Direct medical burden of antimicrobial resistant healthcare associated infections: An analysis with propensity score matching method

Xinliang Liu[1], Dan Cui[2], Hao Li[2], Quan Wang[2], Zongfu Mao[2], Liang Fang[3], Nili Ren[4] and Jing Sun[5]
[1]The University of Manchester, Manchester, United Kingdom; [2]Wuhan University, Wuhan, China; [3]The Third People's Hospital of Hubei Province, Wuhan, China; [4]Hubei University of Medicine, Wuhan University, China; [5]CAMS & PUMC, Beijing, China

Background: Antimicrobial resistance (AMR) and healthcare-associated infection (HAI) are among the biggest global public health challenges, and overlap widely. These infections cause significant morbidity and mortality, put pressure on health systems, and incur rising direct and indirect costs.

Objectives: To analyze the direct medical burden attributable to antimicrobial-resistant healthcare-associated infections in Chinese public tertiary hospitals, and aimed to inform both the medical regulators and hospital managers for better control of HAI and containment of AMR.

Methods: The propensity score matching method (γ=0.25σ, nearest neighbor 1:1 matching) was applied to conduct a retrospective cohort study in five public tertiary hospitals in the Hubei province of China during 2013-2015. Descriptive analysis, Pearson Chi-Square test, Mann-Whitney U test, Wilcoxon signed-rank test and paired/independent Z/T test were conducted. The statistically significant level was set at P < 0.05.

Results: From 2013 to 2015 in overall, the additional total medical expenditure per HAI-AMR inpatient was US$ 15 557.25 compared with that of the non-HAIs, and the additional length of per hospital stay of the HAI-AMR inpatient was 41 days compared with that of the non-HAIs (P<0.001).

Conclusions: In combination with AMR, HAI caused significant additional medical expenses and affected the turnover rate of hospital beds. Most of the increased medical costs fell to patients and their families. These findings call for more effective control of HAI and containment of AMR. A national study is needed to estimate the medical, social and economic burden of HAI in combination with AMR.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3910 | The use of real-world evidence in economic assessments of pharmaceuticals in the United States

Woojung Lee, Victoria Dayer, Boshen Jiao, Josh Carlson, Beth Devine and David Veenstra
University of Washington, Seattle, WA

Background: There is increasing interest in expanding the use of real-world evidence (RWE) for pharmaceuticals with the recent FDA guidance on how drug companies may communicate health care economic information with payers. Health care decision makers and producers of RWE are still faced with uncertainty, however, about how much and what type of RWE should be used in technology assessment. A clearer understanding of recent trends in RWE use can provide insight to this issue.

Objectives: To assess the use of real-world evidence (RWE) in economic assessment of drugs by the Institute for Clinical and Economic Review (ICER).

Methods: We retrieved final evidence reports of pharmaceuticals published by ICER between 2014 and 2019 and reviewed the cost-effectiveness and budget impact analysis in the reports. We calculated the total number of RWE uses and the proportion of model parameters informed by RWE per report to estimate the absolute and relative frequency of RWE use, respectively. We classified model parameters into 15 categories based on their attributes and then examined which parameter category was informed by each RWE to classify the reason for RWE use. Finally, we characterized RWE by study design, data source, and sponsor type using frequency distribution.

Results: We identified 33 final evidence reports, all of which used RWE; the mean RWE use per-report was 12 (range: 4 - 26). The average proportion of model inputs informed by RWE per-report was 32.7% (range: 4.1% - 76.9%). Real-world evidence was most commonly used for disease progression parameters (28.7%) and healthcare resource utilization and costs (21.1%), but rarely used for drug-specific clinical outcomes such as effectiveness (1.5%), adverse drug event rates (0.5%), and discontinuation rates (1.2%). The most frequently used study design and data source were retrospective cohort (56.6%) and registry data (41.4%). About a third (30.2%) of RWE was industry-sponsored.

Conclusions: Real-world evidence has been commonly used to inform pharmaceutical economic analyses by ICER, but there has been relatively limited use to inform comparative drug effectiveness.

3917 | Time in therapeutic range (TTR) values among incident warfarin users and predictors of TTR

Kebede Beyene, Patricia Näslund, Amy Hai Yan Chan and Jeff Harrison
School of Pharmacy, the University of Auckland, Auckland, New Zealand

Background: Time in the therapeutic range (TTR) of international normalised ratio (INR) 2.0-3.0 is a common measure of warfarin anticoagulation quality. TTR value above 60% indicates optimal anticoagulation control, and adverse outcomes increase when TTR ≤ 60%. The quality of long-term anticoagulation and factors affecting anticoagulant control in patients taking warfarin have not been fully explored in New Zealand (NZ).

Objectives: The aim of this study was to determine TTR values in patients who newly initiated warfarin therapy between January 2006 and December 2011 in Auckland, NZ, and to identify the factors affecting TTR in these patients.

Methods: This was a population-based, retrospective cohort study. Information on demographics, warfarin use, and INR values were obtained from national healthcare databases for each patient. Adults (age ≥18 years) who newly initiated warfarin treatment between January 2006 and December 2011 and had more than five INR tests during this time period were included. TTR was computed using the Rosendaal method. Patients were classified into two groups according to their TTR values (>60% vs. ≤60%) and the characteristics of these groups were compared. Multivariable logistic regression was used to examine the association between patient characteristics (gender, age, ethnicity, deprivation index) and TTR.

Results: A total of 4280 patients were included in this study. The mean age of patients was 65±12 years, and 60.3% of them were male. The mean and median follow-up time were 2.76±1.7 and 2.73 years, respectively. The mean TTR was 55.3±17%, and 58.1% of patients had sub-optimal TTR (≤60%). Some patient characteristics were significantly associated with TTR. Age 65-74 years (Adjusted odds ratio (AOR)=1.198, 95% CI 1.027-1.396, p=0.021) was predictive of optimal TTR. Māori (AOR=0.491, 95% CI 0.403-0.597, p<0.001)), Pasifika (AOR=0.516, 95% CI 0.390-0.682, p<0.001), or Asian ethnicity (AOR=0.715, 95% CI 0.547-0.936, p=0.014), and living in the most deprived area of Auckland (AOR=0.716, 95% CI 0.581-0.884, p=0.002) were predictive of sub-optimal TTR (≤60%).

Conclusions: Our study demonstrated that a significantly large proportion of patients on warfarin had sub-optimal TTR. Age, ethnicity and deprivation index were significant predictors of TTR. Identifying these risk factors for suboptimal INR control can help clinicians focus their INR monitoring on those who are most at risk.

3946 | The prevalence of sun protective behaviors across different age groups in the US population: Findings from the 2015 US Health Interview Survey

Ching-Yuan Chang, Haesuk Park and Jenny Lo-Ciganic
University of Florida, College of Pharmacy, Gainesville, FL

Background: The goal stated in the US Healthy People is that third-quarters of adults will use sun protection by 2020 in order to reduce the risk of skin cancer. Prior studies largely focused on examining sun protective behaviors across gender and race. However, little is known about whether/how sun protective behaviors differ by age.

Objectives: We examined the association between age and sun protective behaviors, adjusting for potential confounders.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: This cross-sectional study included a nationally representative of US adults without any skin cancer from the 2015 National Health Interview Survey. Age was categorized into 18-29, 30-49, 50-69, and ≥70 years old. Sun protective behaviors included: 1)wearing sun-protective clothing, 2)shade use, 3)hat use, 4)sunscreen use, and 5)infrequent indoor tanning device use. We estimated the national prevalence for having sun protective behaviors (and any individual behavior) by age group. We used a weighted multivariable logistic regression model to examine the association between age and sun protective behavior adjusting for sociodemographic and health status factors (e.g., smoking). Adjusted odds ratios(aORs)with 95% confidence interval(95%CI)were reported.

Results: Among eligible 236,234,809 participants in 2015, 21.6% aged 18-29, 34.6% aged 30-49, 31.8% aged 50-69, and 12.0% aged ≥70. When compared with participants aged 18-29, participants aged 50-69 (aOR=1.83, 95%CI=1.49-2.25) and aged ≥70 (aOR=6.24, 95% CI =4.07-9.58) were associated with having more sun protective behaviors. Findings were consistent for wearing sun-protective clothing (age 50-69:OR=1.61, 95%CI=1.45-1.79;aged ≥70:OR=3.64, 95% CI=3.21-4.12), shade use (age 50-69:OR=1.41, 95%CI=1.27-1.56;aged ≥70:OR=2.14, 95%CI=1.88-2.43), and using indoor tanning device(age 50-69: OR=0.64, 95%CI=0.54-0.74; aged ≥70: OR=0.22, 95% CI=0.17-0.28).

Conclusions: Younger Americans were less likely to have sun protective behaviors compared to older adults. The findings suggest that healthcare providers may encourage younger individuals wearing sun-protective clothing and shade protection, and reducing indoor tanning exposure. Environmental and policy strategies can focus on provision of shade in school and recreational settings.

4009 | Pharmaceutical care in Chinese public tertiary hospitals: Findings from the 4th National Healthcare Improvement Initiative Survey

Mingshuang Li
School of Public Health, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Pharmaceutical care has been playing an increasingly critical role in Chinese hospitals. However, evidence about the most recent development of pharmaceutical care in China is limited.

Objectives: To analyze the current situation of pharmaceutical care and the capacities of the pharmacists in Chinese public tertiary hospitals.

Methods: All on-duty pharmacists of 143 public tertiary hospitals responded to the Likert-5 pre-set online questionnaire about their pharmaceutical care capacities, and their respective hospitals valued pharmaceutical care in clinical practice from March 18 to 31,2019. The study measured the appraisals of the responding pharmacists as positive ("strongly agree" and "agree") or negative ("neither agree nor disagree", "strongly disagree" and "disagree") results, and performed a descriptive analysis of the responding pharmacists and un-conditional multivariate binary logistic regression analysis to predict the influencing factors of the pharmacists' appraisals of pharmaceutical care. The dependent variable was transformed into binary categories and assigned 1 = positive response,0 =negative response. The independent variables included the characteristics of sample hospitals and the responding pharmacists.

Results: The survey retrieved 10 815 valid responded questionnaires.74.5%, 67.5% and 65.0% of the responding pharmacists made a positive self-appraisal of their abilities of communication with patients and doctors, reviewing prescriptions and communication with particular patients.65.5% had a positive appraisal of their respective hospitals to conduct active monitoring of the clinical use of new medicines, and 68.9% admitted that their respective hospitals value the clinical pharmaceutical care. The doctor degree and senior academic rank of the responding pharmacists, as well as maternal and child hospitals were predictors of higher appraisals of the responding pharmacists about their pharmaceutical care capacities, and their respective hospitals valued pharmaceutical care (all *ORs*>1.5, *P*<0.05).

Conclusions: The study suggested that there is a need to strengthen the pharmacy education, training and staffing of pharmacists with improved professional skills to offer value-added specialized pharmaceutical care in Chinese public hospitals. Patient-centred and interdisciplinary interactions in medical practice should be promoted. There is also a need for public hospitals to provide a platform for the achievement of the professional values of high-quality pharmacists at different carrier development stages.

4119 | Patient, provider and formulary characteristics associated with initiation of a SGLT2i or GLP-1RA among medicare beneficiaries with type 2 diabetes: A retrospective cohort study

Jing Luo, Inmaculada Hernandez, Joseph Gabriel and Walid Gellad
University of Pittsburgh, Pittsburgh, PA

Background: Factors predicting intensification to an SGLT2 inhibitor (SGLT2i) or GLP-1 receptor agonist (GLP-1RA) have not been previously described.

Objectives: To determine factors associated with initiation of a SGLT2i or GLP-1RA among Medicare beneficiaries with type 2 diabetes on prior oral therapy

Methods: Using prescription claims and formulary data from a random 5% sample of all Medicare beneficiaries, we sought to assess the association between plan generosity and risk of initiating a SLT2i or GLP1-RA. Our cohort included patients with diagnosed type 2 diabetes who had at least 1 prescription claim for any oral diabetes medication (excluding SGLT2i) in the 180 days before the start of follow-up (1/1/2015). Patients were excluded if they died before 12/31/16 or if they filled any insulin, SGLT2i or GLP-1RA before 1/1/2015. We developed multivariable logistic regression models controlling for age, race, region, prior medication use, claims-based measures of diabetes severity and clinical comorbidities, provider specialty and 2 measures of formulary restrictiveness.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Of 103,112 eligible patients, 5,076 (4.9%) initiated a SGLT2i or GLP-1RA between 1/1/15 - 12/31/16. After adjusting for baseline demographic, geographic, provider and clinical characteristics; patients enrolled in plans covering 2 or more drugs in tiers 1-3 were more likely (adjusted odds ratio [aOR] 1.18 [95% CI, 1.05 to 1.32] to initiate one of these target medications than patients enrolled in plans covering 0 drugs in preferred tiers. There was no significant differences in use of SGLT2i or GLP-1RA comparing patients with 0 versus 2 or more drugs covered without prior authorization or step therapy requirements.

Conclusions: After controlling for a large number of clinical and other factors, patients with type 2 diabetes on prior first or second-line therapy with more generous prescription drug coverage were more likely to initiate a SGLT2i or GLP-1RA.

4121 | Coverage, formulary restrictions and average retail prices of SGLT2 inhibitors and GLP-1 receptor agonists across medicare part D plans in 2019

Jing Luo, Robert Feldman, Scott Rothenberger and Walid Gellad
University of Pittsburgh, Pittsburgh, PA

Background: Access to SGLT2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1RA) may be limited by high drug prices and insurance related barriers including prior authorization or step therapy requirements. These barriers are particularly challenging for seniors covered under Medicare's prescription drug benefit (Part D).

Objectives: To determine coverage, formulary restrictions and average retail prices of SGLT2i and GLP-1RA across Medicare Part D Plans in 2019

Methods: We used Q1 2019 national Part D Formulary files to examine: 1) the proportion of plans (weighted by enrollment) that cover a SGLT2i or GLP-1RA without prior authorization or step therapy and 2) the average retail price [IQR] for a 30-day supply of each medication.

Results: Among 3,992 plans, the weighted percent of plans that covered canagliflozin, dapagliflozin and empagliflozin without prior authorization or step therapy was 53.2% (95% CI: 49.1 to 57.4), 63.7% (95% CI: 60.1 to 67.3) and 95.4% (95% CI: 94.3 to 96.4), respectively. Coverage without prior authorization or step therapy for GLP-1RA of ranged from 3.2% (95% CI: 1.8 to 4.6) for lixisenatide to a high of 87.4% (95% CI: 85.5 to 89.3) for dulaglutide. The mean retail price for a 30-day supply of a SGLT2i or a GLP-1RA ranged from $295 [285-303] (ertugliflozin) to $512 [501-527] (canagliflozin) and $641.38 [629-657] (lixisenatide) to $946.17 [930-968] (liraglutide), respectively.

Conclusions: In 2019, coverage without prior authorization and step therapy for SGLT2i and GLP-1RA were mixed across Part D plans, with most plans covering at least one drug in each class without either type of restriction. Cost sharing (i.e. high out-of-pocket payments) may be more problematic for patients than either prior authorization or step therapy.

4146 | Cost-effectiveness of Taxane/platinum and doxorubicin/platinum combination therapies in adjuvant treatment of endometrial cancer

Swetha Srinivasan, Joehl T Nguyen and Megan C Roberts
University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Surgical procedures (e.g. total hysterectomy) are used for treatment of endometrial cancer, and postoperative adjuvant chemotherapy is recommended to reduce recurrence in this context. Recent clinical trial data has shown that (i) docetaxel/cisplatin (DOC/CIS), and (ii) doxorubicin/cisplatin (DOX/CIS) regimens are non-inferior compared to the standard adjuvant treatment in endometrial cancer, paclitaxel/carboplatin (PAC/CAR) in terms of overall survival (OS) and progression-free survival (PFS); however, these therapies differ in costs and safety profile which may affect patient quality of life.

Objectives: To evaluate the cost-effectiveness of DOC/CIS and DOX/CIS combination therapies compared to standard PAC/CAR therapy in adjuvant treatment of endometrial cancer to guide decision-making on which combination therapy should be preferred for postoperative adjunct therapy to reduce recurrence.

Methods: We constructed a three-state Markov decision analytic model for progression in endometrial cancer to estimate the cost-effectiveness of three combination therapies (DOC/CIS, DOX/CIS, PAC/CAR) over a 5-year time horizon from a third-party payer perspective. The cohort consisted of 62,000 women presenting the prevalence of those receiving standard surgical treatment for endometrial cancer in the United States per year. Input parameters (transition probabilities and health utilities) and costs were derived from published literature and Medicare Average Selling Price (ASP) data. Outcomes evaluated included mean costs (2019 USD), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). All outcomes were discounted at 3% annually, and deterministic one-way sensitivity analysis was conducted to assess robustness of the model.

Results: The model produced mean costs of $65,221, $91,829 and $76,563, and yielded 3.40, 3.08 and 3.18 QALYs per person for the DOC/CIS, DOX/CIS and PAC/CAR strategies, respectively. The ICER for DOC/CIS dominated the PAC/CAR strategy, due to lower costs and better outcomes, whereas the ICER for DOX/CIS was dominated by the PAC/CAR strategy, due to higher costs and poorer outcomes. Deterministic one-way analysis confirmed that the base-case results were robust to model assumptions on costs and health utilities.

Conclusions: DOC/CIS is cost-effective for postoperative adjuvant treatment of endometrial cancer and may be an alternative to the standard PAC/CAR therapy.

4158 | Cost-related nonadherence for prescription medications: A cross-sectional study in Jordan

Abdallah Y. Naser
Isra University, Amman, Jordan

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Cost-related nonadherence (CRN) to medications is a commonly encountered problem by many patients and specifically among elderly patients who use different multiple medications. Despite that there are many factors that have influence patients' adherence to their therapy, cost of medications is considered as one of the most important contributor to this problem.

Objectives: To explore the prevalence of medications cost-related nonadherence in Jordan and its associated individual characteristics.

Methods: A cross-sectional study was conducted between February 2019 and May 2019 in Jordan to explore the prevalence of medications cost-related nonadherence in Jordan and its associated individual characteristics. Prevalence of medications cost-related nonadherence was estimated by dividing the number of respondents who confirmed that their adherence to their medications was affected by their cost on the total number of the study participants. Logistic regression was used to determine factors that are associated with medications cost-related nonadherence.

Results: A total of 1,129 participants were involved in this study from different governorates in Jordan. The prevalence rate of cost-related nonadherence is around 29.6%. Participants who are married or widowed found to have higher odds of being no adherent due to medications cost with odds ratio of 1.55 (1.19 - 2.00) and 1.95 (1.20 - 3.15) respectively. Having lower educational level was associated with medications cost-related nonadherence, and having college, bachelor degree or higher studies qualification were important protective variable and reduced the odds of nonadherence with around 42% (odd ratio of 0.58 (0.45 - 0.75)). Being retired was associated with higher odds of being non-adherent (2.20 (1.49 - 3.27)). Having higher income was another protective variable from being non-adherent due to medications cost and decrease the probability of this problem by 55% (0.45 (0.21 - 0.97)). In addition, patients' evaluation of their health status was another important variable that influenced patients' adherence positively, as patients who reported that their health status is very good or excellent have 62% of being more adherent compared to other patients (0.38 (0.28 - 0.52)).

Conclusions: The prevalence of cost-related nonadherence is high in Jordan. Married, widowed, retired patients and patients with low educational level were the most commons categories that affected by cost of medications. Higher focus should be directed towards these categories to improve their adherence towards their therapy as it is connected to better health outcomes.

4177 | Comparison of symptoms, treatments and healthcare resource utilization in patients with multiple sclerosis by sex in a real world cohort in the United States

Ia Topuria, Cristi Cavanaugh, Greg Donadio, Kathryn Starzyk and Rich Gliklich

OM1, Inc., Boston, MA

Background: Autoimmune diseases like multiple sclerosis (MS) disproportionately impact women. Research suggests MS susceptibility and relapses may differ due to mechanisms underlying sex differences in disability progression. Such differences may impact disease phenotypes, which in turn, increase need for clinical care and healthcare resource utilization (HRU).

Objectives: To compare symptoms and HRU of MS patients identified from a large, representative database of linked EMR-claims data by sex.

Methods: The OM1 Real World Data Cloud (OM1, Boston, MA) collects and links structured and unstructured data including extensive clinical and administrative claims data on patients from a variety of practice types across the US starting in 2013. This study included MS patients ages ≥18 on the index date defined as the earliest of first observed MS diagnosis or disease-modifying therapy (DMT) initiation who had 12 months of data available after the index date (observation period). MS symptoms (by diagnosis codes), treatments and HRU were assessed during the observation period and stratified by sex with significant differences defined as $p<0.05$ from chi-square tests.

Results: As of November 2019, 306,607 MS patients met inclusion criteria. Mean age was 50.6 years (SD: 13.1), 76.6% were female and 85.8% of patients with known race were white. A higher proportion of males vs females had evidence of the following signs and symptoms during the observation period (all $p<0.001$): gait abnormality (13.8% vs 11.7%), muscle weakness (10.5% vs 9.0%), ataxia (4.7% vs 3.6%), sexual dysfunction (6.1% vs 0.04%) and urinary retention (6.9% vs 3.8%). In contrast, a higher proportion of females vs males experienced the following (all $p<0.001$): depressive disorder (21.7% vs 16.5%), burning, numbness, or tingling (13.1% vs 11.1%), fibromyalgia/myalgia and myositis (7.9% vs 3.4%) and malaise and fatigue (20.9% vs 18.5%). Males were more likely to have a hospitalization (20.4% vs 18.4%, $p<0.001$) and females were more likely to have an emergency room or urgent care visit (21.9% vs 20.6%, $p<0.001$). More females used steroids (12.0% vs 10.0%, $p<0.001$), while more males used a DMT (22.2% vs 21.8%, $p=0.014$).

Conclusions: Depression and sensory-related symptoms were more common in women, while men were more likely to have symptoms related to impaired coordination and urinary and sexual dysfunction. Both groups experienced muscle-related symptoms. While initial analyses indicate differences in HRU by sex, research is needed to characterize the impact on the clinical and economic burden of MS.

4242 | Effect modifications on risk of hospitalization due to heart failure in type 2 diabetes patients receiving dapagliflozin versus empagliflozin

Shih-Chieh Shao[1,2], Kai-Cheng Chang[3,2], Hui-Yu Chen[3], Yuk-Ying Chan[4], Yea-Huei Kao Yang[2] and Edward Chia-Cheng Lai[2]

[1]Keelung Chang Gung Memorial Hospital, Keelung, Taiwan; [2]National Cheng Kung University, Tainan, Taiwan; [3]Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; [4]Chang Gung Medical Foundation, Taoyuan, Taiwan

Background: A recent study indicated the risk of incident heart failure may vary with different sodium glucose co-transporter 2 inhibitors (SGLT2i). However, nothing is known about the effect modifiers, e.g., patients' baseline renal functions and the history of atherosclerotic

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

cardiovascular diseases (ASCVD), on the risk of hospitalization due to heart failure (hHF) in type 2 diabetes patients with different SGLT2i.

Objectives: To evaluate effect modifications from patients' renal functions and ASCVD history on the hHF risks between dapagliflozin and empagliflozin.

Methods: We conducted a retrospective cohort study by analyzing a multi-institutional electronic medical records database, Chang Gung Research Database, containing approximately 1.3 million patients (6% of the Taiwan population). We included type 2 diabetes patients newly receiving dapagliflozin or empagliflozin during 2016-2017. We followed patients from the initiation of SGLT2i to September 31, 2019. We censored patients at the date of hHF, death or last clinical visit. We performed multivariable logistic regression models to compare the hHF risks between dapagliflozin and empagliflozin. Specifically, we used the interaction terms in the regression models to examine possible effect modifications from patients' baseline renal functions (eGFR≥90 vs. eGFR<90 ml/min/1.73m^2) and the history of ASCVD (with vs. without).

Results: We included 6,518 dapagliflozin and 7,940 empagliflozin new users in the analysis. The mean age was 58.6 (SD 11.7) and 59.9 (SD 11.9) years old among dapagliflozin and empagliflozin new users, respectively. Compared to empagliflozin, the adjusted hazard ratio (HR) of hHF was 0.71 (95% CI 0.55-0.92) for dapagliflozin. We found patients' renal functions modified the hHF risks between dapagliflozin and empagliflozin (p value for interaction was 0.01). Specifically, compared to empagliflozin, the adjusted HR was 0.42 (95% CI: 0.25-0.68) and 0.89 (95% CI: 0.66-1.20) for dapagliflozin new users with eGFR≥90 and eGFR<90 ml/min/1.73m^2, respectively. However, we did not observe any interaction of the history of ASCVD with the hHF risks between dapagliflozin and empagliflozin (p value for interaction was 0.24).

Conclusions: patients' baseline renal functions may modify the hHF risks between SGLT2 inhibitors, while the ASCVD history does not. Taking patients' renal functions into account before selecting dapagliflozin or empagliflozin may be important to better reduce hHF risks in type 2 diabetes patients in clinical practice.

4245 | Risk of breastfeeding newborns by hepatitis B surface antigen and hepatitis B E antigen positive mothers

Zhe Chen and Lingli Zhang

West China Second University Hospital, Sichuan University, Chengdu, China

Background: Nowadays the vertical transmission rate of hepatitis B virus (HBV) decreases significantly in HBsAg positive mothers after newborns receive immunization. But vertical transmission of HBV may still occur in 5-10% in HBsAg and HBeAg positive mothers.

Objectives: This study aims at evaluating the risk of breastfeeding newborns by HBsAg and HBeAg positive mothers in mother-to-child transmission (MTCT).

Methods: Seven electronic databases and three clinical trial registry platforms were searched and the deadline was December 2019. Cohort studies evaluating the risk of breastfeeding in HBsAg and HBeAg positive mothers were included by two reviewers. The Newcastle-Ottawa was applied to assessing the risk of bias. The outcomes were analyzed by Review Manager 5.3 software and expressed as relative risk (RR) or mean difference (MD) with 95% confidence interval (CI). Heterogeneity was assessed with I-squared (I^2) statistics.

Results: 17 cohort studies involving 2256 newborns were included in the meta-analysis. Compared to formula milk group, the number of HBsAg positive newborns increased significantly in breast milk group [RR=1.46, 95%CI (1.11, 1.92), P=0.007]. When the HBV-DNA<10^3 in breast milk, there was no difference in the number of HBsAg positive newborns between formula milk group and breast milk group [RR=3.62, 95%CI (1.00, 13.07), P=0.05]. When the HBV-DNA>10^3 in breast milk, the number of HBsAg positive newborns increased significantly in breast milk group compared to formula milk group [RR=2.69, 95%CI (1.09, 6.61), P=0.003]. Meanwhile, there was no difference in the number of anti-HBs positive newborns between formula milk group and breast milk group [RR=0.93, 95%CI (0.86, 1.01), P=0.10].

Conclusions: From the extrapolation of the existing literature, despite newborns received immunoprophylaxis, the risk of breastfeeding newborns by HBsAg and HBeAg positive mothers was still higher than formula feeding.

4286 | Societal impact for patients with psoriasis: A nationwide Swedish register study

Marie Linder

Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

Background: Psoriasis is a common immune-mediated chronic inflammatory disease with worldwide impact on men and women of all ages, affecting 2-4% of the Nordic population. Psoriasis has a significant negative impact on health status, increases community resource use and health care consumption.

Objectives: To observe differences in education, income, employment status, marital status, healthcare consumption and drug utilization between psoriasis patients and a matched reference cohort.

Methods: Cohort study following socioeconomic status and healthcare consumption for patients with psoriasis in the Swedish national patient register. All individuals with a first diagnosis of psoriasis, including psoriatic arthritis (2002 to 2013) were followed until death, emigration or end of study (31/12-2016). Outcomes: time to first increase in education, income, employment status, marital status, health care consumption and drug utilization. Models were adjusted for matching (age, sex, county) and a simple comorbidity index (count of relevant comorbidities at baseline). Models for socioeconomic variables also included baseline education. Time to first increase in education was analyzed by Cox regression. All other outcome variables were compared over time (years) from 1 year before index date until end of follow-up. The corresponding generalized linear regression

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

models were further adjusted for calendar year and follow-up time. An interaction term for follow-up time*cohort was included for differences between cases and controls over time. Normal regression (log link function) was used to model mean income. Proportions of employed and married were compared by logistic regression. Mean number of outpatient visits, hospitalizations and prescriptions were modeled by negative binomial regression.

Results: 109803 patients were included, mean age 51.2 years, 53% women, 36% using topical corticosteroids, matched to 1.08 million controls. The greatest difference ($p<0.0001$) was employment at 2 to 10 years after index with 10% less patients being employed. For marital status, we found a statistically significant difference (1.4%, $p<0.01$) after 4 years, for the remaining time. Incidence rate ratios for outpatient visits stabilized between year 3 and 4 (1.75 to 0.96), whereas hospitalizations increased at year 5 (0.99 to 1.04).

Conclusions: Understanding of socioeconomic impact of psoriasis is extended by showing reductions in employment proportion. Patients treated before diagnosis implies diagnostic delay, so there is room for improvement in management. It is important to monitor healthcare utilization through at least 5 years.

4292 | The practice of early conversion from intravenous to oral antibiotic therapy in uncomplicated urinary and respiratory tract infections: Assessment and evaluation of clinical and economic outcomes in hospitalized patients

Anusha Bellapu[1], Preethi Shanmugam[1], Subeesh K Viswam[2], Vasista Sharma[1] and Stephy T Chacko[1]

[1]M.S.Ramaiah University of Applied Sciences, Bangalore, India; [2]M.S. Ramaiah University of Applied Sciences, Bangalore, India

Background: This study was conducted to evaluate the impact of intravenous (IV) to oral conversion of antibiotic therapy w.r.t clinical and economic outcomes.

Objectives: To identify potential study subjects eligible for early conversion of antibiotics and recommend timely conversion from IV to oral therapy. To compare the clinical and economic outcomes between the retrospective and prospective phases.

Methods: An ambispective study was carried out in department of General Medicine at a tertiary care hospital. This study constitutes two phases, Phase I (retrospective phase) where IV to oral conversion was done before active involvement of the clinical pharmacist. Phase II (prospective interventional phase) consists of active involvement of the clinical pharmacist with recommendations for early conversion of IV to oral. The two phases were compared for statistically significant differences using unpaired t-test for and chi-square test. The economic outcomes were compared between the two phases using cost-minimization analysis, cost burden analysis.

Results: In this study, 83 were in phase I and 88 in phase II. As per criteria for IV to oral switch71 (86%) of phase I and 84 (95%) in phase II were eligible for conversion. Out of which 13 (18%) of phase I and 66 (79%) of phase II were switched. The average length of hospital stay(LOHS) was found to be 4.4±0.7 compared to phase I ($p<0.005$). The duration of IV therapy was 2.7±1.5 and 5.2±1.8 days in phase II and phase I respectively. Most common type of conversion was step down therapy (77%) phase I and (73%) phase II followed by sequential and switch therapy. The reinfection rate and readmission was similar among both the phases ($p>0.05$). The mean cost of hospital stay was analyzed in both phases and was observed that there was a cost reduction of ₹2,118.51 (30.55 USD) in phase II when compared to Phase I. The cost incurred to patients was calculated using cost burden analysis and it was found to be decreased from ₹1,42,622 (2056.75 USD) in phase I to ₹32,333 (466.27 USD) in phase II. The extra number of IV therapy days decreased from 112 (phase I) to 35 days in (phase II).

Conclusions: This study emphasizes that the practice of conversion from IV to oral antibiotic therapy has a considerable impact on clinical and economic outcomes amongst hospitalized inpatients. This study demonstrates a decrease in LOHS and economic burden if predefined switch criteria of IV to oral conversion are practiced meticulously.

4313 | Pharmaceutical health outcomes and policy curricula among Arab countries: An evaluation of 191 academic institutions

Eman Alghamdi[1], Thamer Alshammary[1,2] and Omar Albalawi[1]

[1]Saudi Food and Drug Authority, Riyadh, Saudi Arabia; [2]King Saud University, Riyadh, Saudi Arabia

Background: Pharmaceutical health outcomes and policy is a very fast growing area that is needed in the healthcare culture and has a positive impact on healthcare systems

Objectives: To examine the availability of teaching curricula, type and extent of pharmaceutical health outcomes and policy subjects (i.e. pharmacoepidemiology (PEPI), pharmacovigilance (PV), and Pharmacoeconomics (PE)) in the academic institutions among the 22 Arab countries

Methods: A cross sectional study conducted in the period from 2019-2020. The majority of the institutions among Arab countries were reviewed to list all pharmacy colleges. Then, the colleges' websites were reviewed to examine the study plan, type and extent of these subjects. Five criteria were utilized to assess these subjects; 1) full time mandatory, 2) full time elective, 3) partial mandatory, 4) partial elective, and 5) not offered. Full time means the subject is given as sole course while the partial time means it is part of another main course. The descriptive analyses were conducted using statistical analysis software (SAS®)

Results: About 191 colleges were screened during the study period. Of those, 150 (78.5%) institutions were included in the study and their curriculum was extracted, while, 41 (21.5%) institutions excluded due to the unavailability of their website. The teaching type and extent of the three subjects varied widely among different colleges. Eighty-eight (58.7%) colleges offered PE course, which was the highest offered subjects. Of these, 73 (83 %) colleges have the subject either

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

as full mandatory 40 (54.7%) or as partial mandatory 33 (45.3%). While, 15 (17%) colleges have the PE as elective, in either full or partial elective in 73% and 27%, respectively. On the other hand, PEPI was offered in 50 (33%) colleges, 43 (86%) colleges offered the subject as a mandatory course. It was taught as an elective subject in 7 (14%) colleges, of these 3 (43%) as full elective and 4 (47%) as a partial elective. Lastly, only 22 (15%) colleges provided PV course. The majority were having the subject as partial mandatory 12 (54.5%), followed by full elective 6 (27%), full mandatory 2 (9%), and partially elective 2 (9%). All colleges teach the three courses in the final two years

Conclusions: Pharmaceutical health outcomes and policy specialties were taught in a few colleges among the Arabic countries and still considered in the infancy stage. Providing a well-structured program to pharmacy students can help countries to establish an integrated scientific community that can enhance the safe use of medicine and starts applying PE evidence to healthcare decision making

4315 | Impact of the ICD-10-CM transition on claims-based severe sepsis events among US medicare enrollees

Tiffany S. Woodworth, Kerrin Gallagher, Erik Gunnarsson and Joseph Menzin

Boston Health Economics, Boston, MA

Background: Severe sepsis algorithms using administrative claims encoded in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) have high positive predictive value, but low sensitivity, resulting in use of clinical data to better assess true cases. Availability of clinical data may be limited. ICD-10-CM transition provides an opportunity to characterize the impact of coding changes on claims-defined events.

Objectives: To characterize trends of severe sepsis events using administrative claims data over the ICD-9/10-CM transition period.

Methods: A trend analysis was conducted using a 5% sample of Medicare Fee-for-Service claims data to examine severe sepsis events during 783,184 hospitalizations from January 2014 - March 2016 among Medicare-enrolled patients ≥65 years with no evidence of commercial coverage. Six algorithms were used to examine severe sepsis trends over each ICD era: 2 well-known validated ICD-9-CM-based algorithms (Angus-9, Martin-9); each algorithm forward-backward mapped to ICD-10-CM codes (Angus-10, Martin-10); and use of only explicit ICD-9-CM or ICD-10-CM codes for *severe sepsis* and *septic shock* (Explicit-9, Explicit-10). We calculated the monthly proportion of severe sepsis among all hospitalizations during the study period and visually compared trends. We also calculated severe sepsis prevalence and confidence intervals for the first 6-month period of ICD-10 transition (October 2015 to March 2016) and compared ICD-9-defined prevalence during the same months in 2015.

Results: Consistent with published studies, ICD-9-defined severe sepsis over 6 months was highest for Angus-9 definition (25.9 [25.7, 26.2] per 100 hospitalizations). Prevalence for Martin-9 and Explicit-9 were 10.7 [10.5, 10.8] and 5.0 [4.9, 5.1], respectively. ICD-10-defined conversions over the 1st 6 months of transition yielded slightly higher results for Explicit-10 (5.2 [5.1,5.3]) and Martin-10 (11.0 [10.9,11.2]). Angus-10 was slightly less than Angus-9 (25.3 [25.1,25.6]). For all algorithms, monthly capture of severe sepsis during hospitalizations appeared stable between January 2014 through March 2016.

Conclusions: Though a slight increase in explicit sepsis coding was observed, trends of claims-defined severe sepsis remained stable over the ICD-10-CM transition. These preliminary findings suggest that the transition had minimal impact on identification of severe sepsis. ICD-10-based algorithms may be reasonably used to define cohorts, but clinical data may be required for sepsis surveillance.

4354 | A Bayesian analysis of observational studies: Theoretical and practical considerations

Gisèle Nakhlé[1,2], James Brophy[3,4], Paul Khairy[5,6,7], Jacques LeLorier[8,2,7], Christel Renoux[9,10,2] and Patrick Bélisle[5]

[1]CHUM Research Center, Montreal, QC, Canada; [2]the Canadian Network for Observational Drug Effect Studies (CNODES), Montreal, QC, Canada; [3]Centre for Health Outcomes Research, McGill University, Montreal, QC, Canada; [4]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada; [5]Montreal Heart Institute, Montreal, QC, Canada; [6]Clinical Epidemiology and Outcomes Research, Montreal Health Innovations Coordinating Center, Montreal, QC, Canada; [7]Université de Montréal, Montreal, QC, Canada; [8]Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada; [9]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada; [10]Department of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada

Background: Bayesian analysis offers the ability to integrate previous evidence with current data to construct new knowledge in a given therapeutic field. Defining a "prior" can depend on the analyst's subjective beliefs and presents multiple challenges. As a case-study, a Bayesian analysis of a published trial was undertaken to illustrate considerations behind the choice of a prior and the methodology using different levels of skepticism in prior beliefs.

Objectives: Conduct a Bayesian meta-analysis (MA) using published data on the risk of ventricular tachycardia (VT) and sudden cardiac death (SCD) with use of domperidone in patients with Parkinson's disease (PD) to demonstrate: 1) a Bayesian approach to integrating prior data and 2) the use of probabilities rather than p-values for quantifying uncertainty in statistical inferences.

Methods: In assessing the association between domperidone and VT/SCD in patients with PD, we used the result (RR and CI) from a CNODES database analysis (7 Canadian provinces; 1 UK) as the observed data and combined it with either an uninformative (uniform) or informative prior (Bayesian RR (CI) from observational studies) to calculate the posterior probabilities (PP). We employed a Bayesian hierarchical approach using normal distributions to model the prior and observed data probabilities. Sensitivity analyses were conducted

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

using different weights of the prior data. We defined 4 thresholds of harm (>0%, >20%, >30%, >40%) and estimated the corresponding PP conditional on prior beliefs.

Results: The Bayesian approach with an uninformative prior yielded a RR of 1.28 (95% credible interval (CrI): 0.94 - 1.88) in comparison to the published frequentist RR of 1.22 (95% CI.: 0.99 - 1.50). With an informative prior, the RR was 1.51 (95% CrI: 1.19-2.0) when a weight of 100% was assigned, 1.41 (95% CrI: 1.10 - 1.98) with a weight of 50%, and 1.31 (95% CrI: 1.01 - 1.93) with a weight of 10%. When harm was defined as >30% increased risk, the PPs were 89%, 72%, and 51% with priors weighed at 100%, 50%, and 10%. When harm was defined as >40% increased risk, corresponding PPs were 72%, 51%, and 33%, respectively.

Conclusions: While both frequentist and Bayesian approaches found that domperidone is associated with an increased risk of VT/SCD in patients with PD, only the Bayesian approach directly quantified the probability of various magnitudes of harm, conditional on prior beliefs. Two main advantages of the Bayesian approach are the ability to combine prior knowledge with new data and to report inferences in a probabilistic manner that may be of additional benefit to patients, providers and regulators.

4358 | Association of industry payments to physicians with pimavanserin prescribing and medicare expenditures

Hemalkumar B. Mehta[1], Thomas J. Moore[2] and G. Caleb Alexander[1]
[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;*
[2]*Institute for Safe Medication Practices, Alexandria, VA*

Background: Pharmaceutical industry payments to physicians can influence physician's prescribing behavior. Pimavanserin was approved for Parkinson's disease psychosis. Product approval was based on a single trial suggesting a small treatment effect and occurred after three prior trials failed to meet prespecified endpoints. Post-marketing surveillance has also raised concerns regarding pimavanserin's safety.

Objectives: To quantify the association between industry payments to physicians for pimavanserin, pimavanserin prescribing and Medicare expenditures for its use.

Methods: This retrospective cross-sectional study linked Centers for Medicare and Medicaid Services (CMS) Open Payments and CMS Part D Prescriber Data from 2016 and 2017. We used Open Payments to extract pimavanserin-related payments to physicians for food, travel and lodging, speaking, consulting and education. Part D Prescriber Data was used to quantify pimavanserin prescription volume and pimavanserin Medicare expenditures. We constructed Poisson regression models to quantify the association between physician payments and pimavanserin prescribing. We modeled the association of physician payments with Medicare expenditures for pimavanserin using linear regression.

Results: In 2016 and 2017, 1,609 physicians ordered 43,165 pimavanserin prescriptions incurring $82,376,713 in Medicare expenditures. Overall, 45% of these physicians received $6,369,922 in payments - $5,615,470 for speaking, consulting and education, and $754,452 for food, travel and lodging. Physicians receiving payments wrote 47% more prescriptions (32 vs. 22 mean scripts, p<0.001), and 17% more expensive prescriptions ($2,041 vs. $1,749 mean Medicare expenditure, p<0.001) than those who did not receive payments. Physicians receiving no payments prescribed a median of 16 prescriptions, whereas those receiving $100,000 or more in payments prescribed a median of 96 prescriptions. Each $10,000 of physician payments was associated with increased pimavanserin prescribing by 14% (incident rate ratio 1.14, 95% confidence interval [CI] 1.13-1.14). Each $1 spent on physician payment by the manufacturer was associated with a $1.76 (95% CI $1.62-$1.90) increase in Medicare pimavanserin expenditures. Food, travel and lodging payments had a greater association with pimavanserin prescribing and Medicare expenditures than speaking, consulting and education payments.

Conclusions: Our study shows extensive payments to physicians that were associated with increased number and costs of pimavanserin prescriptions.

4466 | Real-world treatment patterns and adherence of first-line anti-diabetic treatments among T2dm patients using Japanese claims data

Jocelyn Ruoyi Wang, Amanda Patrick, Pattra Mattox and Ashley Jaksa
Aetion Inc., Boston, MA

Background: Global regulatory agencies traditionally use randomized-controlled trials (RCT) to inform decisions. However, a discrepancy often exists between pre-marketing RCT efficacy data and the effectiveness data from real-world evidence (RWE). The Japan Clinical Practice Guideline for Diabetes recommends individualizing first-line treatment with an oral hypoglycemic agent based on patient conditions and safety profiles. Furthermore, medication adherence is critical to ensuring long-term glycemic control.

Objectives: To understand the treatment pathways and real-world adherence to anti-glycemic agents among type-2 diabetic (T2D) patients using a Japanese administrative database.

Methods: We identified newly-diagnosed T2D patients initiating first-line treatment using the Japanese Medical Data Center (JMDC) claims database (2014-2018). JMDC includes inpatient, outpatient, pharmacy claims and Diagnosis Procedure Combination (DPC) codes. Patients <18 years and those with prior anti-diabetic treatment were excluded. Patients were assessed for adherence (proportion of days covered [PDC]>80%) and persistence (i.e., probability of persistency during the assessment period) of first-line treatment during a one-year follow-up. Treatment change (addition, switching, and/or discontinuation) was also evaluated.

Results: Among 5,583 patients, the mean age was 55 years; 71.1% were male. Transition-based treatment pathway showed that dipeptidyl peptidase 4 inhibitors (DPP4i 49.5%) was the most

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

common first-line treatment, followed by metformin (26.6%), and SGLT2-i (10.1%). Nine different treatment pathways were observed for second-line therapy intensification. One-year persistence ranged from 29%-62%; SLGT2-i (62%) and DPP4-i (53%) users had the highest persistence. PDC at one year ranged from 60%-84%, with the highest values in SGLT2-i (84%) and metformin (81%) users.

Conclusions: While most newly-diagnosed T2D patients in Japan received DPP4i as first-line treatment, DPP-4i adherence was suboptimal. New users of SGLT2i, the third most common first-line antiglycemic, demonstrated higher adherence and persistence after one year of follow-up compared to the other antidiabetics. Complex treatment patterns of type-2 diabetic patients -- with frequent switching and less-than-optimal persistence -- highlights the utility of generating RWE from real-world data (RWD) sources to provide contextual information on routine clinical practice.

4492 | Multi-state Markov modelling of long-term outcomes using machine-learned dynamic Bayesian networks

Alind Gupta[1], Darren Brenner[2] and Paul Arora[1]
[1]*Cytel Inc, Toronto, ON, Canada;* [2]*University of Calgary, Calgary, AB, Canada*

Background: Patient-level heterogeneity in response to treatment remains a major challenge in cancer immunotherapy. Long-term individual-level modelling of survival, tumour response and safety outcomes jointly can help improve efficacy and durable clinical benefits.

Objectives: To develop a dynamic Bayesian network model for multivariate risk prediction, survival modelling and long-term simulations of immunotherapy patients using a simulated trial dataset.

Methods: A simulated randomized clinical trial dataset for immunotherapy of patients with renal cell carcinoma was used for analysis. We machine learned a dynamic Bayesian network from censored data with incorporation of prior knowledge. Classification performance, probability calibration, goodness-of-fit metrics and prognostic variables were calculated.

Results: The machine-learned graphical model encoded expected relationships between variables. Visual and numerical goodness-of-fit checks for survival extrapolations showed that the model fitted data well and was appropriate. Probability calibration was <10% from ideal. Classification performance for overall survival was high (c-statistic ~0.85) soon after treatment initiation and gradually plateaued over time. Prognostic variables were calculated by treatment arm for overall survival and severe adverse events.

Conclusions: Dynamic Bayesian network model was useful for transparently representing joint relationships between variables, for multivariate risk prediction and long-term extrapolations that can be used in economic evaluations for health technology assessments.

4520 | Real-world cost-effectiveness of direct oral anticoagulants in the Quebec setting

Philippe Lachapelle[1], Anne Holbrook[2], Mireille Mireille Schnitzer[3], Jean-Éric Tarride[4], Christel Renoux[5], Brian J. Potter[3], Alexis Matteau[3], Denis Talbot[1], Madeleine Durand[3] and Jason Guertin[1]
[1]*Université Laval, Québec City, QC, Canada;* [2]*McMaster University, Hamilton, ON, Canada;* [3]*Université de Montréal, Montréal, QC, Canada;* [4]*McMaster University, Hamilton, QC, Canada;* [5]*McGill University, Montréal, QC, Canada*

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 350,000 Canadians. AF increases the risk of stroke and systemic embolism, a risk substantially lowered by oral anticoagulants (OACs). Direct oral anticoagulants (DOACs) have been rapidly replacing warfarin as the preferred treatment in clinical practice. Previous economic evaluations comparing DOACs and warfarin were all based on RCT data. A full economic analysis based in clinical practice, has yet to be published.

Objectives: To conduct a patient level real-world economic evaluation of warfarin versus DOACs.

Methods: We conducted a cost-effectiveness analysis based on data from the Régie d'assurance maladie du Québec (RAMQ) and the Ministère de la Santé et des Services Sociaux (MSSS), using a MSSS perspective. The study population included all adults aged 18 years and older newly initiated on an OAC for non-valvular atrial fibrillation in the Province of Québec between April 1st 2011 and March 31st 2017. The incremental cost-effectiveness ratio (ICER) of warfarin versus DOAC was measured as the incremental cost per incremental life-year gained. The exposure classification was based on an intention to treat approach. Costs included all medical fee-for-service or medication claims, hospitalizations and emergency room visits. The follow-up period was censored at five years and served as the time horizon of the analysis. The adjusted ICER will be obtained using inverse probability of treatment weighting combined with the high dimensional propensity score (hdPS) algorithm and will account for data censoring. To measure uncertainty on cost and effectiveness parameters, nonparametric bootstrap with replacement was applied. Cost-effectiveness acceptability curves (CEAC) were used to summarize the uncertainty at different willingness to pay ratios.

Results: 60,093 patients were included in the base case analysis (38,579 for DOACs and 21,514 for warfarin). Preliminary results in the unadjusted cohort suggest that the ICER of warfarin versus DOACs was $23,051 per life year gained, warfarin being both more effective (.81 year) and more costly ($18,749) than DOACs. At a willingness to pay threshold of $50,000 per life year gained, the probability that the anticoagulation therapy initiated on DOACs was cost-effective is 0%.

Conclusions: Preliminary results favor the use of warfarin over DOACs. However, further analyses (e.g., adjustment for confounding bias and accounting for data censoring) are required before concluding on the true value of DOACs versus warfarin.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4538 | Selection bias associated with lab records in administrative claims from the United States

Kathleen M. Andersen[1,2], Derek K. Ng[1], Michael J. Blaha[1,3], G. Caleb Alexander[1,2,4] and Jodi B. Segal[1,2,4,5]

[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD;* [2]*Center for Drug Safety & Effectiveness, Baltimore, MD;* [3]*The Ciccarone Center for the Prevention of Cardiovascular Disease, Baltimore, MD;* [4]*Division of General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, MD;* [5]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

Background: Administrative claims are used in the United States for population-level analyses of drug utilization, safety and effectiveness. While clinical encounters and prescription dispensations are well captured, data have limited coverage of laboratory test results. Ongoing monoclonal antibody PCSK9 inhibitor (PCSK9i) treatment requires LDL cholesterol monitoring, therefore PCSK9i users represent a study population in which we can evaluate the generalizability of lab result availability.

Objectives: To evaluate whether the subset of PCSK9i users with available LDL values in IBM MarketScan® Commercial Claims and Encounters Database represents the larger pool of PCSK9i users without available lab data.

Methods: Persons with at least one dispensation for alirocumab or evolocumab were extracted between July 2015 (month of FDA approval) and December 2017. Persons were classified as having at least one LDL result pre- or post-initiation, or no lab result data. We used standardized mean differences (SMD) >10% to define significant differences between groups in a sample size independent manner.

Results: For 5,960 unique PCSK9i users, 16% had lab values reported. Persons with lab values were older (56 vs 57 years, SMD=15%) and more often female (44 vs 39%, SMD=11%). Evolocumab was used more often than alirocumab (68% with labs vs 72% without, SMD=12%), but no significant differences in out-of-pocket cost for 28-day PCSK9i supply were found ($66 vs $67). Important differences were noted in insurance plan type (SMD=24%), with relatively fewer preferred provider organization plans and more health maintenance organization plans in the lab value group. Lab values were more commonly available for patients in the southern United States (SMD=35%) than in the North Central or West.

Conclusions: In the US, insurance plans & associated coverage vary widely, and ultimately impact healthcare and drug utilization. Using MarketScan data, the presence or absence of LDL laboratory results was strongly associated with insurance and regional differences, consistent with differential availability by insurance status rather than a true clinical phenomenon. While PCSK9i use necessitates ongoing LDL assessment, the select subgroup with laboratory results was not a representative sample of PCSK9i users, and therefore is not generalizable. Herein, we present evidence that future analyses using MarketScan data with LDL results may need be restricted to only the subset of persons with lab value coverage. This will work will guide the selection of a dataset and study design for future drug utilization, safety and effectiveness studies of PCSK9i.

4591 | Statin use and the risk of prostate cancer

Wei Ho[1], Dan-Wei Choo[1], Yi-Jung Wu[2], Yu-Sheng Lin[3], Bing-Jyue Chen[4], Chuan-Shen Hu[5], Jui Wang[6], Yu-Wen Wang[1], Po-Yu Chen[2], Ting-Fang Chan[1] and Zhen-Fang Lin[1]

[1]*National Taiwan University, Taipei, Taiwan;* [2]*National Taiwan University, Taipei, Taiwan;* [3]*National Taiwan University, Taipei, Taiwan;* [4]*National Taiwan University, Taipei, Taiwan;* [5]*National Taiwan Normal University, Taipei, Taiwan;* [6]*National Taiwan University, Taipei, Taiwan*

Background: Literature studying statins use and the risk of prostate cancer were mainly done in western countries and yielded inconsistent results.

Objectives: First, to analyze the statins effects on the risk of prostate cancer in Taiwan. Second, to access whether different characteristics of statins will affect the risk of prostate cancer differently.

Methods: This is a retrospective cohort study using National Health Insurance Research Database from January 1, 2000 to December 31, 2013. Patients aged more than 55 and were newly diagnosed with acute coronary syndrome between January 1, 2001 and December 31, 2008 without any cancer diagnosis before or 180 days after the index date were included. The propensity score was used to match statin users and non-users. Time-dependent Cox hazards regression model was used to calculate the risk of prostate cancer between drug exposure group and non-exposed group. The analyses were also stratified to assess the statin's effect in different age groups, the severity of underlying diseases, comorbidities, and hospital levels. The follow-up period was the time from the index date for the outcome of interests, withdraw from the registry, and the end of the study.

Results: After 1:1 propensity score matching, a total of 26,628 men were included. Statin use was associated with significantly lower risk of both total and advanced prostate cancer (Adjusted HR: 0.719, 95% CI: 0.570-0.908; Adjusted HR: 0.718, 95% CI: 0.530-0.972 respectively). Compared with statins non-users, the adjusted HR (95% CI) were 1.328 (0.931-1.654) for the group with cumulative dose <84 cDDD, 1.203 (0.903-1.604) for the group 312>cDDD≧84, 0.712 (0.513-0.989) for the group 818>cDDD≧312, and 0.426 (0.298-0.609) for the group cDDD≧818. Simvastatin, fluvastatin, atorvastatin, and rosuvastatin users showed significant 26.6%, 30.2%, 30.9%, and 37.8% reductions in total prostate cancer risk respectively. Lipophilic statins were not different from hydrophilic statins in total and advanced prostate cancer risk (Adjusted HR: 1.014, 95% CI: 0.638-1.610; Adjusted HR: 0.806, 95% CI: 0.445-1.459). However, high-intensity statins showed a significant reduction in total and advanced prostate cancer risk compared with statins non-users (Adjusted HR: 0.548, 95% CI: 0.367-0.820; Adjusted HR: 0.487, 95% CI: 0.284-0.836).

Conclusions: In Taiwan ACS population, reduction in risk of prostate cancer were observed in statin users, especially patients used

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

simvastatin, fluvastatin, atorvastatin, rosuvastatin or high-intensity statins. Everyone in the world is related to one another.

4609 | Healthcare resource utilization in patients with treatment resistant depression: A national danish cohort study

Kristoffer J. Jensen[1], Frederikkke H. Gronemann[2], Mikkel Z. Ankarfeldt[1], Espen J. Solem[3], Sarah Alulis[4], Jesper Riise[4], Nikolaj Bødker[4], Merete Osle[2] and Janne Petersen[1]

[1]Center of Clinical Research and Prevention, Frederiksberg, Denmark; [2]Center of Clinical Research and Prevention, Frederiksberg, Denmark; [3]Bispebjerg Hospital, Copenhagen, Denmark; [4]Janssen Cilag A/S, Birkerød, Denmark

Background: Treatment resistant depression (TRD) has severe negative consequences for quality of life and has been shown to place a large economic burden on society.

Objectives: In this study we investigated healthcare resource utilization (HRU) and costs in relation to depression severity and calendar time among TRD patients in Denmark.

Methods: Register-based study in Denmark including all adult patients with a first-time hospital contact due to major depressive disorder (MDD) between 1996 and 2015. Patients with a prior diagnosis of other affective disorders were excluded. TRD was defined as the second shift in antidepressant treatment. The HRU and associated costs 12 months prior to and 12 months after the TRD defining date were analyzed as relative risk using Poisson regression, or as difference in average utilization using ANOVA comparing TRD patients to non-TRD MDD patients. Patients were matched 1:2 on sex, age, year of diagnosis, and depression severity (mild, moderate, severe). The HRU data were retrieved from the National Patient Registry (psychiatric and somatic hospital contacts), the National Health Service Register (general practitioner visits), and the Danish National Prescription Registry (redemption of medicine prescriptions). The analyses were stratified on year of diagnosis and depression severity.

Results: We identified 25,321 TRD and 50,638 matched non-TRD MDD patients. For TRD patients, the risk of HRU of any psychiatric service during the 12 months following TRD diagnosis was more than 2-folds higher than that for non-TRD MDD patients. There was no difference for somatic services. Among patients that used healthcare services, the associated HRU costs for TRD patients were increased by 87.6% (95% confidence interval: 83.1-92.3) for all types of healthcare services and 55.0% (50.7-59.4) for psychiatric services, notably demonstrating a decreasing cost burden, with increasing depression severity in TRD patients relative to non-TRD MDD patients. Moreover, there was a trend over time for an increasing cost burden, particularly for acute hospitalizations and emergency department (ED) visits.

Conclusions: TRD was associated with increased psychiatric-related HRU especially in patients with mild depression. Particularly, for acute hospitalizations and ED visits the cost was increasing over the study period, indicating that TRD constitutes an escalating, unsolved health problem.

4644 | Insights into back pain through linkage of digital patient generated data with electronic health records

Alejandra Martinez De Pinillos[1], Toby Helliwell[2], Matthew Cooper[3], Mick Mullane[3], Stephanie Meleck[4], Shaun O'hanlon[5], Pierre Engel[6], Joshua Hiller[1] and Jaskiran Dhanjal[1]

[1]IQVIA, LONDON, United Kingdom; [2]Keele University, KEELE, United Kingdom; [3]National Institute of Health Research (NIHR) Clinical Research Network National Coordinating Centre, Leeds, United Kingdom; [4]uMotif, LONDON, United Kingdom; [5]EMIS, LEEDS, United Kingdom; [6]IQVIA, Saint Ouen, France

Background: Back pain affects up to 80% of the population in industrialised countries and is the largest cause of disability in the UK. Physician and patient engagement are critical to ensure timely and multidisciplinary collection of back pain events and symptoms. A patient-centred approach can also improve self-management of back pain.

Objectives: Quantify the burden of back pain in primary care through digital health technology allowing discrete data collection timeframes. Additionally, assess the impact of an innovative methodology in patient and physician engagement and retention.

Methods: Observational multicentre prospective study of acute/chronic lower back pain in the UK. A recruitment tool was embedded into EMIS (GPs' patient EMR software) to facilitate engagement and alleviate burden on sites and patients. Patients received further study information and provided electronic consent, information on QoL, work productivity along with physical and mental impacts of back pain through the uMotif app on mobile devices. Data generated is linked at the patient level with a data extract from patients' EMR, reflecting care over a specific period of time including back pain.

Results: By October 2019, 46% of GPs across 138 sites showed willingness to participate and invited patients. Among these GPs, 66% of them successfully led to patients consenting to take part in the study. Out of the 322 patients invited, 42% downloaded the app and consented to take part in the study. By the fifth month, 80% of the final study population was recruited. Baseline and follow-up completion rates are 86%, 38% (44 days) and 30% (final timepoint).

Conclusions: Our preliminary results show the potential for improved GP and patient engagement compared with traditional observational studies. The data was generated by patients via the mobile app which meant the study did not require follow up visits with the GP, resulting in a lower burden on recruitment and data collection. Although e-health tools have already shown potential to facilitate engagement in observational studies, this study is the first in England to assess this approach in combining EMR and PRO data in back pain. Leveraging EMR data together with patient generated data, has the potential to shorten the time needed to complete a study, thereby reducing costs, improving quality of research data and reducing recall bias. Study results will be available in the coming months and will allow a better understanding of patients' experience of back pain and consequently, will allow better management of treatment by professionals. *This study was briefly initiated in ICPE 2019*.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4650 | Elevated annual healthcare utilization and direct medical costs associated with diabetes mellitus patients with osteoporosis in China

Zheng Yin[1], Yigong Zhou[1], Jun Liu[1] and Yang Xie[2]
[1]*IQVIA, Beijing, China*[2]*IQVIA, Shanghai, China*

Background: Osteoporosis may be caused by insulin deficiency or hypercalciuria associated with glycosuria.
Objectives: This study assessed elevated healthcare resource utilization (HCRU) overall and at different tiers of medical services among diabetes mellitus (DM) patients with osteoporosis (DMwOP).
Methods: A retrospective cohort study using a city-level administrative claims database between 2012-2015 in China. Adults (aged ≥18 years) with evidence of DM (≥1 claim with a diagnosis of DM or for blood-glucose lowering medication) were firstly identified. Within the DM population, those with evidence of osteoporosis (≥1 claim with a diagnosis of osteoporosis or fragile fracture) were identified. Osteoporosis evidence can be either before or after DM evidence. The rest DM patients were defined as DM without osteoporosis (DMw/oOP). Descriptive analyses and comparison tests between DMwOP and DMw/oOP patients were performed in SAS 9.4.
Results: Of the 41,693 DM patients, 62% had osteoporosis. DM patients with osteoporosis was significantly older (mean age 62.0 *vs*. 57.9, P<0.001). The number of outpatient visits per person per year (PPPY) among DMwOP almost doubled that among DMw/oOP (46 *vs*. 25 times, p<0.001). Outpatient cost PPPY was also significantly higher among DMwOP (USD 1,496.32 *vs* USD 859.09, p<0.001). Over half of outpatient visits were at primary and secondary hospitals and community clinics (58% *vs*. 51% among DM patients with *vs*. without osteoporosis). The number of hospitalization, length of stay PPPY and costs of hospitalization were similar among DMwOP and DMw/oOP.
Conclusions: Given the very high prevalence of osteoporosis in DM patients as well as elevated outpatient visits and costs among DMwOP, targeted screening, diagnosis and treatment of osteoporosis should be promoted in the increasing DM population. The important role of primary and secondary hospitals and community clinics in the service provision to DMwOP also highlight the urgency of increasing the capability of low-tier health care services.

4657 | Cost-sharing increase, adherence and hospitalizations in schizophrenic patients: A population-based difference-in-differences analysis in the Valencia region, Spain

Miquel Serra-Burriel[1], Isabel Hurtado[2], Anibal Garcia-Sempere[2], Gabriel Sanfelix-Gimeno[2] and Salvador Peiró[2]
[1]*CRES-UPF, Barcelona, Spain*; [2]*FISABIO, Valencia, Spain*

Background: Increases in cost-sharing remain a controversial system-wide cost-containment measure for chronic mental health patients.
Objectives: To investigate the association between a cost-sharing increase, adherence to prescribed antipsychotic medication and psychiatric hospitalizations in schizophrenic patients.
Methods: Design: Difference-in-differences regression analysis with patient fixed-effects using a retrospective cohort from the Valencia Health System (VHS) Integrated Databases (VID). **Setting**: Public healthcare system of Valencia, Spain from July 2011 to July 2013, covering about 97% of the region population. **Participants**: Adult patients of the VHS with a prevalent diagnosis of schizophrenia in 2011. **Exposures**: In July 2012, a Spanish National Law raised the cost-sharing rate from 0 to 10% for outpatient medication for some socioeconomic group while leaving others intact. **Main Outcomes Measures**: adherence, measured as a weekly possession rate to prescribed medication, and weekly psychiatric hospitalization rate.
Results: Of 26,913 diagnosed schizophrenic patients, 11,217 (41.6%) were included in the analysis. A total of 5,672 patients were exposed to the reform, while 5,545 were not. There were no differences in adherence and hospitalization trends between exposed and non-exposed patients prior to the implementation of the reform. The proportion of exposed patients that did not fill the issued prescriptions at the pharmacy decreased 6.12 percentage point (95%CI: -8.59; -3.64, p<0.001), a relative decrease of 8.7% compared to the non-exposed group 3 months after implementation. The psychiatric hospitalization rate of exposed patients increased 3.63 per 1,000 patients (95%CI: 1.36; 5.91, *p:* 0.002) the month after the implementation. The change in cost-sharing was not associated with other hospitalization reasons such as pneumonia (0.012 per 1,000 patients; 95%CI: -0.26; 0.28, *p:* 0.92).
Conclusions: Policies raising the cost-sharing rate of medication for schizophrenic patients are simultaneously associated with unintended effects such as decreases in adherence or increases in hospitalization rates.

4670 | Evaluation of cost of illness in patients with rheumatoid arthritis in a tertiary healthcare setting

Rajesh V[1], Nishma D. Khetia[1], Surulivelrajan Mallayasamy[1] and Manjunatha Hande H[2]
[1]*Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, India*; [2]*Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India*

Background: Rheumatoid Arthritis (RA) is a chronic disease associated with poor quality of life of patients, lifelong dependency on medications and long-term disease suffering which leads to both physical and financial disability in terms of cost. RA flare and complications lead to hospitalization and demand in-patient care and these costs impose a significant burden on the patients especially those from a poor socio-economic background in a developing society like India where the country reserves only 1.4% of the income for healthcare.
Objectives: To find the cost of illness associated with hospitalized patients suffering from Rheumatoid Arthritis and understand the prescription pattern of drugs for the same.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: A retrospective research study was conducted on in-patients diagnosed with Rheumatoid Arthritis in the Medicine department, in a tertiary care hospital setting. The patient files were obtained from the In-patient Medical Records Department after obtaining proper ethical approval from the hospital Institutional Ethics Committee. The finance data was collected from the Finance Department in the hospital. Data was collected in case record forms designed for the study and entered SPSS for analysis.

Results: The most commonly prescribed Disease-Modifying Anti-Rheumatic Drugs (DMARDs) was Methotrexate prescribed for 202 patients (62%) followed closely by Hydroxychloroquine prescribed to 194 patients (59.6%). They were also the most commonly prescribed drugs as a combination therapy at 45.9%. The total median cost for single admission was found to be INR 12, 247.

Conclusions: INR 12, 247 is a very high amount in a developing country such as India. First year of symptoms is where most of the patients come to hospital to get RA diagnosis and is also the peak time to start effective treatment regimen, disease education and awareness to ensure that disease progression can be prevented by reinforcing the importance of medication adherence among patients. This is a white space role that can be taken up by health care professionals.

4672 | Association between hydrochlorothiazide use and risk of malignant melanoma: A meta-analysis using epidemiological studies

Md Salman Hussain[1] and Abul Kalam Najmi[2]
[1]*Jamia Hamdard, New Delhi, India;* [2]*Jamia Hamdard, New Delhi, India*

Background: Hydrochlorothiazide (HCTZ) is the most commonly prescribed first-line antihypertensive agent. In recent years studies reported controversial findings and showed protective to detrimental effects of HCTZ use in malignant melanoma.

Objectives: To assess the malignant melanoma risk associated with the use of HCTZ.

Methods: PubMed, Embase, and Cochrane Central databases were searched from inception to January 2020. All the studies assessing the association between HCTZ use and malignant melanoma were qualified for inclusion. Data were abstracted and quality was assessed using the Newcastle-Ottawa scale by two independent investigators. The primary outcome was to compute the pooled effect of HCTZ use and the risk of malignant melanoma. The secondary outcome was to assess the impact of the dose-response relationship between HCTZ use and the risk of malignant melanoma. Meta-analysis was performed using Review Manager v5.3.

Results: A total of four studies (three case-control and one cohort) qualified for inclusion in the meta-analysis. Included studies were conducted in Denmark (2 studies), Korea, and Taiwan. All of the included studies were of high quality. The random-effect model was applied for the meta-analysis due to the presence of significant heterogeneity. HCTZ use was not associated with the malignant melanoma risk, with a pooled risk ratio (RR) of 1.03 (95% CI: 0.85 - 1.25), p = 0.77 in fully adjusted analysis (adjusted for several confounding factors). Subgroup analysis based on cumulative dose of >50000 mg and <50000 mg dose of HCTZ also revealed non-significant association with the risk of malignant melanoma with a pooled RR of 0.95 (95% CI: 0.53 - 1.69), p = 0.85 and RR 0.97 (0.77 - 1.23), p = 0.83.

Conclusions: No significant association was observed between HCTZ use and malignant melanoma risk. Future well-designed epidemiological studies are warranted to confirm or counter the findings.

4715 | The effect of depression on health care utilization and health expenditure in patients with diabetes

Yang Xie[1], Hanyuying Wang[2], Angela Yin[2] and Yigong Zhou[2]
[1]*IQVIA China, Shanghai, China;* [2]*IQVIA China, Beijing, China*

Background: Previous evidence has shown that the psychological burden of diabetes may contribute to depression, and people with diabetes are at twice greater risk of having depression. Global studies reported that diabetic people with depression consumed more health care services than those without depression. However, this has not been fully explored in Chinese population.

Objectives: To compare the health care utilization and expenditures between diabetic patients with and without depression in a metropolitan city in China.

Methods: This is a cross-sectional analysis. A city-level claims database (2012-2015) was used to identify diabetic patients (≥1 claim with a diagnosis of diabetes). Depression was defined by clinical diagnosis as well. Health care utilization included number of outpatient visits, and health expenditures were total medical costs and outpatient-related medical costs. Medical costs were inflated to 2015 RMB and converted to US dollars (USD) using 2015 exchange rate. The comparisons between patients with depression and those without were tested using analysis of variance and Kruskal-Wallis test for normally and skewed distributed variables, respectively, and Pearson's chi-square test for categorical variables.

Results: A total of 41,693 diabetic patients were identified during 2012-2015, of whom 2,025 (5%) had depression. The mean age of diabetic patients with/without depression were similar (62 vs. 60). However, the average number of outpatient visits per person per year (PPPY), the average total medical cost PPPY and outpatient-related medical costs PPPY were all significantly higher in diabetic patients with depression than those without depression (the average number of outpatient visits PPPY: 54 vs. 37, p<0.001, the average total medical costs PPPY: USD 2,922 vs. USD 2,121, p<0.001, and the average outpatient-related medical costs PPPY: USD 1,718 vs. USD 1,166, p<0.001, respectively).

Conclusions: Our study suggests that having depression significantly increases the healthcare burden in diabetic patients in China. Improve management of diabetes and put more efforts to raise the awareness of depression and to prevent its occurrence may potentially reduce this burden.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4813 | Cardinality matching vs propensity score matching for targeted estimands

Stephen Fortin, Stephen S. Johnston and Paul Coplan
Johnson and Johnson, New Brunswick, NJ

Background: Cardinality matching (CM) uses advancements in optimization algorithms and has previously been shown to outperform propensity score matching (PSM) in post-match residual covariate balance and sample size retention. Another unique attribute of CM is the ability to obtain matched sample which are representative of any user-defined target estimand. For example, estimating the average treatment effect on the controls (ATC) may be necessary in studies to understand the impact of expanding medical treatments to previously unserved populations. CM and PSM may differ in their ability to obtain post-match samples which closely mimic targeted estimands.
Objectives: The present study compared the performance of PSM and CM when targeting the ATC estimand in a retrospective study of patients undergoing minimally-invasive surgery (MIS) vs. open surgery (OS) for thoracic segmentectomy.
Methods: Patients aged ≥18 years undergoing thoracic segmentectomy between 1-1-2010 to 6-30-2017 were identified from the Premier Healthcare Database (index=first admission) and classified as undergoing OS or MIS. Targeting the ATC estimand, we conducted PSM through 1:1 nearest-neighbor matching (caliper=0.15) and CM through 1:1 matching permitting a maximum standardized mean difference (SMD) of 0.05 between comparison groups and the ATC. We evaluated PSM and CM on post-match sample size, covariate balance between groups, and balance between the post-matched samples and target ATC estimand. An SMD>0.10 was considered imbalanced.
Results: We identified 5,552 patients (MIS: 3,524, OS: 2,028) meeting the study criteria. Matching was conducted across 37 covariates (74 unique levels). Total post-match sample sizes were similar for PSM=3,604 and CM=3,600. However, CM resulted in better balance between the MIS and OS groups (PSM: mean SMD=0.03, range=0.0—0.19, imbalanced covariates=5; CM: mean=0.03, range=0.0—0.08, imbalanced covariates=0) and post-matched groups which were more similar to the ATC estimand (PSM OS: SMD mean=0.02, range=0.0—0.13, imbalanced covariates=1; PSM MIS: mean=0.04, range=0.0—0.18, imbalanced covariates=7; CM OS: mean=0.0, range=0.0—0.03, imbalanced covariates=0; CM MIS: mean=0.03, range=0.0—0.05, imbalanced covariates=0).
Conclusions: In this applied comparison, CM outperformed PSM on balance between comparison groups and ability to mimic the targeted estimand, while post-match sample sizes were similar between methods.

4850 | Head to head comparisons of therapies using real world data: What is needed to emulate target trials?

Miguel Hernan[1], Thomas Wilke[2], Edward J. Mills[3], Sonal Singh[4]
[1]*Harvard University, Boston, MA;* [2]*Ingress Health, Rotterdam, Netherlands;* [3]*Cytel, Vancouver, BC, Canada;* [4]*University of Massachusetts, Worcester, MA*

Background: Head-to-head comparisons of therapies are essential to determine their value, both from clinical and societal perspective. The increased availability of real-world data (RWD), coupled with sound methods for the emulating of target trials, raises the question of whether RWD can be used to reliably estimate causal effects.
Objectives: To debate the role of RWD in causal inference and what RWD characteristics are needed to perform trial emulation studies when head-to-head RCTs do not exist. Stakeholders from regulatory agencies, HTAs, academia, and life sciences industry will benefit from attending the symposium.
Description: When head-to-head randomized trials are not available, regulators, HTA bodies and others may need to rely on RWD comparisons to assess comparative effectiveness and safety. The use of RWD for causal inference is often challenged due to data limitations. Recent developments are challenging this status quo. Several research projects have already successfully replicated the results of clinical trials using RWD approaches and recently several life sciences companies have supported their regulatory submissions with findings from RWD studies. The issue panel will explore the challenges and opportunities of using RWD for causal inference. The panel will commence with the moderator's introduction of the topic (10min). Existing approaches to head-to-head comparisons will be presented during this overview. Panelists will then present their perspective on the question being debated (20min each). After each presentation, panelists or the moderator will pose challenge questions to a given speaker which will be addressed at the beginning of the debate section (10min). General Q&A will follow (10min).

4874 | Does intraarticular involvement increase the risk of complications after fracture repair surgery?

Zhenna Huang[1], Deepak Krishnan[2], Aatheep Gurubaran[2], Chantal Holy[1], Mollie Vanderkarr[1] and Sparks Charisse[1]
[1]*Johnson and Johnson, New Brunswick, NJ;* [2]*Mu-sigma, Bangalore, India*

Background: Fractures that involve joints are believed to increase the surgical complexity compared to those without joint involvement.
Objectives: This study aims to investigate whether joint involvement increases the risk of surgical complications following fracture repair surgery.
Methods: Through a data partnership with Mercy Technology Services, a retrospective database analysis of Mercy electronic health records was conducted. Adult patients who underwent lower extremity fracture repair surgery between 2011-2018 were identified. Postoperative outcomes assessed included: (1) 3-month infection after surgery, (2) all-cause 3-month readmissions, (3) extended LOS (≥ 3days) and (4) 3-month cardiac/renal/respiratory complications. Propensity score matching was used to maximize similarity between patients with and without joint involvement fracture using the following covariates: age, American Society of Anesthesiologist (ASA) score, body mass index (BMI), health insurance, Elixhauser comorbidity score (ECS), gender, procedure year, New Injury Severity Score (NISS) and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

provider volume. The propensity score matching involved nearest neighbor technique with calipers of width equal to 0.2 of the pooled standard deviation of the logit of the propensity score. Matching ratio was 3:1.

Results: Before matching, this study included 14,044 fracture repaired patients, of which 766 had intraarticular fracture. The mean (standard deviation (±) SD) of age, ASA, NISS, and ECS for non-intraarticular fracture vs intraarticular fracture were 63.6±21.1 vs 51.7±17.8, 2.6 ±0.8 vs 2.5±0.8, 8.9±5.5 vs 12.1±8.5, and 2.8±2.5 vs 2.1±2.1, respectively. After matching, the OR time increased by 52 mins on average (158 mins vs 106 mins) for patients with intraarticular fracture. Intraarticular fracture was associated with longer length of stay (OR: 1.62, 95% CI: 1.35-1.93), infection (OR: 1.28, 95% CI: 1.005-1.64), all-cause readmission (OR: 1.44, 95% CI: 1.15-1.80) and respiratory complications (OR: 1.42, 95% CI: 1.02-1.98). We did not observe significant association between cardiac and renal complications and intraarticular fracture after PS matching.

Conclusions: Joint involvement is associated with longer length of stay and higher risk infection and readmissions after fracture repair.

4908 | Healthcare resource utilisation and cost burden of chronic obstructive pulmonary disease in the United States: A literature review

Anil Dasari[1], Salman Hussain[2] and Pradeep Basa[3]
[1]*Independent Researcher, Delhi, India;* [2]*Jamia Hamdard, Hamdard University, Delhi, India;* [3]*Independent Researcher, Bangalore, India*

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive and debilitating respiratory condition; it leads to significant burden- medically as well as financially. It affects millions of people worldwide and causes significant morbidity and mortality. Understanding the burden of COPD helps the government and policymakers to make better healthcare decisions.

Objectives: To assess the COPD resource utilisation and cost-burden in the United States (US).

Methods: A comprehensive literature search was conducted in PubMed and Cochrane Library by combination of MeSH terms & keywords from July 2017 to July 2018. Google & Google-Scholar also searched for any additional publications. The quality of included studies was assessed by Newcastle-Ottawa-Scale.

Results: The crude hospital admission rate was 3.9% in all states; high in Arkansas (4.4%) and low in Utah (1.8%). Mean length of index hospitalisation stay (IHS) was 4.4 days. Overall 30-day-readmission rate was 19.7%; marginally higher in male (20.1%) than female (18.6%) and higher in Non-Hispanic black (21.5%) relative to Hispanics (19.5%), Non-Hispanic white (19.1%), and others (18.6%). From 2006-to-2012, 30-day-rehospitalisation rate was decreased (20.0% in 2006 vs. 19.2% in 2012, p<0.001). 30-day-readmission rate in patients hospitalized with acute exacerbation of COPD (AECOPD) was 19.2%. AECOPD 30-day-readmission rate was slightly higher in aged ≥65-years (20%) than 40-64-years (18%). Patients with lower median house hold income [compared to ≥$64,000; ≤$37,999-aOR: 1.11, p<0.01], comorbidities [alcohol abuse-aOR: 1.14, p<0.01; congestive heart failure-aOR: 1.13, p<0.0001; and renal failure-aOR: 1.16, p<0.0001], higher number of co-morbidities [compared to ≤5; >5-≤7-aOR: 1.18, p<0.0001; >7 - ≤9-aOR: 1.25, p<0.0001; and ≥9-aOR: 1.38, p<0.0001], and greater length of IHS [compared to ≤2; >5-aOR: 1.23, p<0.0001] had higher odds of AECOPD 3-day-readmission. These factors are also significantly associated with 7-and-30-day readmissions. Mean total Medicaid costs-per-COPD patient $23825. In 2010, total estimated COPD-burden was $36 billion in the US, including direct medical costs and absenteeism costs ($3.9 billion). Median total AECOPD-cost-per-patient was $22535 & $27349 at index hospitalisation and 30-day-readmisson, respectively.

Conclusions: COPD is associated with significant healthcare resource utilisation & cost-burden in the US.

4974 | Lost productivity as a result of cognitive impairment among older adults in the U.S.

Kevin Lu[1], Xiaomo Xiong[1] and Sam Li[2]
[1]*University of South Carolina, Columbia, SC;* [2]*University of Tennessee, Memphis, TN*

Background: Cognitive impairment is a common and prominent symptom among older population, which may potentially impair their daily functions and work productivity. However, no studies have evaluated the impact of cognitive impairment on productivity loss.

Objectives: We aimed to determine the effect of cognitive impairment on productivity loss among Medicare beneficiaries in the U.S.

Methods: A retrospective pooled cross-sectional study was performed using the data from the National Health Interview Survey (NHIS), 2010 - 2018. Cognitive impairment was identified by a response of "yes" to the survey question "limited in any way because of difficulty remembering or because of experiencing periods of confusion." Productivity loss was measured by asking respondents the number of lost workdays in the past 12 months. Descriptive analyses were used to compare the characteristics of the elders with cognitive impairment and those without. A negative binomial regression model was used to determine the association between productivity loss and cognitive impairment. Potential confounding factors included demographic, socio-economic and health-related factors.

Results: A total of 123,869 elders aged 65 years or older were identified out of 868,476 respondents to determine the association between productivity loss and cognitive impairment. All of the characteristics were statistically significantly different between individuals with and without cognitive impairment (P-value < 0.001). Older adults with cognitive impairment were more likely to lose productivity compared to those without (Incidence risk ratio: IRR=1.08, 95% CI: 1.03-1.13).

Conclusions: We found that the older population with cognitive impairment suffered from lost productivity significantly compared to those without, suggesting potential economic loss due to cognitive impairment.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4976 | Estimated costs of pivotal trials for U.S. Food and drug administration (FDA)-approved oncology drugs, 2015-2017

Emily Hsiue[1], Thomas J. Moore[2] and Caleb Alexander[3]
[1]Johns Hopkins School of Medicine, Baltimore, MD; [2]Institute for Safe Medication Practices, Alexandria, VA; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Background: Pivotal clinical trials provide critical evidence to regulators regarding a product's suitability for marketing approval.
Objectives: (1) To characterize select features of trials for oncology products approved by the U.S. Food and Drug Administration (FDA) between 2015 and 2017; and (2) to quantify the costs of these trials and how such costs varied based on trial characteristics.
Methods: We identified novel oncology therapeutic drugs, and their respective pivotal trials, approved between 2015 and 2017 using annual summary reports from the FDA. Cost estimates for each pivotal trial were calculated using IQVIA's CostPro, a clinical trial cost estimating tool based on executed contracts between pharmaceutical manufacturers and contract research organizations. Measures of drug and trial characteristics included trial design, end point, patient enrollment, and regulatory pathway. We also performed sensitivity analyses that varied assumptions regarding how efficiently each trial was conducted.
Results: A total of 39 pivotal clinical trials provided the basis for FDA approval of 30 new oncology drugs from 2015 to 2017. Among these trials, primary endpoints were objective response rate in 20 (51.3%), progression-free survival in 13 (33.3%), and overall survival in 6 (15.4%). Twenty trials (51.3%) were single-arm studies. The median estimated cost of oncology pivotal trials was $31.7 million (interquartile range [IQR], $17.0-$60.4 million). Trials with objective response rate as primary endpoint had a median estimate of $17.7 million (IQR $11.9-$27.1 million), compared with trials examining progression-free survival ($42.3 million, IQR $34.6-$101.2 million) or overall survival ($79.4 million, IQR $56.9-$98.7 million) ($p < 0.001$). Estimated costs for single-arm trials ($17.7 million, IQR $11.9-$23.7 million) were less than for trials with a placebo-controlled ($56.7 million, IQR $40.9-$103.9 million) or active control arm ($67.6 million, IQR $35.5-$93.5 million) ($p<0.001$).
Conclusions: Relative to the estimated costs of drug development, the costs of these oncology pivotal trials were modest, with trials that produced more valuable scientific information costing more than their counterparts.

5027 | Deep joint infection comparison between simultaneous and staged bilateral total knee arthroplasty

Zhenna Huang[1], Deepak Krishnan[2], Aatheep Gurubaran[2], Chantal Holy[1], Julia Hwang[1] and John Wright[1]
[1]Johnson and Johnson, New Brunswick, NJ; [2]Mu-sigma, Bangalore, India

Background: Patients with bilateral knee arthritis are candidates for total knee arthroplasty and may decide between simultaneous (SIMTKA) or staged bilateral TKA (STATKA). Inconsistent outcomes have been reported for SIMTKA and STATKA.
Objectives: This study aims to compare the deep joint infection following SIMTKA and STATKA surgery.
Methods: The Pan-Therapeutic electronic health records (Panther EHR) from the Optum database (2007-2019) were used to identify TKA patients. The EHR data were available for a geographically diverse population of 80 million patients from more than 700 hospitals and 7,000 clinics. Short interval STATKA was defined as having staged surgery within 2 weeks after the first unilateral TKA. The postoperative outcome assessed was deep joint infection six months after surgery. Multivariable logistic regression was developed to investigate association between surgery type and deep joint infection with age, Elixhauser comorbidity score and provider volume adjustment.
Results: A total of 6,135 SIMTKA and 8,203 two-week STATKA were included in the analysis. SIMTKA were younger (mean (standard deviation): 63.2±8.3 vs 66.4±9.5, $p<0.001$), with more comorbidities (Elixhauser comorbidity score ≥4: 21.0% vs 18.6%, $p<0.001$), suffered more pain (back pain: 12.8% vs 6.5%, $p<0.001$; knee pain: 44.6% vs 16.9%, $p<0.001$), and more likely to be treated in facilities with higher volume of TKA surgeries (annual volume: 120.2±95.7 vs 113.5 ±149.3). In the multivariable logistic regression, patients who had SIMTKA were more likely to suffer from deep joint infection six month after surgery compared to patients having 2-week staged TKA (aOR: 3.4, 95% confidence interval: 2.2-5.5, incidence: 1.1% vs 0.3%).
Conclusions: This study demonstrates that SIMTKA is associated with increased risk of deep joint infection compared to 2-week staged TKA. Studies are warranted to investigate the best interval of staged TKA and to compare other surgical outcomes among SIMTKA and STATKA.

5047 | Costs and healthcare resource utilization of patients who escalate P2y12 therapy following acute coronary syndromes

Nicholas Belviso[1], Stephen Kogut[1], Herbert D Aronow[2,3], Jason Simeone[4], Marilyn Barbour[1] and Xuerong Wen[1]
[1]University of Rhode Island, Kingston, RI; [2]Lifespan Cardiovascular Institute, Providence, RI; [3]Warren Alpert Medical School of Brown University, Providence, RI; [4]Evidera, Waltham, MA

Background: For patients with an acute coronary syndrome (ACS) treated with clopidogrel, switching to ticagrelor or prasugrel represents a clinical escalation. There is a lack of research evaluating the costs and frequency of healthcare encounters associated with this treatment escalation.
Objectives: To compare the direct drug and health system costs and healthcare resource utilization (HRU) associated with escalating from clopidogrel, to either ticagrelor or prasugrel following an ACS.
Methods: This retrospective cohort study used the Optum ClinformaticsTM database to study patients that escalated antiplatelet therapy following an ACS from 2012 to 2015. Patients were followed for up to 12-months following date of switch from clopidogrel, until

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

insurance disenrollment, or death. Median and interquartile range (IQR) for per-member per-month (PMPM) all-cause and cardiovascular-related (CV) charges and healthcare utilization were evaluated for each patient following escalation. CV medical encounter cost included subsequent ACS, revascularization, or stroke events. CV prescription costs included charges attributed to dispensed CV drugs. Propensity-score (PS) 1:1 greedy matching was used to adjust for confounders. All cause and CV charges, and frequencies of HRU were compared between two PS-matched groups. Sensitivity studies were conducted using inverse probability treatment weights with a generalized linear model and log-link to estimate the relative differences..

Results: Of the 21,103 clopidogrel initiators, 132 (0.63%) escalated to ticagrelor, and 281 (1.3%) escalated to prasugrel during the 12 months follow-up. After PS 1:1 matching, 123 compared pairs with ticagrelor or prasugrel switching were included in the final analysis. There was no statistically significant difference in adjusted median monthly all-cause charges (Median; IQR: $426; $189-$6,515 vs. $451; $147-$17,312 PMPM; p=0.89), or average frequency of all-cause encounters (Mean ± SD: 2.68 ± 7.5 vs. 3.96 ± 10.5 PMPM, p=0.27) during the 12-month follow-up period between those escalating to ticagrelor or prasugrel. The costs of CV medical encounters (Median; IQR: $44; $17-$148 vs. $246; $95-$621 PMPM, p<0.01) and prescription costs (Median; IQR: $30; $7-$65 vs. $146; $54-$326 PMPM, p<0.01) were lower in those escalating to ticagrelor versus prasugrel respectively. Sensitivity analyses with GLM showed consistent results.

Conclusions: Patients who escalated to ticagrelor experienced lower CV prescription costs compared to prasugrel switchers. Further research with a larger data is warranted.

5066 | Global survey on needs and resources for pharmacoepidemiology: Implementation challenges and lessons learned

Wendy Camelo Castillo[1], Kayleigh R Majercak[1], T. Rose Love[1], Lucia D Juarez[2] and Maribel Salas[3]

[1]University of Maryland Baltimore, Baltimore, MD; [2]University of Alabama at Birmingham, Birmingham, AL; [3]Daiichi Sankyo Inc, Baskin Ridge, NJ

Background: The International Society of Pharmacoepidemiology (ISPE) has led several initiatives for the Latin American and African regions, including a needs assessment global survey to guide future actions. Differences in understanding of the field, access to resources and professional organizations can impact survey distribution and completion rates.

Objectives: To describe challenges in the implementation of a pharmacoepidemiology needs assessment global survey and discuss potential approaches to overcome those challenges.

Methods: The cross-sectional survey, "Global Survey on Needs and Resources for Pharmacoepidemiology" was developed in collaboration with pharmacoepidemiology experts within the regions, ISPE's Global Development Committee, and the University of Maryland Baltimore. Pharmacoepidemiology researchers, who were native speakers, translated the survey to the common official languages across the regions (English, Spanish, Portuguese and French) with review by pharmacoepidemiologists for face validity. To facilitate completion, the survey was distributed both in electronic and paper-based formats in two waves during 2019, and a third wave in 2020 (in-progress). To further improve representativeness across the regions, the third wave was distributed through professional networks via social platforms (i.e., WhatsApp, a preferred communication platform in the regions). The target population were decision-makers familiar with pharmacoepidemiology and/or pharmacovigilance representing government, academia, independent researchers and/or industry. Initial responders were identified by local researchers from the regions.

Results: During the first wave, the response rate was 16% (31/188) with 23.1% of incomplete responses. In this wave, potential participants were contacted through list serves of professional organizations in the field of pharmacoepidemiology and pharmacovigilance. To improve survey response and representativeness, we identified key individuals within the countries of interest, who in turn administered the survey to decision-makers. After the second wave 69.2% of participants were from Brazil. Analysis of the third wave of data are underway.

Conclusions: With the low response rate in the first wave, developing collaborations with key individuals and organizations from Latin America and Africa outside ISPE is fundamental to identify effective distribution channels. Lessons learned from this work could be applied to future initiatives implemented in these regions.

5074 | The 100 million Brazilian cohort: How does the most vulnerable Brazilian population live, born and die?

Gabriela Borges[1], M Sanni Ali[2,1], Rosemeire L Fiaccone[3,1], Liam Smeeth[2,1], Mauricio L. Barreto[1] and Maria Yury Ichihara[1]

[1]Centre for Data and Knowledge Integration for Health - Fiocruz, Salvador, Brazil; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]University of Bahia, Salvador, Brazil

Background: The 100 Million Cohort was formed to analyze social determinants and the impact of social policies on health, such as under-five mortality, low birth weight, prematurity, among other outcomes. The great advantage of this Cohort is that it uses administrative data from the Brazilian federal government, which originates in the routine collection of data by health services, whose information has the national population and geographic coverage and refers to long periods.

Objectives: To present how the population of this Cohort lives (socioeconomic and demographic aspects), the characteristics of mothers and newborns present and the aspects related to the occurrence of deaths.

Methods: The 100M Cohort is derived from individual records of the Cadastro Único (CadUnico), a system that identifies low-income

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

families applying for any of the several social protection programs. The health outcomes in the cohort come from different databases of the Brazilian Ministry of Health(MoH) from 2001 onwards. We used descriptive data analyses and data visualization techniques to present the main results.

Results: About 53% of the cohort are women, 32% joined the Cohort under 10 years old, 62% are black/brown and 52% lived in the Northeast and North region. The family's holder is women (87%), join the cohort aged from 25 to 50 years old (60%), 73% lived in the Urban area, 57% are black/brown, 12% have never attended school and 50% had no income. The number of children born with Apgar under seven is 182,122 and 20% and 18% of them are premature and underweight, respectively. About 7% of the children born with low birth weight (< 2,500g), 6.9% born premature (< 37 weeks of gestational age), and 83.116 children born with a congenital anomaly.

Conclusions: The structure of the linked cohort can be compared with those found in low-middle-income countries; however, it is several times larger and includes a more heterogeneous population. The cohort allows exploring heterogeneity in the effects throughout the country, among subgroups and further effects by mediators

5091 | Characteristics of hospitals participating in low-dose CT lung cancer screening of medicare populations

Shumin Zhang, Duncan Whitney, Matthew Mailman, Iftekhar Kalsekar, Sashi Yadalam, Meijia Zhou and Paul M. Coplan
Johnson & Johnson, New Brunswick, NJ

Background: Lung and bronchus cancer is the leading cause of cancer deaths in the US, with a 5-year survival rate of only 19.4%. Low-dose CT (LDCT) lung cancer screening has been shown to reduce lung cancer mortality in large clinical trials. Although LDCT screening has been added as a covered service for Medicare beneficiaries who meet eligibility and screening requirements since February 5, 2015, its use remains low (<5% in Medicare patients eligible for screening). Data on characteristics of hospitals that offer LDCT screening may help inform the site selection for testing new screening technologies and for understanding the barriers for current LDCT screening to inform the development of effective strategies for increasing the adoption of lung cancer screening.

Objectives: To describe characteristics of hospitals enrolling Medicare patients into LDCT lung cancer screening programs.

Methods: We conducted a cross-sectional analysis of hospitals with CPT/HCPCS code G0297 claims (LDCT scan for lung cancer screening) from February 5, 2015 (effective date of G0297 code and Medicare coverage for LDCT screening) to June 30, 2019 in Medicare standard analytic files, which capture most US people aged ≥65 years with Medicare Fee for Service coverage. We categorized the number of hospital claims for LDCT scans into quartiles and cross-tabulated with hospital characteristics to evaluate their associations.

Results: A total of 2,636 hospitals had 446,643 claims for LDCT scan for lung cancer screening from February 5, 2015 to June 30, 2019. Hospitals that provided LDCT screening are mostly urban (78%), acute care (78%), and 49% are voluntary non-profit private hospitals. The number of LDCT scan claims per hospital ranged from 1 to 2,937, with a median value of 77 (25th-75th percentiles: 19-218). Hospitals that had larger numbers of LDCT scan claims tended to be urban, voluntary non-profit, acute care hospitals in the Northeast region with larger numbers of hospital beds, hospital discharges, and total patient days, and higher operating profit and net income. Integrated delivery network health system status and overall hospital rating did not differ significantly by the number of LDCT scan claims.

Conclusions: LDCT lung cancer screening is mostly provided to US population aged ≥65 years with Medicare Fee for Service coverage by large, urban, voluntary non-profit, acute care hospitals with higher operating profit and net income in the Northeast region.

5123 | Comparing methods for estimating annualized costs using administrative claims

Amanda Kelly, Kammy Kuang, Liza Gibbs, Kaiyi Luo and Natalia Petruski-Ivleva
Aetion Inc, Boston, MA

Background: Studies of health care cost often rely on administrative claims data. While a variety of methods have been used in the literature, the limitations that arise from varied assumptions are rarely discussed.

Objectives: To compare 3 methods that evaluate annualized cost across 2 chronic disease populations: women with endometriosis, which has low mortality, and patients with type 2 diabetes (T2D) and chronic kidney disease (CKD), which affects mostly older patients with high morbidity and mortality at advanced stages.

Methods: IBM Marketscan claims with lab data (Jan 2015 - Mar 2018) were used to identify endometriosis patients (women aged 18-49 with at least 1 inpatient [IP] or 2 outpatient [OP] endometriosis claims) and T2D & CKD patients (2 lab results for impaired kidney function within 90-365d). Patients were followed until disenrollment, end of data, or a maximum follow-up (FU) of 365d. Annual cost estimates were reported for total, medical, IP, OP, and pharmacy costs. Three methods were used to report mean±SD costs: Method A ([A]) captured annual cost among those with ≥365d of continuous FU. Method B ([B]) captured mean population costs by dividing the sum of costs by the sum of FU days for all patients, then multiplying by 365d (medians not estimable). Method C ([C]) captured patient-level mean costs by dividing each patient's cost by their number of FU days, then multiplying by 365d.

Results: Among the 72,840 endometriosis and 14,117 T2D & CKD patients identified, ~64% in each cohort had ≥365d of FU. [C] produced the highest estimates for nearly all costs with large variability, most notably within endometriosis (T2D & CKD total cost: $31,743±65,414; endometriosis total cost: $32,379±171,563). [A] produced the lowest estimates and [B] produced slightly higher estimates for all costs except pharmacy costs, which were similar

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

across all methods. For endometriosis, [A] reported a total cost of $20,950±31,352; [B] reported $22,868. For T2D & CKD, [A] reported a total cost of $27,816±50,567; [B] reported $29,952. For both cohorts, medians were similar across methods. [A] cost estimates may be less generalizable due to selection bias, whereas [B] and [C] may be overestimates due to extrapolation of uneven costs throughout the year. Due to skewed distributions, methods assessing variability ([A] or [C]) may be preferred.

Conclusions: Methods used to annualize costs within claims create varying estimates, and the differences are inconsistent across diseases. When reporting annualized costs, transparency of methodology and sensitivity analyses of multiple approaches should be considered to understand the range of health care costs.

5125 | Characteristics of severe sepsis hospitalizations and sepsis-related mortality in US claims

Tiffany S. Woodworth, Erik Gunnarsson, Kerrin Gallagher, Lu Zhang and Joseph Menzin
Boston Health Economics, Boston, MA

Background: Studies have reported significant under-coding of explicit diagnostic codes for severe sepsis in administrative data. Despite low sensitivity, these codes were associated with high positive predictive value, which may indicate that these codes may be reserved for the most severe cases of sepsis with highest mortality rates.

Objectives: To characterize hospitalizations and mortality rates using multiple claims-based sepsis algorithms.

Methods: Using a 5% sample of Medicare Fee-for-Service claims data, we examined mortality among hospitalizations with ICD-9 and ICD-10 codes for sepsis events. We used 3 algorithms to define sepsis among 750,204 hospitalizations from patients ≥65 years with no evidence of commercial coverage between January 2014 to March 2016. The narrowest definition used explicit ICD-9/10-CM codes for severe sepsis or septic shock (785.52, 995.92, R65.20, R65.21). Two well-referenced broader definitions of severe sepsis using codes for infection and organ dysfunction were also examined (Martin et al, 2003, Angus et al 2001). We defined mortality as hospital discharge status of *dead* or presence of *death date*. Sepsis-related deaths were defined as deaths during hospitalization plus 30 days post discharge. Lastly, we examined associated demographic and clinical characteristics, including number of organ dysfunctions.

Results: Demographic characteristics were similar among all 3 severe sepsis definitions (median age ranged from 78-79 years and percent women ranged from 50.6-54.0%). Per 100 hospitalizations, mortality was highest among Explicit sepsis hospitalizations (41.7%), followed by Martin (30.3%) and Angus (22.1%). Mortality rates per 1000 days were consistent with this trend (Explicit (13.4 [13.2, 13.7]), Martin (7.5 [7.4, 7.6]), Angus (6.8 [6.7, 6.9]). Patients with explicit sepsis codes during hospitalization had a higher mean number of organ dysfunctions (3.5 [1.5]) vs Martin (3.1[1.5]) and Angus (2.8 [1.4]). Higher mortality rates were associated with number of organ dysfunctions (1: 8.5 [7.9, 9.2]; 2: 12.7 [12.2, 13.3]; 3: 14.5 [14.1, 15.5]; ≥4: 14.1 [13.8, 14.4] among explicit-defined sepsis). The same trends were observed using broader sepsis definitions.

Conclusions: Early findings indicate that presence of an explicit severe sepsis code is associated with the most severe sepsis. Hospitalizations with these codes were associated with the largest number of organ dysfunctions and highest mortality rates. Future work should focus on identification of sepsis events among less-severely ill populations.

Informatics

59 | The availability of laboratory data in real-world data and association of temporal and patient factors

Paul Dillon[1], Phil Arnold[1], Nayan Chaudhary[2], Evelyn M Flahavan[3], Anne-Marie Meyer[1] and Jessica Davies[3]
[1]*F. Hoffman-La Roche AG, Basel, Switzerland*[2]*Genentech, Inc., San Francisco, CA;*[3]*Roche Products Ltd, Welwyn Garden City, United Kingdom*

Background: In clinical trials labs are ordered following a protocol, whereas the availability of lab data in RWD may vary according to timing of treatment and patient characteristics. Using RWD lab results requires caution when selecting cohorts or for use in statistical modelling to address biases.

Objectives: To evaluate the availability of lab data and the association of temporal and patient factors within 3 electronic health record RWD cohorts.

Methods: A retrospective study of patients diagnosed with diffuse large B-cell lymphoma (DLBCL), advanced non-small cell lung cancer (aNSCLC) or small-cell lung cancer (SCLC), on or after January 1, 2011, with at least 2 documented clinical encounters in the Flatiron Health EHR-derived database, aged ≥18 years, and who received a standard of care 1st line treatment regimen between January 1, 2011 and January 31, 2018. Index date was the start date for the 1st line regimen of interest. Patients were excluded if they had other malignancies before the index date or a gap in visits of >90 days between diagnosis and index date. The availability of lab data for 33 lab tests (blood counts, hepatic enzymes, inflammatory markers, renal function, and electrolytes) was evaluated 1) before treatment initiation from diagnosis date to index date and 2) during treatment between index date to end of treatment date. For each period, the proportion of patients within each cohort with at least 1 lab result available for any of the labs was determined. Differences in patient factors (gender, age, race, US geographical region, insurance type, ECOG score, disease staging, diagnosis year, and follow-up time) according to lab data availability were quantified by the standardized mean difference (SMD).

Results: In total there were 5182, 12,351 and 3736 eligible DLBCL, aNSCLC and SCLC patients, respectively. For each cohort, patients were more likely to have at least one lab result available during the treatment period (93-98%) than before treatment initiation (63-83%).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Across the three cohorts and two periods of interest, no patient factor was consistently observed to have an SMD<0.1 according to lab availability. Higher variation in lab availability existed in patient characteristics during the treatment period, reflected in higher SMDs. In particular aNSCLC and SCLC patients with shorter follow-up time were less likely to have lab data available during the treatment period.

Conclusions: Lab availability varied according to timing of treatment and patient factors in 3 RWD cohorts. Evaluating variation in lab availability in RWD is important to consider regarding risk of biases such as selection bias.

107 | A standardized and reusable method to link multiple distributed health plan databases to the national death index

Candace Fuller[1], Wei Hua[2], Robert Ball[2], Ryan Carnahan[3], Michael Dizinno[1], Sarah Dutcher[2], Charles E. Leonard[4], Andrew Mosholder[2], Andrew B. Petrone[1], Robert Rosofsky[5], Laura Shockro[1], Jessica Young[1], Margaret Adgent[6], Ingrid Binswanger[7], Denise M. Boudreau[8], Marie Griffin[6], Jennifer Kuntz[9], Cheryl McMahill-Walraven[10], Pamala A Pawloski[11] and Sengwee Toh[1]

[1]Harvard Pilgrim Health Care Institute/ Harvard Medical School, Boston, MA; [2]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD; [3]College of Public Health, University of Iowa, Iowa City, IA; [4]Center for Pharmacoepidemiology Research and Training, Department of Biostatistics, Epidemiology, & Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [5]Health Information Systems Consulting, Milton, MA; [6]Vanderbilt University Medical Center, Nashville, TN; [7]Institute for Health Research Kaiser Permanente Colorado, Aurora, CO; [8]Kaiser Permanente Washington Health Research Institute, Seattle, WA; [9]Kaiser Permanente Northwest, Portland, OR; [10]Aetna, Blue Bell, PA; [11]HealthPartners Institute, Bloomington, MN

Background: In the US, health plan (HP) databases typically capture medically attended deaths during enrollment but many do not capture out-of-hospital deaths. Linkage to the National Death Index (NDI) can augment HP based studies with death and cause of death information, but linkage for multi-site studies can be resource intensive.

Objectives: To develop and test a reusable distributed NDI linkage approach within a use case comprising of antiarrhythmic (AR) medication users and non-users.

Methods: As a test case, we identified a cohort of AR users, known to be at increased risk of death, in 6 HPs in years 2000-2017 and followed them through dispensing data. For reference, we matched AR users 1:1 on age, sex, and time with non-users. We submitted patients with HP-recorded death or potential death to the NDI for linkage. We defined potential death as HP disenrollment between cohort entry and cohort exit plus 365 days, without reenrollment or medical utilization >60 days post-disenrollment.

At 5 HPs that ascertain death with state death records and other sources we examined concordance, sensitivity (Sn), and positive predictive value (PPV) of death identified through NDI linkage compared to HP-recorded death (reference).

We developed and tested reusable distributed NDI linkage programs which avoid sharing identifiable patient information between HPs or the coordinating center. Programs identify cohorts, select potential deaths for NDI submission, quality check NDI records flagged for submission, and select the single best match from returned NDI data.

Results: We identified 60,785 AR users and 60,785 matched non-users at 6 HPs. HPs submitted 33,703 patients (AR=57%, non-users=43%) to the NDI. The NDI returned at least one potential match for 22,542 (67%) patients. Our program for selecting the best NDI match classified 13,498 (40%) patients as dead (AR=51%, non-users=26%). In analyses utilizing HP-recorded death for reference (n=5 HPs), we observed excellent concordance between HP-recorded deaths and NDI identified death (96% agreement; Cohen's Kappa=0.919). The NDI captured 7,402 of 7,671 HP-recorded deaths (Sn=97%, PPV=97%). The NDI identified 238 deaths not identified in HP data; review of discordant records is ongoing.

Conclusions: The developed approach standardized the NDI linkage across HPs. We observed high concordance between the best match chosen by the NDI linkage program and HP-recorded death. Future work will further test and refine the reusable distributed NDI linkage approach, with the goal of providing NDI linkage methods to future studies based in distributed data networks.

2315 | Use of machine learning versus traditional regression to predict multiple sclerosis-related inpatient visits among newly diagnosed patients

Nicole M. Zimmerman, Brenna Brady and Debra E. Irwin

IBM Watson Health, Cambridge, MA

Background: Prior research demonstrated that multiple sclerosis (MS) patients incur significantly more inpatient admissions than matched controls. Machine learning (ML) methodologies are increasingly used to provide insights in a wide variety of life sciences applications and may better identify MS patients at high risk of inpatient admissions.

Objectives: To compare the value of machine learning methodologies to traditional regression models when predicting risk of inpatient (IP) visits among newly diagnosed MS patients.

Methods: Adult patients with 1+ inpatient MS diagnosis, 2+ outpatient MS diagnoses, or 1+ outpatient MS diagnosis with 1+ disease-modifying drugs between 1/1/2012-9/30/2018, with continuous enrollment of ≥1 year before and after their first MS diagnosis (index date) were selected from the IBM® MarketScan® Research Databases. Demographics were assessed on the index date, clinical characteristics were measured over 12 months prior to index, and the presence of MS-related IP visits were assessed over 12 months after index. Logistic regression, ridge regression, random forest, and neural net models were trained using a 75% random selection of patients. Model

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

performance was evaluated on the remaining 25% of patients using area under the receiver operator curve (ROC-AUC) and Brier scores.

Results: 18,381 MS patients were identified, 412 of which had an inpatient visit within the 12-month follow-up period. The neural network model performed best (ROC-AUC =0.692, Brier score=0.0217), followed by the ridge regression (ROC-AUC =0.691, Brier score = 0.0218), random forest (ROC-AUC =0.687, Brier score=0.0216), and logistic regression (ROC-AUC =0.675, Brier score=0.0218). All models identified age, pre-index healthcare expenditures, all-cause ER visits, and number of outpatient visits as important predictors of MS-related IP visits.

Conclusions: ML methods modestly outperform traditional logistic regression at predicting the probability of MS-related IP visits within 1 year of MS diagnosis. The performance improvements should be weighed against the additional analytic complexity and reduced interpretability of the ML models.

2323 | A comparison study based on multi-view latent Dirichlet allocation

Lin Zhuo[1,2], Yu Yang[3], Ruogu Meng[3], Lin Zeng[1], Hongling Chu[1], Liyuan Tao[1], Nan Li[1], Yanyan Shi[1], Hua Zhang[1], Xiaoxiao Wang[1], Weiwei Wang[4], Xiaoli Liu[1] and Siyan Zhan[2]

[1]Peking University Third Hospital, Beijing, China; [2]School of Public Health, Peking University, Beijing, China; [3]Peking University, Beijing, China; [4]Beijing Anding Hospital, Capital Medical University, Beijing, China

Background: There are several methods for multinomial distribution similarity calculation, which work in different scenarios, and the jury is still out on which is the best.

Objectives: To compare the inappropriate prescription detecting performance of topic mapping with three traditional multinomial distribution similarity calculation methods based on multi-view Latent Dirichlet Allocation.

Methods: A multi-view extension of the latent Dirichlet allocation topic modeling algorithm was chosen to generate the diagnosis-medication topic models indicating the underlying health status of patients using diagnosis and medication as variables, with data from the Chinese Monitoring Network for Rational Use of Drugs (CMNRUD) database. Each topic consisted of a set of diagnoses, medications that were highly related to each topic, and the percentages for each of these. On the basis of the topics, topic mapping(TM), a newly proposed multinomial distribution similarity calculation method was used to calculate the similarities of distribution of the diagnoses and medications on the topics built in the previous step and find the inappropriate medication use prescriptions by setting a threshold. The same process was undertaken for Kullback-Leibler(KL), Cosine Similarity(COS), and Vector's Dot Product(DOT) methods to find the anomaly detection thresholds in the scene of multi-view topic models. The prescription manual review result by experts in the Beijing Regional Prescription Review (BRPR) database was used as the gold standard to assess the validity of the model.

Results: A total of 44 million prescriptions were used to generate topics using the diagnoses and medications from the CMNRUD database. A 15,000 random samples of the BRPR database were used for validation. Compared with the other three methods, the DOT had the highest specificity of 63.05% and a positive predictive value of 15.05%. However, TM had the highest sensitivity of 81.84% and a negative predictive value of 96.00% and was superior in terms of area under the curve statistically significantly.

Conclusions: Overall, topic mapping methods can find more inappropriate medication use prescriptions and perform well in terms of model validity assessments. The multi-view inappropriate medication use prescription detection model based on it can be used as a primary screening tool and will likely complement and improve the manual review.

2377 | Feasibility of integrating a web-based tool to monitor adherence to respiratory medications using pharmacy claims data in primary care

Alia Yousif[1,2], Catherine Lemière[3,2], Amélie Forget[1,2], Marie-France Beauchesne[1,4,2] and Lucie Blais[1,5]

[1]Université de Montréal, Montreal, QC, Canada; [2]Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'île-de-Montréal, Montreal, QC, Canada; [3]Université de Montréal, Montreal, QC, Canada; [4]Centre Intégré Universitaire de Santé et de Services Sociaux de l'Estrie-CHUS, Sherbrooke, QC, Canada; [5]Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'île-de-Montréal, Montreal, QC, Canada

Background: Medication nonadherence in patients with asthma or chronic obstructive pulmonary disease (COPD) is associated with poor treatment outcomes. As a large majority of these patients are treated in primary care, family physicians need to assess adherence accurately to propose effective interventions, which is a challenging task. As a potential solution, we previously developed e-MEDRESP, a novel web-based tool that allows physicians to monitor adherence to respiratory medications using pharmacy claims data.

Objectives: 1) To test the feasibility of implementing e-MEDRESP in family physicians' electronic medical records (EMR); 2) To evaluate its use in clinical practice; 3) To assess patients' and physicians' satisfaction with the tool.

Methods: A 12-month feasibility study was initiated in July 2019 in 13 family medicine clinics in Quebec (Canada). e-MEDRESP is available for 16 family physicians and 296 of their patients with asthma or COPD were recruited. Eligible patients had a physician-diagnosed asthma or COPD and must have been prescribed a respiratory controller medication in the prior year. Counters were embedded in the tool to track physician use of e-MEDRESP. Patient and physician satisfaction with the tool were collected, respectively, via phone interviews and online questionnaires. Data were analyzed using descriptive statistics.

Results: To date, 137 patients had at least one medical visit (all-cause) with one of the participating physicians. e-MEDRESP was consulted

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

by 12 physicians for 66 (48%) of these patients. Fifty-seven patients underwent a phone interview; 91% reported discussing their medication use with their physician; 32% confirmed seeing their e-MEDRESP report on the physician's computer and indicated that it was easy to interpret. Using a Likert scale (5=Completely agree; 1=Completely disagree), physicians reported that the tool helped to better evaluate their patients' medication use, with a mean rating of 4.8 ± 0.7. They also felt that the tool facilitated communication on medication adherence and helped them adjust the prescribed therapy, with mean ratings of 4.8 ± 0.5 and 4.3 ± 0.9, respectively. All physicians reported that they intend to continue to use e-MEDRESP and appreciated its seamless integration in the EMR.

Conclusions: Preliminary data suggest that the integration of e-MEDRESP within physician workflow is feasible. Complete results are expected in July 2020. The capacity of e-MEDRESP to enhance adherence and the proportion of patients whose prescription changed following a physician consultation of the tool will be assessed.

2462 | concordance of race information derived from electronic health records and imputed using health plan administrative data

Nancy D. Lin, Laura Yochum and John D. Seeger
Optum Epidemiology, Boston, MA

Background: Real world evidence on potential heterogeneity in the safety or effectiveness profiles of selected medications by race/ethnicity is needed, however directly collected race information is typically unavailable in claims data.

Objectives: To assess completeness and agreement of race coming from health insurer claims data (imputed) compared with race from electronic health records (EHR).

Methods: We identified 3 cohorts in a US health insurer population linked to EHR data: members born between 10/2015-8/2017 (children); female members with a live birth delivery between 10/2015 - 8/2017 (mothers), and members with a heart failure diagnosis between 10/2015 - 8/2019 (HF patients). For each cohort, we calculated measures of concordance, sensitivity, specificity, and positive predictive value (PPV) comparing race/ethnicity from claims data to race/ethnicity available in EHR.

Results: Of 19,600 children, 17,763 mothers, and 33,640 HF patients with linked data, race/ethnicity was classified as "other, multiple, unknown or missing" based on EHR for 16%, 12%, and 28% respectively. When restricted to members with a single recorded race in EHR, all cohorts were predominantly White (children: 84%; mothers: 77%; HF patients: 80%), with 5%, 8%, and 14% classified as African American among children, mothers, and HF patients respectively. The PPV for imputed White race was 94-95% across the 3 populations while PPVs for imputed African American race were lower and more variable (children: 40%; mothers: 66%; HF patients: 74%), likely influenced by differences in the racial composition of the cohorts. Imputed African American race had low to moderate sensitivity (children: 42%; mothers: 47%; HF patients: 70%) but was highly specific (96% - 98%).

Conclusions: Completeness of race information in the EHR, and level of agreement between imputed race vs EHR-derived race, can vary depending on the population studied. Researchers are advised to consider the potential impact that the anticipated racial composition of the study population and specific data environment may exert on the performance of a selected imputation approach.

2489 | Benefits and limitations of using individual and linked English routine data sources to identify incident cancers in cancer epidemiology studies

Helen Strongman
London School of Hygiene & Tropical Medicine, London, United Kingdom

Background: Pharmacoepidemiologists commonly use individual and linked English primary care, hospitalisation, cancer registration and death registration data in cancer studies. We do not know how this choice of data source(s) affects selection of incident cancer populations and measurement of cancer exposures and outcomes for a wide range of cancers.

Objectives: To describe the benefits and limitations of using different individual and combinations of English electronic health data to identify incident cancers.

Methods: We used linked Clinical Practice Research Datalink (CPRD) GOLD primary care, cancer registration, hospitalisation, and death registration data for our descriptive study. We implemented alternative case definitions to identify first site-specific cancers at the 20 most common cancer sites, based on the first ever cancer diagnosis recorded in each individual or combination of data sources between 2000 and 2014. We calculated positive predictive values and sensitivities for each case definition, compared to a gold standard algorithm that used information from all linked datasets to identify first cancers. We described completeness of grade and stage information in the cancer registration dataset.

Results: 168,634 gold standard cancers were identified. Positive predictive values of all case definitions were &ge94% for the four most common cancers (breast, lung, colorectal, prostate) and &ge80% across cancer sites (oral cavity, oesophageal, stomach, liver, pancreas, malignant melanoma, cervix, uterus, ovaries, kidney, bladder, brain, thyroid, Non-Hodgkin lymphoma, multiple myeloma, leukaemia). Sensitivity for case definitions that used cancer registration alone or in combination was &ge92% for the four most common cancers and &ge80% across all cancer sites except bladder cancer, for which sensitivity was 65% using cancer registration alone. For case definitions using linked primary care, hospitalisation and death registration data, sensitivity was &ge89% for the four most common cancers, and &ge80% for all cancer sites except kidney (69%), oral cavity (76%) and ovarian cancer (78%). Sensitivities were generally lower when primary care or hospitalisation data were used alone. Completeness of staging data in cancer registration data was high for most cancers from 2012.

Conclusions: Ascertainment of incident cancers was good when using cancer registration data alone or in combination with other datasets,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and when using a combination of primary care, hospitalisation and death registration data, with variation between cancer sites.

2602 | Availability of secondary healthcare data sources in Colombia: A systematic review

Juan S. Franco[1] and David Vizcaya[2]
[1]Bayer S.A., Bogota, Colombia[2]Bayer Hispania, Barcelona, Spain

Background: Real-world evidence (RWE) is emerging as a fundamental component of the post-marketing evaluation of medicinal products. Even though the focus on RWE studies has increased in Colombia, the availability of secondary data sources to perform this type of research is not well documented.
Objectives: We aimed at identifying and characterizing secondary data sources available in Colombia, which could be used for pharmacoepidemiology studies.
Methods: We performed a systematic literature review on PubMed, EMBASE and VHL using a combination of controlled vocabulary and keywords for the concepts of electronic health records, epidemiologic studies and Colombia.
Results: A total of 323 publications were included in this review. These comprised 123 identified secondary data sources including pharmacy dispensing databases, government datasets from vital statistics and healthcare provision data collected by the Ministry of Health, disease registries, claims databases with insurance data, and electronic heath records, among others. These data sources were particularly used for cross-sectional studies focused on portraying disease epidemiology in a particular population. Almost all of the databases (95%) contained patient demographic information, while pharmacological treatment and specific diagnostic tests were present in 44% and 39% of the databases, respectively. Even though the database owner was identifiable in 94%, access information and requirements was only available in 44% of the articles. Only the pharmacy-dispensing database, local cancer registry and the government databases included a description of quality control measures or of the overall quality of the information available.
Conclusions: The diversity of databases identified shows that Colombia has a high potential to continue enhancing its RWE strategy. Greater efforts are required to improve data quality and accessibility. The linkage between databases will expand data pooling and integration to boost the translational potential of RWE.

2608 | Machine learning and semantic information for unstructured healthcare data: Comparison of methods through the automatic analysis of adverse drug reaction reports

Louis Letinier[1], Julien Jouganous[2], Ghada Miremont[1], Alicia Bel-Létoile[2], Francesco Salvo[1], Franck Rouby[3], Joëlle Micallef[3], Mehdi Benkebil[4] and Antoine Pariente[1]
[1]Centre Régional de Pharmacovigilance, Service de Pharmacologie Médicale, CHU de Bordeaux, Inserm, Bordeaux Population Health Research Center, Team Pharmacoepidemiology, UMR 1219, Bordeaux, France; [2]Synapse Medicine, Bordeaux, France; [3]CRPV Marseille Provence Corse, Service Hospitalo-Universitaire de Pharmacologie Clinique et Pharmacovigilance, Assistance Publique Hopitaux de Marseille, Marseille, France; [4]Surveillance Division, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), Saint Denis, France

Background: Artificial intelligence (AI) could support the work of pharmacovigilance centers in performing routine tasks, as coding adverse drug reaction (ADR) reports with little medical information.
Objectives: The aim of this study was to validate AI pipeline to encode patient reports from the French reporting web portal.
Methods: ADRs reported by patients to Bordeaux Pharmacovigilance Center (BPVC) between March 2017 - March 2019 were used (n=2058). For each report, the PDF form containing the free text from patient, and the corresponding adverse events encoded (in MedDRA preferred terms) by BPVC were obtained. The coded ADRs were used as gold standard to evaluate performance of each AI pipeline, which contained input data processing and a machine-learning (ML) model to learn ADRs encoding. The ML models tested were: logistic regression, support vector machine, random forests, gradient boosting, FastText and deep-learning models (a convolutional neural network and a recurrent neural network). In addition, hybrid models combining ML and a semantic approach were evaluated. Each pipeline was evaluated according to ROC curve/AUC and F-measure. A thousand bootstrap train-test samples (training on 90% of the cases, testing on the remaining 10%) were used to compute 95% confidence intervals (95% CI) for the evaluation metrics of each pipeline. The best pipeline during internal validation was used for an external validation, performed using a random sample of 187 ADRs reported by patients to Marseille PVC (MPVC) during the same period.
Results: Regarding AUC and F-measure, best pipeline was gradient boosting, with an AUC of 0.93 [0.92-0.94] and F-measure (0.72 [0.68 - 0.75]. Gradient boosting showed an AUC of 0.91 and a F-measure of 0.58 when applied to MPVC reports. The hybrid model, gradient boosting with semantic approach, showed a slightly better AUC (0.94 [0.93 - 0.95]). Among other methods, logit (AUC 0.91 [0.89-0.92]; F-measure 0.58 [0.55-0.62]) and recurrent neural network (AUC 0.86 [0.88-0.89]; F-measure 0.35 [0.43 - 0.47]) demonstrate higher performances.
Conclusions: This study showed a promising performance to develop a coding support system applied to patient reports. External validation indicated that our system is less efficient with data from other origin. This study was a pilot study, a second study using data from the 31 French pharmacovigilance centers would improve performance of models and will start in 2020.

2636 | Will data privacy and confidentiality squeeze out research?

Alison Bourke[1], David Miller[2], Amanda Culley[1], Georgina Bourke[3]
[1]IQVIA, London, United Kingdom; [2]UCB, Raleigh, NC; [3]Projects by If, London, United Kingdom

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: As evidence to inform clinical care and regulatory decision making is increasingly based on health data from individual patients and citizens/people, there is a growing tension between the need for privacy/confidentiality and the ability to facilitate research into the effective and safe use of medicines.

Objectives: • To explore the benefits and privacy/confidentiality risks of utilising individual level health data, from the viewpoint of several stakeholders including Pharma, Regulators, Payers, Academics, Individuals & Society.

• To discuss the confidentiality barriers, eg technical, ethical and legal, to sharing individual level RWD for research and to inform both clinical and regulatory decision making, and explore if there are ways to balance the risks and benefits.

This symposium will be valuable for researchers, data providers, regulators, digital health system developers (including apps), payers, clinicians, and patients, to inform and help plan future research and operations with regard to utilising individual level RWD while maintaining privacy/confidentiality.

Description: The symposium will set out why regard for privacy/confidentiality is important, and how it can impact on the use and availability of data for pharmaceutical and medical research for regulatory and clinical decision making. A privacy design expert will join industry and service provider speakers to debate how to anticipate and prepare for the privacy/confidentiality issues of person level data. The differences in legal environment across geographies will also be discussed. Following the talks, the Chair will facilitate an interactive discussion between the audience, and the speakers to answer queries and explore further discussion on finding the right balance between sharing data and safe use. Alison Bourke will introduce the topic and the speakers. David Miller will further talk about issues within the use of data in the development of pharmaceuticals and the impact of the need for confidentiality/privacy. Amanda Culley and Alison Bourke will provide brief examples of systems which allow both cancer and genomics data to be utilised for research while still ensuring anonymity. Finally, Georgina Bourke will explain the latest thinking in designing systems to enable data sharing while ensuring people are fully "informed".

2643 | Comparing the performance of logistic regression versus machine learning tree based classification methods in predicting rare outcomes using real-world observational data

Stella Min, Ellen Thiel, Kristin Evans and Debra E. Irwin
IBM Watson Health, Cambridge, MA

Background: Rare outcomes are commonly observed in real-world data but often misclassified by machine learning algorithms.

Objectives: This study used random undersampling (RUS) techniques and compared the performance of logistic regression versus machine learning classification methods in predicting the rare outcome of bowel impaction (BI) among chronic constipation (CC) patients.

Methods: Adult patients selected from the IBM® MarketScan® Research Databases had at least 2 CC diagnoses during 1/1/2012-9/30/2018 (first diagnosis=index). Patients were continuously enrolled for ≥1 year before (baseline) and after index (follow-up), and had no evidence of CC due to IBS, pregnancy, or chronic opioid use. Patients who were treated with lubiprostone or linaclotide were identified and evidence of BI during follow-up in both treated and untreated groups was the primary outcome. We compared logistic regression and three tree-based machine learning techniques: Random Forests (RF), Gradient Boosted Trees (GBT), and Ensemble Gradient Boosted Trees (EGBT). RUS was applied to patients in the majority class (non-treated CC), to mitigate the effects of severe class imbalance. Class ratios in five training datasets ranged from balanced (1:1) to highly imbalanced (1:9). Each model was run 10 times with 30 variables to predict risk of BI. Demographics were assessed on the index date and clinical characteristics were assessed during baseline.

Results: 10,093 treated and 100,930 untreated CC patients were included. Across all comparisons, EGBT models exhibited the best performance, particularly with a 1:9 sampling ratio (AUC=0.820), followed by GBT (AUC=0.802), RF (AUC=0.799), and logistic regression (AUC=0.724). Top predictive characteristics include age (>60), female sex, comorbidity index, treatment, and chronic obstructive pulmonary disease.

Conclusions: Machine learning combined with RUS techniques can be an effective approach for predicting rare outcomes. The applied sampling ratio used for training datasets is consequential for outcome predictions and the overall performance of the model.

3730 | "That Tablet Made Me Sick as a Dog (MedDRA PT: Nausea)"

William G. Dixon[1], Nabarun Dasgupta[2], Andrew Bate[3], Niklas Noren[4], Florence van Hunsel[5]
[1]*The University of Manchester, Manchester, United Kingdom;* [2]*UNC, Chapel Hill, NC;* [3]*GSK, London, United Kingdom;* [4]*Uppsala Monitoring Centre, Uppsala, Sweden;* [5]*Netherlands Pharmacovigilance Centre Lareb, Herkenbosch, Netherlands*

Background: Consumer technologies such as smartphones have the potential to transform large-scale population research - including pharmacoepidemiology (as evidenced by the new ISPE Digital Epidemiology SIG). Key ingredients of pharmacoepidemiology studies include medication use, its benefits and harms. Whilst symptom tracking apps are well-established allowing the measurement of treatment response, few tools exist that rapidly and easily allow patients to report coded, accurate information on drug side effects. Patient-centric apps can also open a hitherto blocked channel for feedback and iterative messaging.

Objectives: The aim of this workshop is to consider, together with the audience, the essential components for the design, development, testing and evaluation of a system to collect coded and structured data on adverse drug reactions direct from patients, focused on using

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

smartphones. Through the workshop, we will co-design a research protocol for the development and testing of the side effect reporting app. This will be educational for the audience by describing and following a framework for digital health study design including validation, plus learning about patient reporting of medication side effects.

Description: Short presentations will describe

- Current pharmacovigilance and pharmacoepidemiology data and gaps for patient involvement
- Short videos from patients describing what they feel are key road blocks to reporting side effects
- An initial outline plan for a study to design, develop, test and evaluate a smartphone app to collect patient-generated lay descriptions of side effects and convert to valid, coded data
- Considerations in the design of a smartphone app to collect patient-generated health data, including opportunities for optimising patient engagement
- Perspectives from different stakeholders for patient-generated health data about medication side effects to support pharmacovigilance and pharmacoepidemiology (timeliness; data quality; causality; volume of data)
- Overview of experience from existing pharmacovigilance mobile apps
- Experiences, opportunities and challenges in converting lay descriptions of experienced side effects into MedDRA etc., including ongoing research combining NLP with vector-based representations of drugs and adverse events

Following each presentation, we will update our study design to incorporate suggestions from the audience. We will close the workshop by summarising the refined study design and collecting interest in contributing to a pre-competitive consortium and study team that would support and deliver the study.

4088 | Validity of a state-based death certificate/health plan linkage to support mortality studies

Margaret Adgent[1], Candace Fuller[2], Tony Morrow[1], Christine Whitmore[1], Carlos Grijalva[1], Wei Hua[3], Sarah Dutcher[3], Sengwee Toh[4] and Marie Griffin[1]

[1]Vanderbilt University Medical Center, Nashville, TN; [2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [3]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD; [4]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: Mortality is an important outcome for post-market drug safety and other longitudinal studies. Health plans typically capture medically attended deaths, but not those occurring out of hospital or outside plan enrollment. Linkage of health plans to state death registries can support mortality studies by integrating data on death status, date and cause, but the validity of linkages is often not documented.

Objectives: To examine the validity of a probabilistic linkage between Tennessee (TN) Medicaid (TennCare) data and TN death certificates using National Death Index (NDI) linked TennCare records as reference.

Methods: Beginning with 2001 enrollment, records of TennCare patients undergo annual probabilistic linkage to TN death certificates. We submitted records for a sample of 4753 patients to NDI for national-level death certificate linkage. These patients either linked to a TN death certificate (n = 3505) or were presumed alive and had disenrolled from TennCare as of 12/31/2016 (n = 1248). NDI classified records as "presumed dead" (reflecting a high-quality match between record and death certificate), or "presumed alive" (a low-quality match or non-matching record). We examined the sensitivity (SEN), specificity (SPE), positive (PPV) and negative predictive values (NPV) of death status according to TN death certificate linked records using NDI-determined deaths status as reference. We compared date of death and underlying cause of death codes between TN and NDI-linked death certificates.

Results: NDI identified possible matches for 4714 of 4753 patients, 3591 (76%) of which were high-quality matches, i.e., deaths. All 3505 patients that linked to TN death certificates were also identified by NDI as deaths (PPV = 100%); 36 (1%) of these were TN resident deaths that occurred outside TN and 25 (<1%) were non-TN residents at time of death but died in TN. The TN linkage missed 86 deaths identified by NDI (SEN = 98%). Having both residence and state of death outside TN was a primary reason for discordance (65 of 86 deaths [76%]). The SPE and NPV of the TN death certificate linkage were 100% and 93%, respectively. Of deaths identified in both sources, death date and cause of death codes were identical for 3505 (100%) and 3502 (>99%), respectively.

Conclusions: Our probabilistic state-based record linkage performs well as compared to NDI, but does not capture all deaths, particularly those occurring among TennCare enrollees who moved and died outside of TN. Additional investigation is needed to understand other factors contributing to potentially missed linkages.

4114 | Identifying comorbidity-based subtypes of type 2 diabetes: An unsupervised machine learning approach

Zeynep Icten and Joseph Menzin

BHE, Boston, MA

Background: Type 2 Diabetes (T2D) is a heterogeneous disease with different phenotypes and prognostic profiles. Understanding T2D subtypes may help with screening for comorbidities and support a personalized disease management approach.

Objectives: This study assessed comorbidity-based T2D subtypes using k-means clustering applied to medical claims data.

Methods: Medicare 5% Part A/B claims from 2010-2015 were used to identify patients 65 years or older with at least 2 T2D diagnoses, continuous enrollment during the 12 months post index period and no evidence of T1D diagnosis. From this cohort of eligible patients, 15% was selected randomly for analyses. All available diagnosis codes were grouped using Clinical Classifications Software (CCS) excluding

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

comorbidities of pregnancy. The resulting 16 groupings were represented as binary vectors to be included in the clustering. Demographics and healthcare utilization (HCU) variables were used to evaluate the clusters. All variables included in clustering and its evaluation were extracted from the post index period. We used the k-means algorithm by Hartigan and Wong where k was the number yielding the minimum within-cluster sum of squares for values 2 to 7 with initial cluster centers randomly chosen for 10 trials.

Results: A cohort of 49,554 patients were included in analyses yielding three clusters. The first cluster (C1) comprised 34% (n=16,671) of the cohort and was characterized by the highest prevalence of comorbidities (Mean CCS groupings=12) followed by the second cluster (C2) (n=14,426, 29%, CCS groupings=10). The third and largest cluster (C3) had the lowest prevalence (n=18,457, 37%, CCS groupings=6). Mean age was similar across all clusters (C1=76; C2=74; C3=73) with the greatest proportion of females in C1 (C1=60%; C2=51%; C3=54%). C1 had the highest prevalence for all CCS groupings except for neoplasms (C1=43%; C2=78%; C3=11%), skin/subcutaneous tissue (C1=51%; C2=77%; C3=13%) and infectious disease (C1=81.1%; C2=81.4%; C3=55%). Mental illness was the only comorbidity where C3 patients did not have the lowest prevalence (C1=71%; C2=16%; C3=18%). C1 patients had the highest HCU (Total costs: C1=$31,194; C2=$7,708; C3=$3,516, inpatient (IP)/ER visit: C1=52%/42%; C2=13%/19%; C3=6%/11%). Regression models adjusting for age and gender using the clusters showed improved performance over using the Charlson Comorbidity Index when predicting an IP visit (C-Stat: 80% vs 76%) and total costs (Adjusted R-squared: 0.35 vs 0.24).

Conclusions: This study analyzed patterns of comorbidities and observed 3 clinically meaningful subtypes of T2D patients.

4326 | Business Intelligence data in Central Denmark region and quality assurance in psychiatry: Possibilities and challenges

Martin V. Borg[1,2], Nickolai Gaardsvig-Kjær[1,2], René B.K. Brund[2], Jacob D. Redder[3], Søren D. Østergaard[1,2] and Christiane Gasse[1,2]

[1]Aarhus University Hospital, Aarhus, Denmark; [2]Aarhus University, Aarhus, Denmark; [3]Business Intelligence Center, Central Denmark Region, Aarhus, Denmark

Background: The reality of big data in health care is undeniable. With the increasing spread of electronic health care records (EHRs), more and more studies investigate the potential of big data in quality assurance, research and clinical decision making.

Objectives: To demonstrate potential usage of Central Denmark Region's in-hospital big data model.

Methods: For all psychiatric inpatients in Central Denmark Region (CDR) between 2014 and 2018, we extracted data from Region's business intelligence portal, which automatically extracts data from the Region's EHRs. We collected time stamped data about patient characteristics, cytochrome P450 (CYP) interacting drug usage as well as pharmacogenetic testing (PGx) and therapeutic drug monitoring (TDM). We linked this data to determine the frequency of use of the above. Lastly, we investigated differences in TDM frequency for a patient group treated with clozapine or olanzapine when concomitantly treated with interacting drugs.

Results: From 2014-2018 78,682 patients had a psychiatric hospital contact in Central Denmark Region. Of these, 16,182 had at least one inpatient contact and 14,068 were treated with CYP drugs. There was an equal distribution of men and women, and the most frequent diagnoses were affective/mood disorders (ICD-10, F30-39). The most frequently administered CYP drugs were paracetamol, quetiapine and olanzapine. PGx was only performed in 1.3/1000 patients. Of patients with a schizophrenia, schizotypal and delusional disorder diagnoses (F20-29) 2128 received inpatient treatment with either clozapine, olanzapine or both. When treated with other drugs interacting with CYP1A2, relevant drug plasma-levels were measured 4.4 times more often in clozapine treated patients and 3.3 times more often in olanzapine treated patients compared with patients with no interacting treatment.

Conclusions: Business intelligence data can provide relatively easy access to large quantities of hospital patient data that is already collected as part of the clinical workflow. We demonstrated how this data can be used to answer relevant clinical questions about a given patient population and potentially reveal areas where improvements or increased awareness might be relevant.

4331 | Evaluation of a novel enriched study approach to complement electronic medical records (EMR)

Timo Smieszek[1], Dorothea von Bredow[2], Tina Kunz[2], Sabine Piesch[2], Benno Antoni[2], Gianluca Lucrezi[1], Iris Winkler[3], Timo Rockel[3] and Johanna Engelhard[3]

[1]IQVIA, Basel, Switzerland; [2]IQVIA Commercial GmbH & Co OHG, Munich, Germany; [3]IQVIA Commercial GmbH & Co OHG, Frankfurt, Germany

Background: Real world (RW) studies are often used to complement insights from clinical studies. Collection of RW data can be difficult due to limited time for study data entry at sites. Alternative approaches using EMR databases often lack data on relevant clinical parameters. Therefore, we developed an "enriched study approach" that allows combining existing EMR with data collected at study sites in a short electronic case report form (eCRF), to capture essential data with minimal burden on study sites.

Objectives: The study aimed to 1) investigate the technical feasibility of the enriched approach 2) quantify how much additional information can be collected in the enriched approach, compared to EMR data only 3) evaluate consistency of overlapping data from the two data sources.

Methods: This is a retrospective, non-interventional study with 818 heart failure patients treated between 2016 to 2018 in an outpatient setting (7 cardiologists, 6 general practitioners) in Germany. Anonymized patient-level EMR data were enriched with available clinical assessments collected in an eCRF: New York Heart Association

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

class [NYHA], N-Terminal pro-Brain Natriuretic Peptide [NTproBNP], Left Ventricular Ejection Fraction [LVEF], estimated Glomerular Filtration Rate [eGFR]). Descriptive statistics were applied. The protocol had ethics committee approval.

Results: EMR and eCRF data could be combined for 793 of 818 patients (97%) enrolled. For 108 patients, a total of 221 NTproBNP records was found in the EMR data, and 673 NTproBNP records for 350 patients in the eCRF. Combining data of both sources resulted in 362 patients with NTproBNP records, showing that the enriched approach increased the number of patients and records available for NTproBNP analysis more than threefold compared to EMR only. For 96 of these patients, overlapping NTproBNP records were available in the two data sources. Comparison of NTproBNP values on patient level for the same day showed identical values, suggesting consistency and high quality of data. The enriched approach also allowed an increase of available records for the other parameters of interest compared to EMR only.

Conclusions: The enriched study approach allows fast and efficient collection of data and mitigates some of the limitations of EMR data. Quantitative assessment of data collected demonstrated a more than threefold increase of records compared to EMR only. Comparison of overlapping data points confirmed consistent results. In summary, we conclude that the enriched approach is technically feasible and allows collection of patient level data which are not sufficiently available in EMR.

4353 | Application of gradient-boosted trees to model the association between anatomical metrics and functional outcomes

Sudhir Venkatesan[1], Emily Wilkes[1], Natasha Pillai[2], Moshe Havilio[3] and Ray Griner[4]

[1]IQVIA, London, United Kingdom; [2]IQVIA, Basel, Switzerland; [3]Notal Vision Ltd, Tel Aviv, Israel; [4]IQVIA, Cambridge, MA

Background: Traditional methods employed in understanding associations and thresholds between continuous variables and dichotomous outcomes include linear modelling of a continuous variable, or categorisation based on the variables' frequency distribution (quantiles) or *a priori* clinical knowledge. In instances where the relationship between biological processes and anatomical metrics are poorly understood and defined it can be difficult to model such associations using traditional linear methods. Gradient-boosted trees (GBT) are a type of non-parametric, tree-based classification algorithms.

Objectives: To apply GBTs to evaluate the association between anatomical metrics (fluid volume and retinal thickness) and improvement in visual acuity (VA).

Methods: We used Medisoft data (UK-based ophthalmology EMR data) linked to optical coherence tomography (OCT) metrics derived by Notal Vision. The study population comprised patient eyes aged ≥50 years diagnosed with degenerative eye disease who had at least one anti-VEGF injection between 01/09/2010 and 04/10/2017, and a record of an OCT scan. The outcome of interest was change in VA of >5 letters (encoded as a binary variable) from baseline to month 12. The features included in the GBT models were: values of IRF volume, SRF volume, PED and CRT at month 12. We implemented a GBT model with 50 trees and evaluated model performance using the AUROC derived from 5-fold cross validation.

Results: 711 patient-eyes (from 670 unique patients) were included in the analysis, of which 467 patient eyes had OCT scans eligible for analysis at month 12. 216 (46.3%) patient-eyes gained VA by >5 letters from baseline to month 12. An examination of feature importance revealed that CRT and IRF volume were the top two features relating to improved visual acuity (AUROC = 63.1). An examination of the tree splits revealed that patients with CRT >199 μm and IRF volume < 0.01 mm^3 were associated with the strongest improvement in visual acuity.

Conclusions: GBTs can be applied to establish a relationship between continuous metrics of interest and binary outcomes. GBTs can help guide hypothesis generation where threshold values for anatomical metrics have not been established and can be used to inform further research to ascertain their validity. Using GBTs to model this association has a number of important advantages including that they are robust to overfitting, are able to model complex non-linear relationships between the feature set and the outcome, and they inherently account for interactions between independent variables (interactions do not need to be pre-specified).

4376 | Assessment of the global landscape of real world databases

Bayarmagnai Munkhjargal, Ayo Adeyemi, Geetanjoli Banerjee, Nicole Tsao, Angela Paradis and Charles Makin

Biogen, Cambridge, MA

Background: The FDA's recent framework emphasizes the importance of the reliability and relevance of real-world data sources. A better understanding of the landscape and capabilities of real-world data (RWD) sources would inform evidence generation strategies that meet stakeholder requirements.

Objectives: To identify, characterize and assess the use of non-disease specific (generic) RWDs and registries for Multiple Sclerosis (MS), Spinal Muscular Atrophy (SMA) and Progressive Supranuclear Palsy (PSP) in North America (NA), Europe (EU), Asia-Pacific (APAC) and Latin America (LATAM).

Methods: Longitudinal and patient/encounter-level RWD sources were identified through a pragmatic literature review and in-depth consultations with local real-world data experts. Data sources were characterized by type of data (claims, electronic medical records [EMR] etc.), granularity (encounter/patient-level), population size, geographic coverage, data span and availability of demographic, clinical, economic and patient/clinician-reported outcomes. Included were patient-level and longitudinal databases while less granular, aggregated data sources were excluded. Each eligible database's linkage capability, accessibility and capability to address health economics,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

treatment patterns, safety & effectiveness, natural history of disease and quality of life [QoL] studies were then assessed.

Results: Of 325 databases identified at initial review, 141 generic longitudinal and encounter-level databases, 35 MS, 27 SMA and 3 PSP registries across 91 countries were selected for in-depth review due to access to the required information. The distribution of generic databases was: 57 (40.4%) in NA, 36 (25.5%) in EU, 30 (21.3%) in APAC, and 18 (12.8%) in LATAM. Medical/prescription claims was the most common type of generic data source, 82 (61.2%) followed by EMR 37 (27.6%). Generic databases were commonly amenable to studies of treatment patterns, safety & effectiveness and health economics but less to natural history of disease and QoL studies. In comparison, registries were more amenable to studies of treatment patterns, safety & effectiveness, natural history of disease and QoL studies but less to health economics studies.

Conclusions: While the availability, accessibility and capability of RWDs vary significantly across regions, there is an abundance of rich data. Collaborations between diverse parties to facilitate the possibility of linkage is recommended to improve the relevance and capability of RWDs.

4415 | Performance assessment of machine learning and logistic regression in identifying risk factors for diabetic ketoacidosis in adults with type 1 diabetes using electronic health records data

Lin Li[1], Chuang-Chung Lee[2], Chuntao Wu[1], Fang Liz Zhou[1], Cliona Molony[2], Zoran Doder[1], Evgeny Zalmover[1], Kristen Sharma[1] and Juhaeri Juhaeri[1]

[1]*Sanofi, Bridgewater, NJ;* [2]*Sanofi, Cambridge, MA*

Background: Artificial intelligence including machine learning has been increasingly used to analyze healthcare data. However, the benefits of machine learning over conventional analysis approaches are mixed in real-world settings.

Objectives: To assess the performance of machine learning approaches and conventional regression in predicting diabetic ketoacidosis (DKA) in adults with type 1 diabetes (T1D) and identifying the risk factors of DKA by using an electronic health records (EHR) database.

Methods: A case-control study nested in patients with T1D was conducted using Optum® de-identified Electronic Health Record dataset from 2007 to 2018. The patients were randomly split into a training data set and a test data set in a ratio of 4:1. Machine learning approaches (XGBoost, distributed random forest [DRF] and deep learning) and conventional regression (logistic regression and least absolute shrinkage and selection operator [LASSO]) were utilized to identify important risk factors for DKA. Model performance (e.g., area under the receiver operating characteristic curve [AUC]) was assessed in the training and test data sets separately.

Results: A total of 41 risk factors were selected to build predictive models using the data of 3,400 DKA cases and 11,780 controls. Both machine learning and conventional regression approaches selected some known risk factors for DKA (e.g., HbA1c, hospitalization) as the top ten features out of 41 risk factors. The machine learning approaches included more laboratory results (e.g., hemoglobin, random glucose level) in the top ten features, while conventional regression approaches included more socioeconomic status factors (e.g., insurance type, geographic region). In the training data set, deep learning and XGBoost yielded higher AUCs (0.95 and 0.88) than conventional approaches (0.83 for logistic regression and LASSO) with the full set of 41 risk factors. However, in the test data set, the performance was similar among these 5 approaches with AUCs ranging from 0.80 for deep learning to 0.83 for XGBoost.

Conclusions: In our study to predict DKA using EHR data sources, the machine learning and conventional regression approaches demonstrated similar performance, and identified overlapping, but different, top ten risk factors. Further research is needed to better understand the reasons for differences in ranking of importance of DKA risk factors between these approaches and to identify the appropriate application of machine learning techniques in analysis of health records data.

4423 | Training the machine: Deployment of federated learning algorithms for machine learning models across electronic health record networks

Jon Ruffin[1], Yunlong Wang[1] and Christina Mack[2]

[1]*IQVIA, Plymouth Meeting, PA;* [2]*IQVIA, Durham, NC*

Background: Deep learning models require training on large, fit-for-purpose patient datasets to provide accurate predictions while avoiding bias or lack of scalability. Access to training data within high dimensional datasets can be a challenge, especially for single entities who only have access to their own patients; however, combining datasets across sources has privacy implications. Federated learning (FL) - a machine learning technique where a model is trained on data across a network of individual electronic health record (EHR) systems with no data sharing between institutions - can solve this problem. Prediction of disease progression for Alzheimer's patients is a setting where this novel method meets an unmet clinical need.

Objectives: Deploy a FL algorithm on a network of disparate EHR systems that can train a shared predictive model to be as accurate as if it had access to full network data.

Methods: EHRs consisting of 23,813 early and 6,339 Alzheimers patients from 20 hospitals (mean 1500 records/hospital; range 560-2452) in the RxDx database were converted into “edge nodes” within a decentralized, undirected federated learning framework by combining two non-convex optimizations. Each hospital node received the newest version of the model; improved it by training the model on its own patient data; and released an updated version of the model to the rest of the network. This allowed individual institutions to participate in collaborative training across a shared prediction model while keeping training data private. Progression to late-stage Alzheimer's was predicted over a 3 year period.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: The FL model was able to predict progression to late-stage Alzheimer's with an accuracy of 42%, a 23% improvement over predictive ability when trained on a single hospital's EMR. The FL algorithm converged to the optimum solution with 90% fewer communication rounds than traditional models and was able to track model updates across the full network.

Conclusions: The decentralized FL framework represents a new approach for combining disparate hospital EHR systems to enable disease progression prediction while retaining patient privacy and reducing potential bias. Advantages are three-fold: 1) data privacy is preserved; 2) computational burden is reduced; and 3) communication efficiency is increased. This has high practical utility for real-world studies, as this approach joins disparate institutions to create a rich patient dataset in a way that is technically optimized, allowing for efficient, accurate predictions.

4486 | Using machine learning to identify heterogeneous treatment effects: DPP-4i versus sulfonylurea on cardiovascular outcomes in US medicare

Tiansheng Wang[1], Alexander P. Keil[1], Virginia Pate[1], Michele Jonsson Funk[1], Michael R. Kosorok[2] and John B. Buse[3]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: The CAROLINA trial suggests the use of DPP-4 inhibitor (DPP4i) linagliptin compared with sulfonylurea (SU) glimepiride resulted in a noninferior risk of cardiovascular (CV) outcome in type 2 diabetes patients (HR 0.98, 0.84-1.14), while a previous observational study in Medicare showed DPP4i may decrease CV risk compared to SU (HR 0.75, 0.72-0.79).

Objectives: Apply generalized random forest (GRF) to Medicare data to assess potential heterogeneous treatment effects (HTEs) and explore the reason for this inconsistency.

Methods: We implemented an active comparator, new user (ACNU) cohort design identifying initiators of DPP4i and SU using 20% random sample of fee-for-service Medicare beneficiaries aged 65+ without prior diagnosis of myocardial infarction (MI), stroke, and heart failure (HF). CV outcome was a composite endpoint of death (proxy for CV death), MI, and stroke. Follow-up started at the 2nd prescription within 365 days ignoring treatment changes. We estimated propensity scores (PSs) to balance age, comorbidities, medications, and other potential confounders. PSs were used to estimate treatment effects via 1:1 greedy matching and standardized mortality ratio weighting. The PS matched ACNU cohort was randomly divided into halves: one half for training and the other half for testing. We trained a GRF in the training set, then divided the training set into quintiles by conditional average treatment effect estimate and assessed covariates distributions across all quintiles to identify split factors for subgroups. The HTE was assessed in the test set over subgroups by PS-weighted risk difference (aRD).

Results: In 77,300 PS matched patients initiating DPP4i or SU, crude 1-year CV risks were 5% (DPP4i) and 6% (SU). The aRD was -0.7% (-1.1% to -0.2%) in the test set. The GRF identified 4 subgroups defined by age, coronary artery disease (CAD), and hypertension (HTN) with distinct CV risk differences for DPP4i versus SU. In the test set, patients aged >75 without HTN had the most pronounced benefit from DPP4i, aRD= -5.2% (-7.8% to -2.7%, number needed to treat 19). The remaining 3 subgroups (age ≤75 without CAD, age≤75 with CAD, age>75 with HTN) still suggested DPP4i benefits, but of smaller magnitude (-0.2%, -1.5% and -0.3%, respectively).

Conclusions: Machine learning analysis of our large ACNU cohort suggests that age, CAD, HTN may help individualize prediction of the benefit from DPP4i versus SU. The HTE and differences in the study populations may explain the differing results between Medicare real-world evidence and the CAROLINA trial (only 20% aged 70+).

4545 | Real world data utilization in adverse drug reactions (ADRs) information in China

Yan Wang, Yuyao Huang and Shusen Liu

Sanofi Medical, Shanghai, China

Background: The significant underreporting of adverse drug reactions (ADRs) has always been a major issue in drug postmarketing safety evaluation. China has started to find solutions for active safety monitoring.

Objectives: Aim to describe the current status of real-world data utilization in ADRs reporting and identification in China.

Methods: Searched and reviewed relevant information and literature about ADR reporting in China from the Chinese National Knowledge Infrastructure Database (CNKI), WangFang databse, Chinese Science and Technology Periodical Database (VIP), Pubmed, Embase, Baidu post bar, Sina micro-blog, Webchat public accounts.

Results: The Chinese Food and Drug Administration (CFDA) in 2017 has established the intensive Safety Monitoring Program based on hospital information system. By 2019, this program has been implemented in more than 100 hospitals. The number of ADR reports has rapidly increased since then. Rather than reporting to monitoring system, people may tend to publish scientific literatures or to speak up in the open social media about AEs/ADRs. There was a report that AEs of a Chinese patent medicine were 10.49%, 1.54%, and 0 certain ADRs respectively reported in CFDA monitoring data, identified from papers, and from social media. Although Chinese ADR system contributes a lot to public health protection, there are still limitations led to search complementary data approaches for ADRs report. Currently the EMR has already included in-patients medical records; however out-patients medical records especially ADR data should be included. Difficulties in automatically extracting ADR information from unstructured data form will be challenging for EMR data utilization. Social media shares knowledge of ADRs and offer possibility of collecting

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patient-centric and near real-time ADR data. In order to improve the data availability, social-media-derived data should be validated by healthcare providers (HCPs) and then more reliable reports can be generated and submitted to CFDA. All types of literatures can be considered to be evidence for safety information. However, the framework and approaches to use data from EMRs, social media, and literatures for ADRs reporting have not been established In China.

Conclusions: Multiple data sources should be integrated for safety information collection. There is still a long way to go for China to establish a high-level active pharmacovigilance system to ensure drug safety. Chinese authorities, academia and industry are exploring some more efficient and reliable ways for active safety monitoring.

4597 | Building an active drug safety surveillance system in Taiwan: An adaptation of the U.S. Sentinel System

Chi-Chuan Wang[1], Fang-Ju Lin[2], Kelly Huang[1], Huang-Tz Ou[3] and Chien-Ning Hsu[4]

[1]National Taiwan University, Taipei, Taiwan; [2]National Taiwan University, Taipei, Taiwan; [3]National Cheng Kung University, Tainan, Taiwan; [4]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Background: Using real world data to support for regulatory decision has become a global movement. Sentinel Initiative is a well-known active surveillance system that allows the U.S. FDA to evaluate the effectiveness and safety of medical products. However, a quality active surveillance platform for drug safety has not been established in Taiwan.

Objectives: To build a U.S. Sentinel Initiative-compatible platform to support for drug safety surveillance in Taiwan.

Methods: Following the structure of Sentinel Initiative, we built the Taiwan Sentinel Common Data Model (TSCDM) from the Taiwan Health and Welfare Database with data from 2011 to 2017. Two data sources, the National Health Insurance Database (NHID) and the Cause of Death Data, were used to build this platform. The quality assurance of the TSCDM was performed with three million stratified sample by age and sex due to the limited hardware input/output efficacy at the Health and Welfare Data Center. Level one to level three checks from the Sentinel Data Quality Review and Characterization Programs were performed.

Results: Age and sex distribution are similar across the three million TSCDM sampled cohort, the whole TSCDM, and the full population data of the NHID. The sampled TSCDM data generally fulfilled the requirement of quality assurance. About six percent of data related to sex and 0.0007% of data related to birth year were missing. As sex was coded based on the national identification number of Taiwan, missing values were likely to be attributed to foreign workers who often have National Health Insurance coverage but different identification numbers. Less than five per million of the data had illogical dates.

Conclusions: TSCDM could be a tool for domestic pharmacovigilance analyses and cross-country epidemiology evaluation.

4623 | Approaches to evaluate the interchangeability of laboratory test results in real world data to derive prognostic scores

Paul Dillon[1], Phil Arnold[1], Nayan Chaudhary[2], Evelyn M Flahavan[3], Anne-Marie Meyer[1] and Jessica Davies[3]

[1]F. Hoffman-La Roche AG, Basel, Switzerland; [2]Genentech, Inc., San Francisco, CA; [3]Roche Products Ltd, Welwyn Garden City, United Kingdom

Background: Lab results can be used to derive variables such as prognostic scores, however many prognostic scores rely on treating lab results as continuous variables. Generally lab results should be categorised with regard to test-specific normal ranges. In Real World Data (RWD) lab data mapped from an EHR-derived database, continuous variables may not be appropriate given the heterogeneity of normal ranges resulting from variation in testing procedures and equipment.

Objectives: To describe approaches to evaluate the interchangeability of continuous lab tests and apply to the neutrophil-to-lymphocyte ratio (NLR), a component of prognostic scores for advanced non-small cell lung cancer (aNSCLC).

Methods: Patients diagnosed with aNSCLC on or after January 1, 2011, with at least 2 documented clinical encounters from the US nationwide Flatiron Health EHR-derived aNSCLC database, aged ≥18 years, who received 1st line treatment with carboplatin and pemetrexed, or carboplatin and paclitaxel between January 1, 2011 and January 31, 2018 were included. Index date was defined as start of 1st line treatment. Patients with history of other malignancies before diagnosis date or any gap in visits of >90 days between diagnosis and index date were excluded. Neutrophil and lymphocyte test results between diagnosis and index date were evaluated separately. To assess interchangeability, the reported lab test methods were identified and the distribution of results grouped by method was compared. The reported normal ranges were evaluated using scatterplots of the minimum normal value against the maximum normal value.

Results: Of eligible patients (N=12351), 43% had at least one neutrophil and 68% had at least one lymphocyte test result available between diagnosis and index date. For both tests two methods were reported, automated and manual counts. However for 89.4% of lymphocyte cases and 83.6% of neutrophil cases this detail on test method was not available. Variation in the distribution of test results grouped by test method was observed with differences in mean values, indicating methods may not be comparable. The reported min normal and max normal ranges for neutrophils were 0-2.5 x 10^3/uL and 4.9-11.2 x 10^3/uL and for lymphocytes 0-1.9 x 10^3/uL and 2.2-6.5 x 10^3/uL respectively, highlighting substantial variation in RWD lab normal ranges.

Conclusions: This study describes approaches to evaluate the interchangeability of RWD lab results and in this case suggests results are

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

not interchangeable. Continuous variables such as the NLR should be derived with caution from a EHR-derived database.

4658 | Standardisation of disease registry data to the OMOP common data model: The pulmonary hypertension experience—Challenges and achievements

Patricia Biedermann[1], Alexander Davydov[2], Alexandra Orlova[2], Rose Ong[1], Graham Wetherill[1] and Eva-Maria Didden[1]
[1]*Actelion Pharmaceuticals Ltd, Allschwil, Switzerland;* [2]*Odysseus Data Services, Inc., Cambridge, MA*

Background: The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) can be used to transform observational health data to a common format to allow for systematic analysis of disparate data assets. Mainly large commercial and hospital databases have been converted to CDM. We report here one of the first efforts to transform disease registry data to CDM. Pulmonary Hypertension (PH) is a fatal disease with several rare subgroups. Transforming PH registry data to a standardised format would efficiently generate evidence across databases.

Objectives: Share experience in transforming PH registry data to CDM, discuss the process and highlight challenges.

Methods: Two observational studies were transferred from SDTM (Study Data Tabulation Model) to CDM: OPUS (NCT02126943), a prospective, US, multicentre, drug registry (04/2014-now) and OrPHeUS (NCT03197688), a US, multicentre chart review (10/2013-03/2017). Both studies enrol PH patients newly treated with macitentan, an endothelin receptor antagonist. OMOP CDM version 5.3.1 with SNOMED version 09/2019 was used. Since CDM requires complete dates, imputation rules were defined and implemented on partial dates (month and/or day missing) to avoid record loss. Further, as PH has several rare subgroups, standardised SNOMED concepts in CDM do not cover all subgroups and clinical assessments. To allow enough granularity and transform disease-specific medical terms, customised concepts were introduced.

Results: Data were transformed to CDM for 99% and 97% of patients enrolled in OPUS (N=2521) and OrPHeUS (N=3142). Patients were excluded due to: missing birth year (n=106), duplications within OrPHeuS (n=23), violating study eligibility criteria (n=9), missing/inconsistent treatment start/end date (n=25). To differentiate PH subgroups, a combination of standardised SNOMED concepts was used, e.g. "pulmonary arterial hypertension (PAH)" and "connective tissue (CT) overlap syndrome" for "PAH associated with CT disease". When conversion to SNOMED was not possible, customised concepts were introduced, e.g. for drug and toxin induced PAH. CDM does not distinguish between not performed and not available medical assessment, e.g., the 6-min walking test, could only be converted to CDM when the assessment was documented in the SDTM.

Conclusions: Standardising PH registry data to the CDM made data more widely available with little loss of information and deviation from SDTM. The CDM creates opportunities to generate disease evidence across PH-specific and general health databases.

4740 | Challenges in using electronic medical records datasets to describe patients with porto-pulmonary hypertension

Sandrine Leroy[1], Eva-Maria Didden[1], Wassim Fares[1], Loïc Perchenet[1], Erica Voss[2] and Daniel Rosenberg[1]
[1]*Actelion Pharmaceuticals Ltd, Allschwil, Switzerland;* [2]*Janssen, Titusville, FL*

Background: Porto-Pulmonary Hypertension (PoPH), a rare life-threatening disease, is pulmonary arterial hypertension (PAH) associated with portal hypertension. The majority of PoPH patients have cirrhosis and may require liver transplantation (LT); however, PAH can increase risk of perioperative mortality and severe PAH is a contraindication for LT.

Objectives: To describe the clinical course of PoPH, including post-LT outcome in coded electronic medical records (EMR), to validate in larger populations the findings from detailed but small registry cohorts.

Methods: In the Optum® de-identified EHR dataset and TriNetX Research network, PoPH patients were selected using a coding algorithm based on a conservative approach combining codes for portal hypertension, procedure code for RHC followed within 12 months by a PH diagnosis code (S0); sensitivity analyses explored the impact of more inclusive (S1) or more restrictive (S2 to S4) or strict (S5 - with a PH drug code) algorithms. Analyses were run on ALL (ie. overall patients) or LT (ie. transplanted patients) sets.

Results: The main analyses (S0) included 1175/164 PoPH/LT in OPTUM, 1174/296 in TriNetX. Median age at diagnosis varied from 59 to 61 years old, males were 50% to 60% and cirrhosis represented >75% of PoPH aetiology. The proportion of patients with PAH treatment records was of 41% in OPTUM and 16% in TriNetX whereas it was >85% in disease-specific registries, reflecting the disease severity and absolute need for a treatment to control PAH. In OPTUM, the proportion of patients with PAH treatment records decreased to 17% in the inclusive S1 while it stayed of 42% in the more restrictive S2 to S4 analyses; the proportion ranged from 12% to 18% across sensitivity analyses in TriNetX. One can hypothesise that treatment information is under-reported in EMRs, specifically in PoPH patients who are mostly outpatients with prescriptions renewals from general practitioners and external pharmacies. In OPTUM, 2-year survival ranged from 94% to 96% in ALL set, and from 98% to 100% in LT set across sensitivity analyses. This contrasts with the worse survival found in standard PoPH cohorts, highlighting the potential lack of death reporting and specificity of the code algorithms used for PoPH.

Conclusions: Observational research on rare conditions is challenging in EMRs due to (i) lack of specific and sensitive code-based definitions, and (ii) the gaps in longitudinal patient journey coverage from primary, up to tertiary care settings. Further work which links EMRs

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

to clinically rich datasets is needed to refine and validate a more robust code algorithm for PoPH.

4884 | Explaining the inexplicable: Irregularities in electronic health record derived data

Megan Delgado[1], Sofia Dard[2], Michele Jonsson Funk[1] and Timothy Carey[3,2]

[1]*University of North Carolina, Chapel Hill, NC;* [2]*University of North Carolina, Chapel Hill, NC;* [3]*University of North Carolina, Chapel Hill, NC*

Background: Electronic health records (EHRs) are a valuable source of real-world data for pharmacoepidemiology research. While its primary purpose is clinical care, the depth and completeness of clinical data relative to other common data sources, such as healthcare claims, makes it particularly useful in filling data gaps. Despite this, little is known about the quality of these data. For instance, apparent post-death healthcare encounters raise questions about whether EHR data are 'fit-for-purpose' in settings where death is an important outcome.

Objectives: To identify patients who appear to have a healthcare encounter after the recorded date of death and describe reasons for this error.

Methods: In a large single health system, a probabilistic matching algorithm was used to link EHR data with state-level death data. A chart review of patients who had evidence of a post-death healthcare encounter in the EHR from 2014 to 2017 was performed. Vital status and reason for post-death healthcare encounter were ascertained based on a detailed review of the medical record. Patients who had an active medical chart were classified as 'alive'. Those with confirmatory evidence of death were classified as 'deceased' (D), and those with healthcare activity relating to terminal status or end of life care were classified as 'likely deceased' (LD). Patients without evidence of death, terminal status or end of life care were classified as 'unknown'. Reasons for post-death healthcare encounters were documented.

Results: Among 56,162 deaths, 0.5% (n=282) appeared to have a post-death healthcare encounter in the EHR. After reviewing all charts, 1.4% (n=4) were classified as alive, 65.6% (n=185) as D/LD, and 33.0% (n=93) as unknown. Patients classified as alive initially appeared to be deceased due to EHR data entry or merge issues. Patients classified as D/LD had post-death healthcare encounters due to administrative and billing issues, data entry or merge issues, and medical activities (e.g., autopsy procedures, organ donation, out-of-hospital imaging readings). Patients classified as unknown often had healthcare encounters due to billing issues, but their true vital status could not be determined from the chart.

Conclusions: Reassuringly, only a small number of individuals were reclassified as alive after chart review. The fact that a third could not be resolved is a concern. Improvements to billing practices and bundled visits, such as avoiding billing adjustments that are charted as visits and canceling radiation oncology recurring visits, could greatly reduce the number of patients with an apparent post-death health encounter.

4887 | Deep learning techniques to predicting depression in rheumatoid arthritis patients: A real-world data analysis

Santosh Murugan, Julius Asubonteng, Sara Haredasht, Sapthagirishwaran Sivarama, Ejim Mark and Robertino Mera

Gilead Sciences Inc., Foster City, CA

Background: Patients with rheumatoid arthritis (RA) suffer from higher rates of major depressive disorder (MDD) than the general population. Although treatable if diagnosed, undiagnosed depression can worsen disease state and dramatically decrease quality of life.

Objectives: We develop deep learning techniques to predict the development of MDD, by analyzing <1 year, 1 - 2 year, and 3+ year windows of patient data.

Methods: Data were extracted from a claims database of commercially insured patients in the U.S. from 2010-2019. Each RA patient was matched to two non-RA patients in the pre-processing phase based on age and gender, and only incident cases of RA in patients with at least 60 days of insurance history were considered. As baselines, logistic regression and random forest classifiers (which provides feature importance's) were implemented. We then developed 21 additional model setups involving convolutional neural networks, stacked dense neural networks, and recurrent neural networks (bidirectional LSTM, LSTM, and GRU). Models were evaluated on the dataset with regard to accuracy and area under the receiver operating characteristic curve (AUROC).

Results: Our best deep learning models yielded 94% accuracy and 0.81 AUC on a real-world cohort of 77,767 patients. The three RNN models (specifically, bLSTM, LSTM, and GRU, each with 3 layers, trained for 20 epochs, with a batch size of 4096) outperformed all others with respect to AUROC, with values above the 0.8 threshold. Furthermore, from the random forest classifier, we were able to ascertain which features contributed most highly to depressive risk. The five most important features were comorbid Type 1 diabetes, age, rituximab use, rheumatoid arthritis, and bone marrow failure. Rituximab is a late stage-treatment for crippling autoimmune diseases such as RA, and bone marrow failure often results from moderate-to-severe immune conditions or anti-inflammatory or auto-immune drug usage. All five factors are plausible contributors to worsened disease state, which increases the credibility of our approach.

Conclusions: The machine learning and deep learning techniques in this paper thus represent a significant improvement in our ability to predict depressive risk, within specific timeframes, in an at-risk population. Information supplied by the model could potentially be used to intervene ahead of time in high depressive risk cases, thus improving both actual health outcomes and quality of life.

4897 | Mapping national drug codes (NDCs) and drug concept unique identifiers (RxCUIs) to the Rx-risk comorbidity index using RxNorm

Jared J. Vanderbleek[1], Justin K. Owensby[2], Jeffrey R. Curtis[2] and Huifeng Yun[1]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Alabama at Birmingham, Birmingham, AL

Background: Identifying and controlling comorbid conditions in large, real-world data sources is crucial for cohort establishment and confounder adjustment. However, the ability to conduct proper confounding control may be challenging when data for diagnosis codes and lab tests are incomplete, such as in a single-specialty Electronic Health Records (EHR) system where comorbidities are incompletely recorded by specialists. Thus, we updated a method to allow researchers to identify comorbid conditions using only medication information in circumstances where diagnosis codes are under-captured.

Objectives: We mapped National Drug Codes (NDCs) and Drug Concept Unique Identifiers (RxCUIs) to comorbidity categories of the Rx-Risk Comorbidity Index via validated Anatomical Therapeutic Chemical (ATC) Classification System codes using the RxNorm (standardized nomenclature for clinical drugs) application program interface (API).

Methods: For each of the 46 Rx-Risk categories previously mapped to 5th-level ATCs, we identified corresponding RxNorm ingredients, and then expanded them to all RxCUI term types (TTYs) using the RxNorm API. Only four TTYs can be reconciled with a NDC value, these include: semantic clinic drug (SCD), semantic brand drug (SBD), generic pack (GPCK), and brand pack (BPCK). We further mapped these TTYs to NDCs using the same API but different function calls. Descriptive analyses were performed in SAS (version 9.4) to measure scope of RxNorm coverage.

Results: Using RxNorm, we identified 988 (73.3%) ingredient RxCUIs from a total of 1,347 ATCs representing the 46 Rx-Risk comorbidity categories. After obtaining 3,952 RxCUIs for the relevant TTYs, we identified 111,921 unique NDCs and mapped them to 43 Rx-Risk categories. Approximately 14.8% of NDCs were classified in at least two Rx-Risk categories. To provide a comprehensive list of RxCUIs, we examined all TTYs associated with an RxNorm ingredient, yielding 29,343 unique RxCUIs. No RxCUIs or NDCs for SCD, SBD, GPCK, and BPCK were identified for categories 'malnutrition', 'hyperkalemia', and 'pancreatic insufficiency'. Additional analyses using the First Databank database to reconcile unmapped NDCs and RxCUIs are ongoing to compare with more traditional, diagnosis-based comorbidity indices.

Conclusions: This study offers an approach in workflow design for mapping NDCs and RxCUIs to comorbidity categories of the Rx-Risk Index. Additional studies are needed to expand breadth of the RxCUI and NDC compilation and to validate its utility in identifying comorbid conditions.

4919 | a novel artificial intelligence algorithm of synthetic sampling for boosting accurate machine learning prediction of infrequent health outcomes

Gang Fang and Izabela Annis
University of North Carolina Chapel Hill, Chapel Hill, NC

Background: Real-world clinical health outcomes are usually not balanced or evenly distributed (occur infrequently). For example, the incidence of severe adverse drug events is often less than 5%. Imbalanced classes of outcome create a significant problem in developing machine-learning (ML) prediction models. The problem includes low sensitivity (the ability to predict the occurrence of an outcome event). Low sensitivity renders ML prediction model clinically not useful or meaningful. We developed a novel artificial intelligence (AI) algorithm (SynSam) that generates synthetic samples to boost samples with infrequent health outcome occurrence. The algorithm can handle clinical health data with both continuous and categorical predictors.

Objectives: The aim of this project was to compare the performance of ML prediction models with the SynSam sampling to random over-sampling (bootstrap), and to no over-sampling (naïve) when the outcome is rare or infrequent.

Methods: We simulated a virtual patient cohort (N=50,000) with a 1% adverse drug event occurrence. Using the U.S. National Health and Nutrition Examination Survey (NHANES) data we also assembled a cohort of adults who suffered from asthma (N=6177) for the prediction of emergency department visits due to asthma (rate = 9%). With the split-validation design, we set aside 20% random sample of each cohort as an independent validation dataset and used the rest of 80% for prediction model training with the Extreme Gradient Boosting algorithm. We applied the 5-fold cross-validation for final model training and selection. We compared the performance of the final prediction model with respective over-sampling approaches for the validation datasets.

Results: In the virtual patient cohort, the naïve model correctly predicted the events 55% of the time (sensitivity) while predicting all non-events (specificity). The application of bootstrap increased sensitivity to 70%. The SynSam approach increased the sensitivity to 90% while maintaining the specificity at 96%. In the NHANES cohort, the naïve model had a 19% sensitivity and 95% specificity. The bootstrap approach increased the sensitivity to 24%. The SynSam approach achieved a sensitivity of 51% with a specificity of 88%.

Conclusions: The AI-based SynSam approach may be useful to boost ML prediction model performance for infrequent health outcomes.

4920 | Identifying predictors of a composite cardiovascular outcome among diabetes patients using machine learning

Zeynep Icten and Joseph Menzin
BHE, Boston, MA

Background: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in type 2 diabetes (T2D) and understanding the predictors of major cardiovascular events may help reduce its burden.

Objectives: This study aimed to identify predictors of a composite CVD outcome using machine learning applied to medical claims data.

Methods: Medicare 5% Part A/B claims from 2010-2015 were used to identify patients 65 years or older with at least 2 T2D diagnoses,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and continuous enrollment during the 12 months baseline and follow up periods. Patients with T1D diagnosis or commercial insurance were excluded. The composite outcome was defined as an inpatient visit with congestive heart failure, stroke, ischemic heart disease or peripheral artery disease during the follow up. Features extracted from the baseline included demographics, diagnoses, procedure utilization and service location variables. Data were partitioned using a 60%/20%/20% split to train, validate models and test performance on unseen data. Traditional and regularized logistic regression, XGBoost (XGB), support vector machine, and random forest models were built, and the best model was selected using the area under the ROC curve (AUC). Accuracy, recall, precision, F1 score and negative predictive value (NPV) were also assessed.

Results: The study population included 292,045 patients (mean age=74.6; females=55%; CVD outcome=10.04%). The best performing model was XGB (Validation AUC=77.6%; accuracy=74.6%; recall=66.1%; precision=22.8%, F1=0.34 and NPV=95.3%) with test AUC of 77.4%. Top 15 XGB predictors according to the gain metric included age and features related to the history of existing CVD (ie., congestive heart failure, coronary artery disease, peripheral vascular disease, atrial fibrillation), chronic airway obstruction, chronic kidney disease, electrocardiogram, baseline IP and ER visits (positively associated with the CVD outcome) and mammogram screening (negatively associated). Top 5 predictors common to all models identified using the relevant feature importance metrics were history of congestive heart failure, atrial fibrillation, chronic airway obstruction, baseline IP visit and age.

Conclusions: Our study identified predictors of a composite CVD outcome among T2D patients with high predictive accuracy and our findings are overall consistent with established risk factors, while indicating opportunities for further research.

4988 | machine learning applications using real-world data: A literature review

Nicholas Adair, Zeynep Icten, Mark Friedman and Joseph Menzin
Boston Health Economics, LLC, Boston, MA

Background: Machine learning (ML) is increasingly being applied to the field of medicine and more specifically using EHR and claims data sources. As the field expands, it is important to understand how researchers leverage different data and methodological options.

Objectives: We aim to describe the current landscape (i.e. common themes in data sources, algorithms, and performance metrics) of ML applications using EHR and/or claims.

Methods: A targeted literature review was performed. PubMed was searched using the criteria ("machine learn*" OR "artificial intelligence") AND ("claims" OR "electronic medical record*" OR "EMR" OR "electronic health record*" OR "EHR") in 2018 and 2019. Exclusion criteria included ML applications in imaging, genetics, drug discovery and target development, molecular subtyping, protocols, reviews, and opinions. ML applications were categorized as natural language processing (NLP), clustering, risk prediction, or other. Data source, algorithm, performance metric, and journal information were collected. The Abridged Index Medicus, also referred to as the "core clinical journals", was used as a gold standard for determining a journal's clinical status.

Results: Search criteria returned 1,039 results. After application of exclusion criteria, 273 papers were included in the final review. Of the 273 papers, 172 (63%) were categorized as risk prediction, 43 (16%) as NLP, 36 (13%) as clustering, and 22 (8%) as other. The 5 most common algorithms used were boosting methods (48, 18%), such as XGBoost and AdaBoost, neural networks (42, 15%), random forest (41, 15%), lasso logistic regression (20, 9%), and support vector machines (19, 7%). The 5 most common data sources were multi-site EHR (102, 37%), single-site EHR (75, 27%), claims (38, 14%), multisite clinical notes (24, 9%), and registry (12, 4%). The 5 most commonly reported model performance metrics were sensitivity/recall (251, 91%), AUC (224, 82%), specificity (177, 65%), F1 score (114, 42%), and PPV (90, 33%). Additionally, ML papers were published in 13 of the 118 core clinical journals.

Conclusions: ML utilizes EHR and claims data mainly for risk prediction. We have shown that boosting methods and multi-site EHR data sources were the most widely reported. Moreover, the presence of ML applications in clinical journals underscores the importance of non-machine learning experts, such as clinicians and physicians, to focus efforts in understanding the most common methods.

5004 | Agreement between ICD mortality codes and drug mentions for opioids in the drug-involved mortality database (2010-2017)

Richard S Swain, Sara Karami and Celeste Mallama
Food and Drug Administration, Silver Spring, MD

Background: The Drug-Involved Mortality (DIM) database combines cause-of-death, demographic, and geographic data from the National Vital Statistics System-Mortality (NVSS-M) database with information related to drug involvement extracted from the death certificate literal text. Previous research has demonstrated strong agreement between ICD-10 T-codes for drug toxicity and drug mentions in DIM; however, research is needed to determine if strong agreement is typical for opioids.

Objectives: To calculate agreement between ICD-10 T-codes for opioid toxicity and drug mentions recorded in the DIM database.

Methods: We performed a descriptive analysis to identify drug-involved mortality (DIM 2010-2017) with any opioid mention and/or T-codes for opioid toxicity (T40.1-T40.4 or T40.6) and by opioid class: opium (T40.0), heroin (T40.1), natural and semisynthetic (T40.2), methadone (T40.3), synthetic (T40.4), and unknown opioid (T40.6). We calculated Kappa scores by comparing agreement between drug mentions (DIM) to ICD-10 T-codes (NVSS-M) and described additional ICD codes (substance abuse: F-codes; poisoning: X-codes or Y-codes) associated with discordant and concordant deaths.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: There were 21,020,961 total deaths recorded in NVSS-M between 2010-2017, of which 265,075 (1.3%) had one or more drug mention for an opioid and 252,108 (1.2%) had an ICD T-code for opioid toxicity. Agreement between any opioid T-code and a mention for opioid-involved mortality was strong [Kappa=0.952 (95%C.I. 0.951-0.953)]. Within classes of opioids, agreement was strong for heroin [0.955 (0.954-0.956)], natural and semisynthetic [0.917 (0.916-0.918)], methadone [0.947 (0.945-0.948)], and synthetic opioids [0.951 (0.950-0.953)], while opium [0.539 (0.375-0.702)] and unknown opioid [0.706 (0.700-0.711)] had moderate agreement. Of 18,678 deaths with an opioid mention but no opioid T-code, 12,072 (64.6%) had an ICD code (F11) for opioid abuse disorder. Among deaths with an opioid T-code (with or without an opioid mention), approximately 96% had an additional ICD code indicating poisoning (X/Y-codes); however, among deaths with an opioid mention without a T-code, only 26% had any ICD X-code or Y-code for poisoning.

Conclusions: While ICD T-codes typically encompass entire drug classes, the DIM dataset has the unique capability to identify specific substances allowing for national estimates of drug-involved mortality. Agreement between drug mentions and ICD-10 T-codes was very strong for opioid-involved mortality, suggesting high predictive value for opioid mentions within DIM.

5064 | Continuity and completeness of electronic health records: Findings from three delivery systems in Taiwan

Chien-Ning Hsu[1,2], Chi-Chuan Wang[3,4,5], Fang-Ju Lin[3,4,5], Huang-Tz Ou[6], Kelly Huang[3] and Sengwee Toh[7]

[1]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [2]Kaohsiung Medical University, Kaohsiung, Taiwan; [3]National Taiwan University, Taipei, Taiwan; [4]College of Medicine, National Taiwan University, Taipei, Taiwan; [5]National Taiwan University Hospital, Taipei, Taiwan; [6]National Cheng Kung University, Tainan, Taiwan; [7]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: Electronic health records (EHR) contain rich clinical information and therefore serve as another data source for epidemiological studies. However, data completeness and continuity are of concern. It remains unclear to what degree an EHR database can capture longitudinal exposure, outcomes, and important confounders.

Objectives: 1 To evaluate the continuity of EHR from three deliver systems in Taiwan, and 2 to assess the completeness of a single center EHR by comparing EHR to the linked claims data from the National Health Insurance Database (NHID) of Taiwan.

Methods: For data continuity, we evaluated EHR from the three health-care delivery systems between June 2011 and December 2016. Patients who were prescribed an oral hypoglycemic agent (OHA) and had at least one diabetes diagnosis on or before the first OHA prescription were included. The first OHA prescription date served as the index date. Data continuity was assessed in 90-day intervals before and after the index date. Patients were considered having continuous data if they had at least one encounter or medication record in a 90-day interval. Different lengths of baseline and follow-up periods were evaluated: 6-month and 12-month baseline, 1-year, 2-year, and 5-year follow-up. EHR data completeness was evaluated at one of the centers where access to linked patient-level claims data was available, and in this analysis, patients with at least six months of baseline and two years of follow-up based on EHR were included. Data completeness was measured by mean capture proportion (MCP). We further evaluated the degree of outcomes being captured in the EHR database, including cardiovascular events, nephropathy, and heart failure admission.

Results: Among the three health-care delivery systems, 40% to 69% of the included patients had 6-month continuous baseline data; among patients with 6-month baseline, 68% to 75% of them had follow-up encounters or medication records for two years. For patients with continuous EHR data for 6 months of baseline and 2 years of follow-up, MCP was 56% (SD 32%), and only 44% and 25% of the patients had MCP ≥ 60% and ≥ 80%, respectively. Only 58%, 69%, and 75% of the cardiovascular events, nephropathy, and heart failure admissions were captured in EHR respectively.

Conclusions: EHR data continuity for diabetes patients varied across delivery systems, and data completeness was suboptimal. Additional research should follow to identify factors for variation in MCP in term of access of out-of-system care to optimize utility of EHR systems for robust research data analytic platform.

5077 | Challenges and opportunities to use secondary data in country level for promoting evidence-informed policy and management decisions in healthcare: Case study in Chile

Felipe D. Vera[1], Juan Roldan Roldan[2], Dino Sepulveda[3], Lisiane Leal[4], Maribel Salas[5], Monique Elseviers[6] and Luciane Cruz Lopes[7]

[1]Sheffield University, Sheffield, United Kingdom; [2]Health Institute Chile, Department of Pharmacovigilance, Santiago, Chile; [3]Department of Health Technology Assessment and Evidence Based Medicine, Ministry of Health, Santiago, Chile; [4]McGill University, Montreal, QC, Canada; [5]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [6]Ghent University, Flandes, Belgium; [7], University of Sorocaba, São Paulo, Brazil

Background: It is broadly recognized that health policy and decisions not often reflect research evidence. Healthcare database analyses (e.g. claims, electronic health records, pharmacy records) have been identified as important sources to generate evidence on the effectiveness, harm, and value of medical products in clinical practice. Hence, it is vital to determine if available healthcare databases have been used to improve evidence-informed decision-making at country level.

Objectives: This study aims to describe available databases on pharmaceutical use and to identify studies that specifically used those databases to generate research for informed decision-making in Chile.

Methods: The strategy to develop this study was based on the following framework: i. building capacity and; ii. scoping review of the literature and governmental websites. I. The network of researchers

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

included academic experts in Pharmacoepidemiology, members of the government and health regulatory agencies ii. The researchers made a scoping review based on previous knowledge of the team members, using scientific literature databases, from inception to December 2019; researchers included grey literature. Two researchers independently screened eligible pharmaceutical databases and checked any study or document. Possible divergences were analyzed by a third researcher. The pharmaceutical databases were characterized for accessibility, coverage granularity, provider, type of data sources, and setting. The selected documents and studies were characterized by design, type of data generated, funding and accessibility.

Results: Eleven pharmaceutical databases were identified, of those, only 4 (36%) are partially publicly and conveniently accessible. The access is limited or only accessed by researcher working in the institution; 4 databases (36%) include data from both sectors public and private health; the majority of data (5 databases) is provided by patient record information and only one has data from pharmacy records. Also, only three databases provide data from ambulatorial setting. 94 documents were retrieved that analyse data from 6 (67%) of pharmaceutical databases in Chile.

Conclusions: Although Chile's government could organize data provided by users of healthcare, there is poor production of national data used for decision making. Increasing healthcare database accessibility and implementing the network capacity building could improve evidence-informed decision-making.

5080 | Predicting gout flares using electronic medical records

Maranda Russell, Sujin Kim and Nayef Kazzaz
University of Kentucky, Lexington, KY

Background: Gout is the most common inflammatory arthritis characterized by deposition of monosodium urate crystals in joints and tissues. Patients often discontinue prescribed urate lowering therapy due to increased frequency of gout flares during the first 6 months of ULT.

Objectives: Our project is to determine whether gout flares in electronic medical records (EMR) are associated with the prescription of major gout medications such as allopurinol, febuxostat, and colchicine.

Methods: 1. Design: We used retrospective administrative data to identify gout patients with more than 1 medical claim with ICD-9-CM diagnosis code 274.xx. For medications, we identified national drug codes representing three gout drugs. Gout flares were determined as an average number of claims during their clinic visits. 2. Setting: Our sample was extracted from electronic medical records using the University of Kentucky HealthCare (UKHC) EMR. For rheumatology notes, we applied natural language processing (NLP) to identify the three medications mentioned in the notes. 3. Exposures or interventions: We chose three major gout medications block uric acid production (allopurinol and febuxostat) and a pain reliever (colchicine). 4. Main outcome measures: Our main outcome is an association between frequency of gout flares and gout medication prescriptions. 5. Statistical analysis: Correlation and multiple regression analyses were conducted to examine the relationship between gout diagnostic codes and three medication prescription records.

Results: Our data includes 5,590 gout patients (Male = 3,999, Female = 1,591) who visited the clinic between January1, 2000 and April 31, 2019. Average age is 61.50 (std.=14.13) with predominantly White patients (81.2%), followed by African American (N=857, 15.3%). Our results indicate that gout flares is positively and significantly correlated with the prescription of three gout medications, indicating that those with higher frequency of these variables tend to have higher gout diagnosis. The results from the NLP shows significance with the three drugs, but their frequencies are lower compared to the prescription claims in the EMR. The multiple regression model with all three predictors produced R^2 = .508, F(3, 94) = 32.28, p < .001, while joint pain codes with the three medications predicting their flares, show insignificant results (R^2 = .160, F(3, 61) = 3.865, p > .01).

Conclusions: Gout flares can be predicted over the course of long-term treatment using retrospective claims. Further study to follow up on when gout flares occur can reinforce the need for gout patients to adhere to ULT.

5122 | The disproportionate importance of data quality and feature engineering: Demonstrations with machine learning examples in a surgical ICU setting

Andy Wilson[1], Jenny Alderden[2], Amanda R Shields[1] and Kathryn Drake[3]
[1]*Parexel, Durham, NC;* [2]*University of Utah, Salt Lake City, UT;* [3]*Boise State University, Boise, ID*

Background: Emerging machine learning techniques, coupled with EHR data, represent an opportunity to predict complications before they occur, enabling early preventive intervention.

Objectives: To evaluate the impact of feature selection, data processing decisions, and algorithm selection on the performance of prediction models using open-source machine learning tools in Python and R.

Methods: This retrospective cohort study used EHR data from 5,101 surgical ICU patients at the University of Utah to predict hospital-acquired pressure injury (HAPI) development. We evaluated the effect of choices in feature selection and data processing against model performance in a 20% held-out test data set. Choices included: a) use of all available variables (27 inputs) versus selection of an easily accessible, parsimonious, group of variables (5 inputs); b) use of single value random forest imputation versus substituting a '0' for missing data in the case of informatively-missing variables; c) choice of approach to imbalanced data; and finally, d) algorithm selection - neural network, random forest, logistic regression, adaptive boosting (AdaBoost), and extreme gradient boosting. We evaluated model performance in the held-out (testing) dataset via the area under the [ROC] curve (AUC), F1-score, and the confusion matrix.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: HAPI occurred among 333 (6.6%) of the SICU patients. Model performance was similar between models using the full and parsimonious predictor variables, and using single value random forest imputation versus substituting zeroes for missing values. The approach to imbalanced data was important in model performance; without adjusting for the imbalance, models tended to predict mostly zeroes resulting in misleadingly optimistic ROC performance relative to accuracy in predicting the minority class. Synthetic minority oversampling technique (SMOTE) resulted in improved accuracy in predicting the minority class in the full and parsimonious data sets. After applying SMOTE, all algorithms performed similarly; the best performing algorithm was a weighted logistic regression model.

Conclusions: Results demonstrate the importance of adjusting for the class imbalance to promote the inclusion of the minority class and underscore the limited ability of the AROC as an evaluation metric in imbalanced datasets. The robust performance of the parsimonious group of variables suggests that it may be possible to develop more focused guidance for clinicians and caregivers, to reduce caregiver burden without compromising care.

5127 | Studying uninsured Americans through the lens of survey data and electronic health records

Dawn Albright[1], Elizabeth C. Dabrowski[1], Nicolle Gatto[1], Liza R. Gibbs[1] and Dana Y. Teltsch[2]
[1]*Aetion, Boston, MA;*[2]*Apellis, Waltham, MA*

Background: Insurance claims databases are commonly used for healthcare research, and as such, uninsured patients are not represented in these studies. MEPS (Medical Expenditure Panel Survey), a survey conducted by AHRQ (Agency for Healthcare Research and Quality) on a random sample of households, is often used for information on the uninsured population. However, it is updated infrequently (current data 2015; 2018 coming this year), thus not reflecting any recent changes in regulations that affect the healthcare industry. It is possible that by combining these panel data with current electronic health records (EHR), we can better study uninsured Americans.

Objectives: To explore the MEPS and Optum® de-identified EHR datasets in order to understand the most fit-for-purpose database for research questions related to the American uninsured population.

Methods: We used the Optum® de-identified EHR dataset to identify a cohort of patients treated in 2015. We then focused on uninsured patient-time, defined as time periods during which all recorded activity was not covered by insurance. Using the Aetion Evidence Platform version 3.18, descriptive statistics were computed using Optum® de-identified EHR for the demographics reported in MEPS, including age, sex, census region, number of emergency room visits, and number of inpatient visits.

Results: Comparing 2015 statistics for the uninsured between Optum EHR (n=982,161) and MEPS (n=26,149,337) we found that the age (18-26 MEPS: 19.2%, 18-26 EHR: 20.1%), race (white MEPS: 76.2%, white EHR: 61.2%), and gender distributions (male MEPS: 57.7%, male EHR: 52.3%) were substantially similar. The geographic distribution differed with 49.0% of uninsured EHR patients being from the Midwest, compared to 16.8% in the MEPS data. The EHR cohort had a higher proportion of ER visits and hospitalization compared to MEPS, likely due to the EHR population exclusively including patients with medical activity versus MEPS capturing household information whether medical activity occurred or not.

Conclusions: MEPS is a better source to study overall rates of care, while the EHR can add recent data, detailed healthcare utilization information, and near-real-time insight on how changing regulations reflect in medical care.

5136 | Insurance journeys: Quantifying transitions through insurance types

Dawn Albright[1], Elizabeth C. Dabrowski[1], Nicolle M. Gatto[1], Liza R. Gibbs[1] and Dana Y. Teltsch[1,2]
[1]*Aetion, Boston, MA;* [2]*Apellus, Waltham, MA*

Background: Claims data provide rich information on large populations, but by definition do not have information on uninsured individuals. This limits generalizability of Real World Evidence (RWE) studies to the employed population. Electronic Health Records (EHR) such as the Optum® de-identified Electronic Health Record dataset may provide the opportunity to study uninsured populations including their transitions from one health coverage to another.

Objectives: To assess feasibility of using EHR data to understand patient journeys through three major categories of health insurance -- fully uninsured, partially insured, and fully insured in patients who do not have insurance at baseline.

Methods: We used the Optum® de-identified EHR dataset (Jan 2007-March 2018) to identify patients with a diagnosis of Major Depressive Disorder (MDD) or Rheumatoid Arthritis (RA) and with a fully uninsured baseline period (≥90 day baseline period with no evidence of insurance). The year pre and post the fully uninsured baseline period was categorized into 90 day periods and then traced to observe insurance category switches. Insurance types were categorized as either fully insured (all encounters in the 90 day period were insured), fully uninsured (none of the encounters in the 90 day period were insured), and partially insured. Partially insured was defined as patients with over two encounters of which at least one had some form of insurance coverage and the other did not, presumably including both patients who gained or lost eligibility in a time period, as well as those whose insurance did not cover their full utilization. We created Sankey plots to visualize the changes over time.

Results: We followed 12,805 RA patients and 73,883 MDD patients. In the year before the uninsured baseline period, the largest subgroup was previously partially insured (41% MDD, 45% RA). After the 90 day fully uninsured baseline period, the largest subgroup of patients continued to have no insurance for at least the next 270 days. (For RA, 0-90days after baseline: 60% were fully uninsured, 91-180d: 47% were fully uninsured, 181-270d: 34% were fully

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

uninsured. For MDD, 0-90d: 56% were fully uninsured, 91-180d: 43% were fully uninsured, 181-270d: 38% were fully uninsured.) The pattern in both cohorts was similar. The majority of partially insured patients continue to be partially insured.

Conclusions: Many patients had no evidence of insurance after a period with no coverage. The majority of partially insured patients continued to be partially insured in the following time periods, possibly due to insurance consistently not covering some services instead of starting or stopping coverage.

5159 | Data transparency for building a stronger healthcare ecosystem: A case study from Argentina health system administrative databases

Marrtin Cañás[1,2], Gustavo H Marín[3], Raquel Herrera Comoglio[4], Martin A Urtasun[1,2], Lisiane Leal[5], Maribel Salas[6,7], Monique Elseviers[8] and Luciane Cruz Lopes[9]

[1]FEMEBA, La Plata, Argentina; [2]Universidad Nacional Arturo Jauretche, Florencio Varela, Argentina; [3]Universidad Nacional de La Plata, La Plata, Argentina; [4]Universidad Nacional de Córdoba, Córdoba, Argentina; [5]McGill University, Montreal, QC, Canada; [6]Daiichi Sankyo, Inc, Basking Ridge, NJ; [7]CCEB/CPeRT, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [8]Ghent University, Ghent, Belgium; [9]University of Sorocaba, Sao Paulo, Brazil

Background: The need for research-based knowledge to advise health policy building and implementation is a long-lasting global concern impacting health systems and blocking the provision of quality healthcare. Health data is continuously collected but analysis of that data and strategy around it is restricted. Knowledge of national sources for drug utilization data (DU) in Argentina is uncertain.

Objectives: To develop an inventory of national data sources for DU in Argentina and to verify publicly available data sources.

Methods: A network of national representatives, liaising with national data providers and academic researcher expert in Pharmacoepidemiology searched websites from Argentina (government, academic, private). The information collected from data sources included: accessibility, geographic granularity (national, regional, municipality, organization multi-site) data provider (public health, private sector, both), type of data sources (wholesaler, pharmacy records, electronic health records, other), setting (ambulatory, hospital, both), years coverage, if the data are aggregate or individual level and the custodian.

Results: We identified 28 data sources for DU, of which only 2(7.2%) were publicly available and conveniently accessible; only 4 (14.3%) of them reported national data; 27 of them (96.4%) included only data from public health sector; only one included patient record information and the majority of data was from pharmacy records. No information of hospital data was found in the data sources. The majority of the data sources provided individual level data. In Argentina, there are 24 Provincial Healthcare systems, mainly for public servants and their families. Each provincial healthcare system has its own administrative database, which would be a potential source for DUR. However, the entity that brings together all provincial social works does not have data available to the researcher or stakeholder to improve decision making.

Conclusions: There are great number and variety of Argentina datasources for DU in Argentina, However, access is an important barrier for researchers and policy makers. It is important to involve other stakeholders, manufactures, private data custodians and stewards that could decrease the fragmented data and grant more access to raw data specially those patient-centered to improve outcomes in health care. Increasing health data transparency by publicly available data sources to analyze public health information is crucial for structure a stronger healthcare ecosystem.

Medical Devices

2431 | Digital breast tomosynthesis in diagnosis and screening of breast cancer: A systematic review

Lu Xu[1], Baoqi Zeng[1], Siyan Zhan[1,2] and Feng Sun[1]

[1]Peking University, Beijing, China; [2]Research Center of Clinical Epidemiology, Beijing, China

Background: Digital mammography (DM) will be affected by the breast parenchymal overlap, and only one image can be collected for each position in breast cancer screening. As a new digital photography method, digital breast tomosynthesis (DBT) enables imaging of the breast, and reduces parenchymal overlap.

Objectives: To compare digital breast tomosynthesis (DBT) combined with digital mammography (DM) versus DM in screening and diagnosis of breast cancer.

Methods: We did a systematic review and meta-analysis by searching English databases (Medline, Embase, Cochrane Library and Web of Science) and Chinese databases (Sinomed, CNKI, VIP and Wanfang) from inception until December 2, 2019. For using DBT in diagnosis, meta-analysis and SORC curve were completed via the bivariate model and HSROC model, respectively. For using DBT in screening, we calculated relative risk (RR) and 95% CI by random effects meta-analysis. Quality assessment was based on the Revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist.

Results: Fifteen diagnostic studies and 21 screening studies were included. In diagnostic setting, sensitivity was 0.90 (95% CI 0.86-0.94) for DBT plus DM versus 0.81 (95% CI 0.74-0.86) for DM. Specificity was 0.77 (95% CI 0.70-0.83) versus 0.71 (95% CI 0.63-0.79). Area under curve (AUC) was 0.91 (95% CI 0.88-0.93) versus 0.83 (95% CI 0.80-0.86). Positive likelihood ratio was 3.9 (95% CI 3.0-5.2) versus 2.8 (95% CI 2.1-3.8). Negative likelihood ratio was 0.13 (95% CI 0.08-0.19) versus 0.27 (95% CI 0.19-0.37). Diagnostic ratio was 31 (95% CI 17-57) versus 11 (95% CI 6-18). In screening setting, compared with DM, DBT plus DM can increase the detection rate of breast cancer (RR = 1.24, 95% CI: 1.17-1.32, I^2 = 22.9%), increase the detection rate of invasive breast cancer (RR = 1.26, 95% CI:

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

1.16-1.33, I^2 = 37.2%), increase the detection rate of in situ cancer in breast duct (RR = 1.24, 95% CI: 1.06-1.46, I2 = 58.3%), and reduce the recall rate (RR = 0.83, 95% CI: 0.78-0.87, I^2 = 95.7%), increase the positive predictive value of recall (RR = 1.40, 95% CI: 1.22-1.61, I^2 = 86.1%), and increase the biopsy rate (RR = 1.12, 95% CI: 1.03-1.22, I2 = 87.9%). For the positive predictive value of biopsy, there was no statistically significant difference between the two groups (RR = 1.01, 95% CI: 0.87 ~ 1.19, I2 = 91.2%).

Conclusions: DBT plus DM is better than DM in the diagnosis of breast cancer. Compared with DM, DBT plus DM can increase the detection rate of breast cancer and reduce the recall rate.

2470 | Effect of several optimization strategies in a clinical decision support system for drug-drug interactions on alert burden and alert acceptance

Katoo M Muylle[1], Kristof Gentens[2], Alain Dupont[1] and Pieter Cornu[1,2]

[1]Vrije Universiteit Brussel, Brussel, Belgium; [2]UZ Brussel, Brussel, Belgium

Background: Clinical decision support systems (CDSS) are associated with a high alert burden and too many alerts of low clinical importance leading to alert fatigue and high override rates compromising the primary objective of patient safety.

Objectives: To evaluate the effect of the implementation of an optimized CDSS for drug-drug interaction (DDI) screening on alert burden and alert acceptance.

Methods: This retrospective pre-post study was conducted at a 721-bed university hospital. Only inpatients were included in the analysis. The intervention comprised of several optimizations in the CDSS including the customization of the knowledge base and alert severity classification together with different required actions in order to override the alerts according to DDI severity level, the creation of individual screening intervals, patient-specific alerting, a new alert design, and the creation of a follow-up system. This pre-post study analyzed in detail the alert burden in the pre- and post-intervention period. The alert acceptance was evaluated not only based on in-dialog actions (i.e. prescription discontinued directly from the alert screen), but also based on the actual administration of the drugs involved in the DDI.

Results: In the pre-intervention period, 1087 alerts (92.0% level 1 alerts) were triggered, accounting for 19 different class-based DDIs. In the post-intervention period, 2630 alerts (38.4% level 1 alerts) were triggered, representing 86 different class-based DDIs. The relative risk for alert acceptance based on in-dialog analysis in the post-intervention period compared to the pre-intervention period was 4.019 (95% confidence interval (CI) 3.170 - 5.097; 25.5% versus 6.3%). This relative risk was 1.164 (95% CI 1.083 - 1.252; 54.4% versus 46.7%) when alert acceptance was measured based on administration rates. Analyzing only level 1 alerts, the relative risk for prescription acceptance was 5.504 (95% CI 4.262 - 7.109; 34.1% versus 6.2%) and for administration acceptance was 1.78 (95% CI 1.364 - 1.602; 67.3% versus 45.5%).

Conclusions: The implementation of the new CDSS was successful given the significant higher alert acceptance. This increase in alert acceptance was mainly due to the higher acceptance of level 1 alerts, which is probably related to the optimization strategies leading to more specific alerts. Alert acceptance based on administration rates was about twice as high as the alert acceptance based on prescription rates.

2578 | Incidence of ocular adverse events associated with mometasone implants among patients with nasal polyposis

Efe Eworuke[1], Emmanuel Ojo[2], Miya Paterniti[3], Emily C Welch[2] and Mayura Shinde[2]

[1]US Food and Drug Administration, Silver Spring, MD; [2]Harvard Pilgrim Health Care Institute, Boston, MA;[3]US Food and Drug Administration, Silver Spring, MD

Background: Long term use of oral or intranasal steroids has been previously linked to the development of cataracts (posterior subcapsular cataracts) and increased intraocular pressure. It remains unknown whether sinus mometasone implants carry similar risk, given the route of administration (endoscopically) and location of stent placements (nasal).

Objectives: To determine the incidence rates of diminished visual acuity, glaucoma, and cataracts among patients who had a single mometasone implant.

Methods: We conducted a retrospective cohort study using data from 01/2016-09/2018 in the IBM® MarketScan® Commercial and Medicare Supplemental Databases. We included patients, 18 years and older with a diagnosis of nasal polyposis (ICD-9: 471.x or ICD-10: J33.x) who had a procedure code and/or national drug code for insertion of mometasone 370μg implant. Patients with a diagnosis of diminished visual acuity, glaucoma, cataracts, or nasal septal perforation during the baseline period were excluded. We also excluded patients who received treatment for glaucoma during the baseline period and those with evidence of eye laser surgery, trabeculoplasty or cataract surgery. Follow-up began on the date of mometasone implant insertion for a maximum of one year or earliest of the following events: outcome of interest, loss of medical or drug coverage, study end date or death.

Results: We identified 957 patients with mometasone stent who met the study inclusion/exclusion criteria. The mean age of the cohort was 45.8 ± 13.2 years with 60% male. The majority of patients used oral (74.3%) and intranasal (42.7%) steroids before implant insertion. Only 2.9% had sinus surgery before implant insertion. The incidence of glaucoma, cataracts and diminished visual acuity was 23.4, 32.9 and 6.2 per 100,000 person-years, respectively.

Conclusions: Our study explores the risk of glaucoma, cataracts and diminished visual acuity following mometasone stent implants. Additional studies are needed to characterize the risk of these adverse events.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3693 | Long-term survival and healthcare utilization following deep brain stimulation for Parkinson's disease in Ontario, Canada

James A. G. Crispo[1,2,3], Melody Lam[4], Britney Le[4], Salimah Z. Shariff[4], Dominique R. Ansell[3,5], Melanie Squarzolo[3,5], Danielle Ouellette[3], Dylan P. Thibault[1], Connie Marras[6], Allison W. Willis[1] and Dallas Seitz[7]

[1]*University of Pennsylvania Perelman School of Medicine, Philadelphia, PA;* [2]*ICES North, Sudbury, ON, Canada;* [3]*Northern Ontario School of Medicine, Sudbury, ON, Canada;* [4]*ICES Western, London, ON, Canada;* [5]*Health Sciences North, Sudbury, ON, Canada;* [6]*Toronto Western Hospital, University of Toronto, Toronto, ON, Canada;* [7]*Queen's University, ICES-Queen's, Kingston, ON, Canada*

Background: Regional variations in the use of deep brain stimulation (DBS) surgery for Parkinson's disease (PD) may be attributed to long-term safety concerns. Presently, there are limited data on long-term outcomes following DBS surgery for PD in Ontario, Canada.

Objectives: The objectives of our study were (1) to compare the long-term survival of PD patients who received DBS surgery to that of matched controls and (2) to examine whether undergoing DBS surgery for PD was associated with differences in the use of publicly funded healthcare services.

Methods: Using administrative health data (Ontario, Canada), we retrospectively examined outcomes following DBS surgery within a cohort of individuals diagnosed with PD between 1997-2012 at age 40 years or older. Patients receiving DBS surgery were matched with up to 4 non-DBS controls by age, sex, PD diagnosis date, time with PD, and the logit of the propensity score (clinical and sociodemographic factors). Differences in survival between DBS and control groups were assessed using the log-rank test and marginal Cox proportional hazards regression. Cumulative incidence function curves and marginal subdistribution hazard models were used to assess the effects of DBS surgery on the probability of long-term care placement and the use of home care services. For all analyses, death was classified a competing risk.

Results: A total of 23,290 individuals with PD were included in our unmatched cohort. There were 811 patients (260 DBS recipients, 551 controls) included in our survival and long-term care placement analyses, while 798 patients (258 DBS recipients, 540 controls) were included in our home care analyses. Relative to controls, patients who underwent DBS surgery for PD did not experience a significant survival advantage (log-rank test p = 0.50; HR: 0.89, 95% CI: 0.65-1.22). However, patients who underwent DBS surgery prior to 65 years of age experienced a significant survival advantage compared to patients within the same age group who did not receive DBS (HR: 0.49, 95% CI: 0.28-0.84). Long-term care placement was similar between DBS and non-DBS groups (Gray's test p = 0.82; HR: 1.11, 95% CI: 0.75-1.65); however, patients who received DBS surgery were more likely to utilize home care services (Gray's test p < 0.01; HR: 1.59, 95% CI: 1.32-1.90).

Conclusions: Undergoing DBS surgery for PD may offer a survival advantage for patients who receive DBS at an earlier age. Future studies should examine the effects of DBS on survival in other populations with PD, and whether survival benefits may be attributed to effects on PD or comorbidities that may influence mortality.

3712 | The risk of myocardial infarction and venous thromboembolism after partial or total knee arthroplasty: A self-controlled case series

Danielle E. Robinson, Albert Prats-Uribe, Klara Berencsi, Victoria Y. Strauss and Daniel Prieto-Alhambra

NDORMS, University of Oxford, Oxford, United Kingdom

Background: Prior studies comparing patients undergoing knee replacement (KR) with non-KR controls have described a short-term increased risk of post-operative myocardial infarction (MI) and venous thromboembolism (VTE). Residual confounding could bias these findings. Despite seldom use in surgical epidemiology, self-controlled case series (SCCS) controls for time-fixed within-person confounding by design and can therefore be used to quantify any excess risk associated with knee replacement.

Objectives: To estimate the increase in risk of MI and VTE in the 3 months (91 days) after two types of KR: partial KR (PKR) and total KR (TKR).

Methods: Data from two UK databases (National Joint Registry and Hospital Episode Statistics) were linked to identify KR and outcomes. Adults (18+) undergoing KR who experienced a) MI and b) VTE within 1 year either side of first KR were identified for the SCCS cohorts. Six months wash-outs were required for a new outcome of the same type to be considered a new event. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated for up to 3 months post-surgery compared to the 6-12 months prior to and 3-12 month post-surgery together (reference period). A 6-month pre-exposure period was included prior to surgery date. Interactions with gender, ASA stage and TKR v PKR were assessed using a cut-off p-value <0.1. The assumptions of SCCS were assessed in sensitivity analyses: 1) assessing the risk for the first adverse event only, and 2) excluding patients who died within the 3 months post-KR.

Results: Of 354,494 patient undergoing KR, 6,947 had 7,207 MIs and 4,227 had 4,284 VTEs. Patients who had an MI were on average 73 years old, with 61% male. 64% were ASA 1 or 2 and 5% had a partial KR. Patients who had a VTE were on average 72 years old, with 43% male. 78% were ASA 1 or 2 and 3% had a partial KR. In the 3 months post KR, IRR were 1.22 (95% CI 1.15, 1.30) and 9.26 (8.68, 9.89) for MI and VTE respectively. Interactions were identified for gender and ASA stage with the pre-exposure period only. Patients undergoing PKR were not at increased risk of MI in the 3 months after surgery, IRR 0.74 (0.53, 1.02), and at a lower increased risk of VTE than patients undergoing TKR (5.51 [3.87, 7.84] vs 9.43 [8.82, 10.08]). The assumptions of SCCS held with little change in the no death and first event models.

Conclusions: Patients are at a 20% and 9-fold increased risk of MI and VTE respectively in the 3 months post KR surgery compared to the reference period. No strong interaction was seen with gender or ASA stage, but patients undergoing PKR were not at excess risk of MI and at lower risk of VTE.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3817 | Risk of mortality up to 90 days following uncemented vs cemented total hip arthroplasty for primary osteoarthritis

A Cohort Study Based on the Nordic Arthroplasty Register Association Data

Alma Pedersen[1], Aurelie Mailhac[1], Søren Overgaard[2], Anne Garland[3], Ove Furnes[4], Stein Atle Lie[5], Anne Marie Fenstad[4], Cecilia Rogmark[6], Johan N. Karrholm[7], Ola Rolfson[7], Jaason Haapakoski[8], Antti Eskelinen[9], Keijo T. Mäkelä[10] and Nils P. Hailer[11]
[1]Aarhus University Hospital, Aarhus, Denmark; [2]Odense University Hospital, Odense, Denmark; [3]Uppsala University, Uppsala, Sweden; [4]Haukeland University Hospital, Bergen, Norway; [5]University of Bergen, Bergen, Norway; [6]Skåne University Hospital, Malmo, Sweden; [7]Sahlgrenska University Hospital, Gothenburg, Sweden; [8]National Institute for Health and Welfare, Turku, Finland; [9]University of Tampere, Tampere, Finland; [10]Turku University Hospital, Turku, Finland; [11]Uppsala University, Uppsala, Sweden

Background: Although total hip arthroplasty (THA) is a successful procedure, 90-day mortality following THA is still about 1%. Several studies suggest that cemented THAs are associated with an increased risk of early mortality compared with uncemented THAs, due to the bone cement implantation syndrome and thromboembolism. Only few previous studies account for comorbidity as important confounder in their study design.

Objectives: We compared the mortality up to 90 days of uncemented vs cemented THA for primary osteoarthritis.

Methods: The study was based on the Nordic Arthroplasty Register Association data including all primary cemented and uncemented THA performed due to primary osteoarthritis in Norway, Finland, Sweden and Denmark from 2005 to 2013. We calculated the Charlson Comorbidity Index two years prior to THA based on data from the national patient registries. Outcome was 90-day mortality. Using Cox regression, we calculated adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) comparing uncemented with cemented THA, adjusting for, as well as stratifying on age, sex, comorbidity, nation and year of surgery.

Results: We included 80,034 uncemented and 108,572 cemented THA procedures. The uncemented THA cohort was younger, had a lower proportion of men, and lower prevalence of comorbidity than the cemented THA cohort. Within 14 and 90 days of follow-up, mortality was 0.09% and 0.26% in the uncemented cohort and 0.15% and 0.41% in the cemented cohort. The aHR for death within 14 and 90 days of THA was 1.10 (CI: 0.77-1.56) and 1.03 (CI: 0.84-1.27) for uncemented vs cemented THAs. No large differences in mortality were observed after stratification by sex, age, Charlson comorbidity index, and year of surgery. However, our data indicate a tendency toward lower aHR for death for uncemented vs cemented THA in patients with more comorbidities, and for procedures performed in recent years. In addition, among patients younger than 59 years, aHR for death was 0.29 (CI: 0.11-0.73) for uncemented vs cemented THAs. The absolute differences in mortality between the two fixation techniques were about 0.1%, overall and by stratification groups.

Conclusions: After adjustment for comorbidity as an important confounder, we observed no clinically relevant relative or absolute difference in 90-days mortality between uncemented and cemented THAs due to osteoarthritis in Nordic countries. Cemented THA can thus be considered as safe as uncemented THA in terms of early mortality.

3913 | Real-world use of oscillating positive expiratory pressure devices for chronic obstructive pulmonary disease or chronic bronchitis: A retrospective study of hospital claims linked to medical and prescription claims

Keiko Wada[1], Yi Wang[1], Jason Suggett[2], Jenny Tse[1], Vladimir Kushnarev[2], Dominic Coppolo[3] and Aimee Near[1]
[1]IQVIA, Falls Church, VA; [2]Trudell Medical International, London, ON, Canada; [3]Monaghan Medical Corporation, Plattsburgh, NY

Background: OPEP devices facilitate airway clearance and have been shown to reduce COPD exacerbations, when added to standard of care. Few studies have investigated OPEP device use in real-world hospital settings.

Objectives: To compare characteristics and treatment patterns of COPD and chronic bronchitis patients (pts) given an OPEP device in hospitals and assess disease-related 12-month readmission.

Methods: Hospital claims data (IQVIA Charge Detail Master, CDM) linked to medical and prescription claims (DxLRx) were used. Adult pts given the Aerobika (Trudell Medical International) or Acapella (Smiths Medical) OPEP device for COPD or chronic bronchitis in 9/2013-4/2018 (index) were grouped into 2 mutually exclusive cohorts. Pts had ≥1 CDM record in 12 months pre-index (baseline) and pharmacy/provider stability and patient eligibility (continuous enrollment proxy) in DxLRx in 12 months pre/post-index (follow-up). Pts with asthma pre-index or post-operative OPEP device use within 30 days pre-index were excluded. Measures were baseline patient characteristics before/after propensity score matching and follow-up treatments and disease-related 12-month readmissions in matched pts.

Results: Of 662 Aerobika and 4367 Acapella pts, the mean age was 72-73 years (p=0.17); 56% and 49%, respectively, were female (p<0.01). Most were insured by Medicare (74-73%), with the mean Charlson Comorbidity Index of 4 (all p<0.05). Geographic region of residence differed, with more Aerobika pts in the Midwest (56%) and Acapella pts in the South (52%; p<0.01). During baseline, 46-49% had maintenance medications; 68-72% used rescue inhalers (all p>0.05). 93% of Aerobika and 68% of Acapella pts used oxygen therapy (p<0.01). After 1:3 matching (619 Aerobika vs 1857 Acapella pts) baseline measures were well-balanced. During index hospital visit, 35-38% used maintenance medications (p=0.24). Fewer Aerobika pts used rescue inhalers (67% vs 77%); more Aerobika pts used oxygen therapy (93% vs 74%; all p<0.01). During follow-up, treatments were similar, but the readmission rate was lower for Aerobika pts (40% vs 45%; p=0.01).

Conclusions: Baseline demographics, except sex and region, and maintenance medication and rescue inhaler use were similar between Aerobika and Acapella users. During index visit, more Aerobika users received oxygen therapy, and more Acapella users received rescue

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

inhalers. In the subsequent 12 months with similar treatments, fewer Aerobika users experienced a readmission.

4083 | Risk of heart failure in patients undergoing arthroplasties of the hip

Jennifer Wood[1], Zhongyuan Wei[2], Hélène Hardy[3], Anna Wallace[1], Richard Beech[4] and Stephen Marcello[4]
[1]*Johnson & Johnson, New Brunswick, NJ;* [2]*Johnson & Johnson, New Brunswick, NJ;* [3]*Janssen Scientific Affairs, Titusville, NJ;* [4]*Johnson & Johnson, New Brunswick, NJ*

Background: Inconsistent findings have been reported in the literature for the risk of acute heart failure (aHF) following Metal-on-Metal (MoM) arthroplasties of the hip.
Objectives: To estimate the incidence and risk of aHF among patients undergoing MoM arthroplasties of the hip compared with those with alternative types of arthroplasties (non-MoM) or osteoarthritis without arthroplasty (OA).
Methods: This retrospective cohort study was conducted using the Medicare Standard Analytic Files which capture the majority of the United States (US) population age 65 or older. The datasets utilized included Medicare Part A and Part B claims. Included patients underwent total hip arthroplasty (THA) or had a diagnosis of OA without arthroplasty between October 1, 2005, and March 31, 2019. Three exposure groups were created based on International Classification of Disease Codes, 9th and 10th revisions: MoM, Non-MoM, and OA. Index date was defined (or assigned to OA) as THA procedure date. Identified patients were followed until a diagnosis of aHF, THA or THA revision, knee arthroplasty, end of enrollment, death, or end of the study, whichever occurred first. Censoring criteria including diagnosis of aHF and person-years (p-yrs) at risk for each patient was calculated from 30 days after index date. Descriptive statistics were used to describe the three exposure groups. Propensity score matching (PSM) was conducted and pre and post-PSM incidence rates (IR) and hazards ratios (HR) with 95% confidence intervals (95% CI) were calculated. HRs were adjusted for exposure, age, and Elixhauser score.
Results: There were 54,237, 392,285, and 2,042,507 patients identified in the MoM, Non-MoM, and OA groups, respectively. Post 1:1 PSM, there were 54,220 patients in each group of the MoM versus Non-MoM comparison and 54,121 in each group of the MoM versus OA comparison. The IR for aHF among the MoM patients was 26 per 1,000p-yrs; likewise the IRs were 22 and 25 per 1,000p-yrs for the Non-MoM patients, for pre and post PSM, respectively. The crude and adjusted HRs (95% CI) for aHF were 1.12 (1.09-1.15) and 1.04 (1.00-1.07) for MoM patients compared to Non-MoM patients. In the comparison of MoM and OA patients, the IR for aHF among the MoM patients remained 26 per 1,000p-yrs. Pre and post-PSM IRs for aHF were 39 and 34 per 1,000p-yrs for the OA patients, respectively. The crude HR (95%CI) was 0.67 (0.65-0.68) for MoM patients compared to OA patients, and the adjusted HR was 0.72 (0.69-0.74).
Conclusions: No clinically meaningful increased risk was observed among US patients 65 and older undergoing MoM arthroplasties compared to patients with Non-MoM arthroplasties or patients with OA.

4283 | Evaluating the use of social media as a recruitment strategy for women participating in mobile medical device research: Experiences and participant engagement

Pauline De Corte, Clare Barnett and Christoph Wenger
Center for Epidemiology and Health Research Berlin, Berlin, Germany

Background: Identifying engaged study participants remains a common challenge in research. Using social media as a research recruitment method is increasing and might serve as a useful tool for delivering study information to a broader target population. Due to the lack of specific regulatory/IRB guidances and policies, social media as recruitment method is still not common practice.
Objectives: To summarize experiences and identified challenges with social media as recruitment strategy for mobile medical device research.
Methods: We conducted a prospective, observational cohort study of 300 study participants using Facebook as the only recruitment method. Study participants were required to enter data daily into two mobile medical apps for a minimum of 3 months and a maximum of 6 months. Interested women who clicked on the Facebook advertisement were re-directed to a study specific website with detailed information on the study tasks. Women willing to participate had to complete an eligibility questionnaire via an Electronic Data Capture (EDC) system. Eligible women were then asked to register for a face-to-face (F2F) training and study on-boarding. During this training, every participant was requested to complete and sign informed consent. This approach was reviewed by the Berlin Ethics Committee.
Results: Over a period of one month, 7,500 unique clicks on the Facebook advertisement were registered. The eligibility questionnaire was completed by 1,500 (20.0%) women. Of those, 777 (51.8%) were eligible. Approximately 300 women aged between 18 and 40 participated in the F2F training and all signed informed consent. Almost half (48.8%) of enrolled participants were willing to participate for more than the minimum of 3 months.
Conclusions: Despite some identified challenges, e.g. data protection and optimizing targeted search, social media has shown to be a very powerful and targeted approach for this kind of research methodology.

4338 | Comparison of data collected via cardiac device registry versus electronic health records

Katherine Weiner[1], Joao Monteiro[1], Kara Southall[1], Andy Iverson[1], Jove Graham[2] and Edgar P Simard[1]
[1]*Medtronic, Minneapolis, MN;* [2]*Geisinger, Danville, PA*

Background: Traditional clinical study data collection requires substantial effort to manually review medical records and enter data into

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

a database. However, electronic health record (EHR) data collected during routine care may offer the opportunity for automated collection of standard data elements.

Objectives: To quantify how patient characteristics sourced directly from existing EHRs compare to those collected manually at a baseline study visit.

Methods: We examined baseline data elements including demographics (birth year, sex, ethnicity, race), physical exam (height, weight), and medical history (heart failure (HF), atrial fibrillation (AF), diabetes, cardiac ablation) from 319 Geisinger patients enrolled in an implantable cardiac device registry (2013-2018). Registry data were compared at the patient level with data extracted from EHR (Epic) per the PCORnet Common Data Model (CDM). Medical history was identified in the CDM based on pre-specified problem list and encounter codes. For categorical data, we measured congruence as the percent of patients having the same value from both sources (registry and CDM), and we assessed sensitivity considering the registry as truth. Empiric 95% confidence intervals (CIs) were estimated using 50,000 bootstrap samples. Differences in continuous values were also measured.

Results: Congruence between registry and CDM data was high for demographics: 98.7% (CI 97.5-99.7%) for sex, 99.1% (CI 97.8-100.0%) for ethnicity, and 99.7% (CI 99.1-100.0%) for race and year of birth. Ninety percent of CDM physical exam values were within 1.9 in (height, CI 1.3-2.0 in) and 8.3 lbs (weight, CI 7.6-10.5 lbs) of the patient's registry value. Congruence for medical history ranged from 85.6% (CI 81.5-89.3%) for HF to 93.4% (CI 90.6-95.9%) for AF. Sensitivity varied: 58.8% (CI 41.7-75.0%) for cardiac ablation, 90.3% (CI 85.7-94.4%) for HF, 95.0% (CI 91.4-98.1%) for AF, and 97.5% (CI 94.5-100.0%) for diabetes.

Conclusions: These results from one integrated healthcare system demonstrate that demographic and physical exam data collection may be automated from EHRs, potentially lessening clinical study data collection burden. However, moderate differences in physical exam data need further investigation. Varying sensitivity for medical history suggests that automated sourcing of such data may differ from the output of manual review depending on the condition of interest. Establishing procedure history (e.g. ablation) may be particularly challenging. Future work should evaluate additional data elements and determine if results are consistent across different provider EHR systems.

4385 | Characterizing medical device exposure in observational studies: Role of the unique device identifier (UDI)

Edgar Simard[1], Christina Mack[2], Shumin Zhang[3], Jackie Elkin[1] and Joseph Drozda[4]

[1]Medtronic, Minneapolis, MN; [2]IQVIA, Boston, MA; [3]Johnson & Johnson, Titusville, PA; [4]Mercy Health, Chesterfield, MO

Background: Observational studies of medical devices differ from drug studies for numerous reasons, with exposure classification as one of the most important. The ability to record and recoup exposure details for a specific device, and its components, implantation/explantation details, software versioning, and combination with drugs is critical to classifying patients so safety and effectiveness can be assessed.

Objectives: To describe the history, importance, challenges, and potential solutions allowing for Unique Device Identifier (UDI) inclusion in real world electronic health record data.

Methods: 78 CFR 58785 (2013) requires device manufacturers to include the UDI on their product labels and in some cases on the device itself and submit the UDI to the Global Unique Device Identification Database (GUDID). The UDI is a numeric or alphanumeric code that consists of two components: 1) Device Identifier (DI), a fixed portion that identifies the labeler and the version/model of a device via a Global Trade Items Number (GTIN), and 2) Production Identifier (PI), a conditional, variable portion that identifies one or more of the lot number, serial number, expiration or manufacture date, or other features.

Results: Device manufacturers are required to submit DIs to regulators and record them for inventory management once devices enter the healthcare system. A key challenge is that variability exists in how UDIs are recorded. Many UDIs are tracked electronically via inventory systems which are not integrated with documentation of clinical care, including electronic health record (eHR) platforms. Also, UDIs may be recorded in unstructured eHR fields, further complicating the quantification of UDIs in large databases. These and other gaps in the ability to know the unique combination of products received and utilized by a patient makes recalls and the interpretation of results for real-world effectiveness studies more challenging for devices. Barcode scanning at the point of care with eHR integration is one possible solution but requires the development of systems to facilitate this from eHR vendors and ways for this information to be captured by providers in clinical workflows without additional burden.

Conclusions: Recording of UDIs as part of routine care and leveraging a Total Product Life Cycle (TPLC) approach will enable end-to-end medical device assessment from premarket safety and effectiveness, manufacturing quality, and post-market surveillance. Authors will present case studies of how UDIs are present in RWD and may be used in observational studies.

4549 | Real-world performance of magnetically controlled growing rods in early onset scoliosis

Lukas G. Keil[1], Christina D. Mack[2,3], Alysa B. Nash[1], Joseph D. Stone[1], James O. Sanders[1] and Craig R. Louer[1]

[1]UNC School of Medicine, Chapel Hill, NC; [2]IQVIA, Durham, NC; [3]School of Public Health, UNC, Chapel Hill, NC

Background: Posterior spinal fusion (PSF) remains the workhorse of scoliosis surgery, but PSF in early onset scoliosis (EOS) prevents further spinal growth. Traditional growing rods (GRs) control deformity and allow growth but require repeated surgeries to lengthen. Magnetically controlled GRs (MCGRs) lengthened transcutaneously are

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

thought to reduce morbidity, complications, and iatrogenic deformity stiffness. Few studies have investigated real-world performance of MCGRs since approval in 2014.

Objectives: Characterize deformity, thoracic height, radiation exposure, and complications throughout MCGR treatment.

Methods: This retrospective cohort included EOS patients who underwent MCGR implantation at age ≥7 then definitive PSF. Notes and radiographs were reviewed. Primary outcomes were T1-12 height (surrogate of thoracic cavity size) and coronal deformity (Cobb angle) pre- and post-GR implantation, post-growth phase (GP), and post-PSF. Secondary outcomes were intended/actual lengthening achieved, radiation exposure, and complications. Descriptive statistics were used.

Results: Twelve patients with 15 GRs (9 single, 3 dual) met criteria with median age 10.0 years at implantation (IQR 2.8, range 7.2-13.8), median 19.6 cm T1-12 height (IQR 4.8), and median 70° Cobb angle (IQR 29). Median coronal deformity correction at GR implantation was 50% (IQR 15) with median 1.9 cm increase in T1-12 height (IQR 1.8). During GP (median 30, IQR 7 months) median intended lengthening was 2.0 cm (IQR 1.4, range 0.4-3.5) with median actual lengthening 1.7 cm (IQR 1.6, range 0.0-3.1). Patients underwent median 31 spine radiographs and 1 CT scan during GP. During GP T1-12 height changed by median 0.0 cm (IQR 2.5). Coronal deformity recurrence by 37% (IQR 19) during GP was not fully corrected at PSF for median net deformity correction pre-GR to post-PSF of 49% (IQR 25). Median increase in T1-12 height pre-GR to post-PSF was 4.0 cm (IQR 2.1), median 59% occurring at GR implantation (IQR 34) and 51% at PSF (IQR 40%). Ten device-related complications occurred: migration/failure of fixation (7), failure to lengthen at all (2), and spontaneous shortening (1).

Conclusions: MCGRs are promising but not a panacea. Median 4 cm of thoracic height was gained primarily at GR implantation and PSF, with deformity recurrence dominating GP. Iatrogenic stiffness and osteopenia prevented greater deformity correction at PSF (up to 80% in primary PSF cohorts). Complications were ubiquitous and radiation exposure extensive. Matched comparison to primary PSF will elucidate whether the additional surgery, radiation, and complications of MCGRs are warranted.

4679 | Incidence and risk factors of proximal junction failure after multi-level spinal fusion in an integrated network delivery care setting

Zhenna Huang[1], Katherine Corso[1], Deepak Krishnan[2], Aatheep Gurubaran[2], Chantal Holy[1] and John Pracyk[3]

[1]*Johnson & Johnson, New Brunswick, NJ;* [2]*Mu Sigma, Bangalore, India;* [3]*Johnson & Johnson, Raynham, MA*

Background: Proximal junction failure (PJF) is a serious post-operative complication of multi-level spinal surgery. PJF can lead to additional complications such as pain and reoperations, making it a costly complication. Furthermore, there are few cohort studies that evaluate PJF in non-academic hospital settings.

Objectives: This study aims to describe the incidence and risk factors of PJF in an integrated delivery network (IDN) of community hospitals.

Methods: Through data partnership with Mercy Technology Services, adult patients who underwent multi-level thoracic and/or lumbar spine fusion surgery were extracted from 2011-2018 Mercy electronic health records (EHR), which is one of the comprehensive real-world databases including preoperative and intraoperative information. Occurrence of PJF 24 months after fusion was collected from the EHR using natural language processing. Kaplan-Meier curves for the overall cohort and by spinal anatomy were generated. To evaluate risk factors for PJF, cox proportional hazard models were fitted with anatomy and patient characteristics as covariates.

Results: Of the 585 patients included for analysis, 45 (7.7%) experienced PJF within 24-months of the index fusion surgery. The incidence of PJF for patients who had thoracic or lumbar fusion was 5.5% (23 out of 414) versus 12.9% for thoracolumbar group (22 out of 171). Compared to patients without PJF (n=540, 92.3%), after covariate adjustment, significant risk factors for PJF were fusion surgeries spanning the thoracolumbar spine (adjusted Hazard Ratio (aHR), 2.35, 95% Confidence Interval (CI), 1.30-4.25; p: 0.005) and older age (aHR, 1.02, 95% CI, 0.998-1.05; p: 0.068). No significant association between higher BMI (aHR, 0.999, 95% CI, 0.991-1.01, p: 0.86), and osteoporosis (aHR, 1.29, 95% CI: 0.60-2.76, p: 0.51) were observed with PJF.

Conclusions: The observed 24-month incidence of PJF in an IDN setting is 7.7%. Spinal fusion surgeries spanning both the thoracic and lumbar regions were significantly associated with a higher incidence of PJF. Further investigations with a larger cohort size are needed to appropriately identify potential risk factors for PJF.

4716 | Country-specific preparation practices for the insertion of intrauterine devices: HCP-reported insertion procedures from the EURAS-LCS 12 study

Christine Hagemann, Anja Bauerfeind, Jens Lange and Klaas Heinemann

ZEG Berlin, Berlin, Germany

Background: Intrauterine contraceptive methods have a high contraceptive efficacy and are commonly used. However, the insertion procedure can be painful, and there are different procedures available to make the insertion less unpleasant, such as pain medication.

Objectives: To identify insertion related procedures reported in the "European Active Surveillance Study on LCS12" (EURAS-LCS12) among users of intrauterine devices in ten European countries (Austria, Czech Republic, Finland, France, Germany, UK, Poland, Spain, Italy, and Sweden).

Methods: Large, prospective, controlled, non-interventional, long-term cohort study with active surveillance of approximately 60,000 study participants in ten European countries. Women are enrolled by their HCP after the insertion. HCPs and participating women complete a baseline questionnaire including information on insertion related procedures and issues. Patients receive 5 follow-up

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

questionnaires within 3 years. All patient-reported outcomes of interest are validated with the treating physician.

Results: Until end of August 2019, 55,793 women were enrolled, thereof 5,988 (11%) Jaydess, 26,183 (47%) Mirena, 3,671 (7%) Kyleena and 18,840 (34%) copper-IUD users. Users of the smaller hormonal IUDs were considerably younger compared to Mirena and copper-IUD users; and 77% of Jaydess and 54% of Kyleena users were nulliparous compared to 15% of Mirena and 40% of copper-IUD users. Pharmacological preparation (e.g. prostaglandins, painkiller) were used in 48% of Jaydess, 53% of Kyleena, 26% of Mirena and 31% of copper-IUD users, however, large differences were observed in the different countries, ranging from 7% in UK to 67% in Austria. Prostaglandins were most frequently used in Austria (44%) and Germany (33%), and painkillers in Sweden (57%), Austria (38%) and Finland (30%). This is also related to parity: of nulliparous women, 20% received prostaglandins and 32% painkillers, compared with 9% prostaglandins and 13% painkiller used in parous women. Use of general anesthesia was low in all countries (1 to 4%), and local anesthesia was most frequently used in the UK (43%) and Austria (31%), and less often in the other countries: Czechia (1%), Spain (2%), Finland and Italy (3%), France (6%), Poland (7%), Germany (10%) and Sweden (11%).

Conclusions: In the EURAS-LCS12 study, differences regarding preparation of the insertion procedure were observed in the participating countries. They are not only related to age or parity, but also country-specific standard practices are relevant.

4732 | Risk Factors for aseptic loosening after primary total knee arthroplasty with cemented knee implants

Chantal E Holy[1], Juan Daccach[2], John Leopold[3], Bidusee Ray[4], Paul Coplan[1], Daniel Hoeffel[5] and John Wright[6]

[1]Johnson & Johnson, New Brunswick, NJ; [2]DePuy, Warsaw, IN; [3]DePuy, Warsaw, IN; [4]Mu Sigma, Bangalore, India; [5]DePuy, Warsaw, IN; [6]DePuy Synthes, Raynham, MA

Background: Aseptic loosening (AL) is a cause of failure of total knee replacement (TKR). Risk factors for AL are not well established.

Objectives: This study is designed to evaluate risk of AL in patients with cemented TKR. (Protocol registration on ENCePP: EUPAS31269).

Methods: A retrospective cohort study was conducted using the Optum PanTher Electronic Health Records database. The study period was from October 1st, 2015 (for ICD-10 availability) to most recent available. Patients > 21 yrs with elective cemented TKR (TKA = intervention - date of TKA is the "index") and ≥ 12 months of naïve period in the database with no knee procedures or diagnoses other than osteoarthritis were identified. Patients with bone cancer prior to index were excluded. Patients were followed up to last available data. The main outcome of interest was aseptic loosening, at any time after index and up to most recent available data or end of enrollment. Variables included surgeon and patient characteristics. Bivariate and adjusted cumulative incidence of AL, Kaplan-Meier and weighted Cox survival models and regressions to evaluate risk factors for AL were conducted.

Results: 123,947 patients were identified, 59.80% females, mean age 66.47 (standard deviation (SD): 9.44), 13.10% smokers, average body mass index: 33.18 (SD: 6.72); surgeons had an average 107.55 surgeries prior to index (SD: 105.17). Up to 3 years post-operative, 494 patients presented with AL (cumulative risk at 1, 2 and 3 years: 0.24%, 0.62% and 0.99%, respectively). Bivariate analyses indicated that AL patients were younger at index, and more likely to have a BMI ≥ 35. TKRs in the AL cohort were performed by surgeons with fewer counts of pre-index TKR surgeries than those from the non-AL cohort (average count of prior TKRs: 80.09 (SD: 85.48) in AL cohort vs 107.66 (SD; 105.23) in non-AL cohort, $p<0.001$). Logistic regression models further identified high BMI, low age and low surgeon volume, as well as other factors, as significant risk factors for AL.

Conclusions: The TKR experience of the surgeon in the twelve months prior to index, as well as patient factors such as age and BMI, were independently associated with AL risks.

4743 | Heterogeneity of patients treated with multi-planar software-assisted external fixation systems—Analyses of operative complications

Spence Reid[1], Chantal E Holy[2], Mollie Vanderkarr[3], Bidusee Ray[4], Abhishek S Chitnis[2] and Charisse Sparks[5]

[1]Penn State Health, Hershey, PA; [2]Johnson & Johnson, New Brunswick, NJ; [3]DePuy Synthes, West Chester, PA; [4]Mu Sigma, Bangalore, India; [5]DePuy Synthes, West Chester, PA

Background: Multi-planar ring fixation systems (MPRF) are medical devices used for deformity correction and bone repair. Risks and outcomes following MPRF application are not well documented.

Objectives: Understand risk factors for peri-operative complications following application of multi-planar ring fixation systems (MPRF).

Methods: This retrospective study used the Premier Hospital Billing Database to identify patients undergoing MPRF application between 2007 and 2018. Patients were grouped based on primary diagnostic categories: acquired or congenital deformity, fractures or sequela from prior fractures (deep infection, non-union, other), arthropathy, other. The Elixhauser comorbidity index, demographic and hospital variables and intraoperative (prior to discharge) complications were analyzed. Logistic regression models were developed to evaluate risk of intraoperative complications.

Results: 14,519 patients were included in the study. Bleeding was the most common peri-operative complications (12% of all patients), followed by dysrhythmia (7%) and infection (6%). There were significant differences in peri-operative complication rates between diagnostic categories: after adjusting for age, gender and Elixhauser comorbidity index, patients treated for congenital deformity were at significantly lower risk for all complications compared to patients treated for fractures or fracture sequelae. Adjusted odds ratios (OR) for complications in patients with fractures vs congenital deformity: for bleeding: 1.89 (95% confidence interval (CI): 1.39-2.63); for infection: 2.90 (95% CI: 1.73-5.35); for dysrhythmia: 12.96 (95%CI:

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4.16-78.26). Overall 57% patients were discharged home, with again significant difference based on diagnostic category (home discharge: pediatric deformity correction: 93%, adult deformity correction: 75%, fracture: 56%, deep infection: 30%).

Conclusions: There is significant heterogeneity in patient presentation within MPRF-treated patients. Research to understand outcomes from medical devices like MPRF require thorough understanding and segmentation of target populations.

4755 | Assessment of the risk and economic burden of surgical site infection following colorectal surgery using a US longitudinal database: Is there a role for innovative antimicrobial wound closure technology to reduce the risk of infection?

David J Leaper[1], Chantal E Holy[2], Maureen Spencer[3], Abhishek S Chitnis[2], Andrew Hogan[4], George Wright[4], Brian P.H. Chen[5] and Charles E Edmiston[6]

[1]University of Newcastle upon Tyne and Professor of Clinical Sciences, University of Huddersfield, United Kingdom; [2]Johnson & Johnson, New Brunswick, NJ; [3]Infection Prevention Consultants, Boston, MA; [4]Cornerstone Research Group, Burlington, ON, Canada; [5]Ethicon, Somerville, NJ; [6]Medical College of Wisconsin, Milwaukee, WI

Background: Colorectal surgical procedures place substantial burden on healthcare systems because of the high complication risk, especially surgical site infections.

Objectives: Determine the incidence and true cost of infections after colorectal surgery and potential economic impact of using antimicrobial wound closure to improve patient outcomes.

Methods: This was a retrospective observational cohort analysis and probabilistic cost analysis (perspective: US payer), using the IBM® MarketScan® Claims databases. A total of 107,665 patients undergoing colorectal surgery ("index") from 2014 to 2018 were identified. Revision and patients with infection at time of index were excluded. Rate of post-infection was identified between 3-180 days postoperatively. Logistic models were used to evaluate risk for infection and generalized linear models were developed to estimate 2018 inflation-adjusted payer cost of infection within 24 months post surgery. Potential cost avoidance from avoided infections using antimicrobial sutures were estimated from probabilistic decision-trees using Monte Carlo simulation.

Results: Post-operative infections were diagnosed in 23.9% of patients (4.0% superficial incisional (SS) and 19.9% deep incisional/organ-space (DIOS)). Risk factors for DIOS infections included obesity, and admission type (emergency vs elective) among others. After 12-months, payer costs associated with superficial incisional and deep incisional/organ-space infections averaged $36,196 (95% confidence interval (CI): $32,840-$39,691) and $77,043 (95%CI: $75,179-$78,941) for Commercial payers and $17,323 (95% CI: $12,805-$22,191) and $55,089 (95%CI: $52,340-$57,940) for Medicare, respectively. Use of antimicrobial suture wound closure for colorectal surgery was estimated to reduce mean payer costs by $1,435-$2,405 per patient compared with traditional wound closure.

Conclusions: Our study suggest overall savings from use of antimicrobial sutures as a component of a comprehensive evidence-based surgical care bundle for reducing infection risk.

4764 | Evaluation of the association between 30-day post-operative infection types and change in operation room time among patients who underwent spinal fusion procedures

Zhenna Huang[1], Katherine Corso[1], Chantal Holy[1] and John Pracyk[2]

[1]Johnson & Johnson, New Brunswick, NJ; [2]Johnson & Johnson, Raynham, MA

Background: Prior research suggests operation room time (ORT) is associated with increases in post-operative infections among patients undergoing spinal surgery. Fusion is a common surgery among patients who have spinal pathologies; however, there is little research on the association between types of post-operative infection and incremental changes in ORT among patients who underwent fusions.

Objectives: To investigate the association between infection types and operating room time among patients with spine fusion surgeries.

Methods: Through data partnership with Mercy Technology Services, adult patients who underwent multi-level spinal fusions were extracted from 2011-2018 Mercy electronic health records, which is one of the comprehensive real-world databases including preoperative and intraoperative information. Superficial, deep, general or no infection within 30 days of fusion were the outcome variables; if a patient had several infections, patient was assigned the highest level of infection (general organ system infection). To evaluate the association between infection outcome and 10-minute changes in ORT compared to patients without infection, multinomial logistic regression models, controlling for patient characteristics, were fitted.

Results: Among the 775 patients in this study, the incidence of 30-day superficial, deep, and general infection was 3.5% (n=27), 1.5% (n=12), and 10.6% (n=82), respectively. Of the overall cohort, mean age (standard deviation (SD)) of patients was 60.3 (14.7) years, 52.5% were female, mean (SD) Elixhauser score was 3.1 (2.3), mean (SD) body mass index was 30.6 (6.7) and mean (SD) ORT was 251.9 (101.1) minutes; differences in mean Elixhauser scores and ORTs by infection category were statistically significant. Among the cohort, with a 10-minute increase in ORT, the odds for superficial, deep, and general infection increased by 4.9% (adjusted Odds Ratio(aOR): 1.05, 95% Confidence Interval (CI), 1.02-1.08)), 4.6% (aOR, 1.05, 95% CI,1.00-1.10) and 3.1% (aOR, 1.01, 95% CI,1.00-1.05), respectively, compared to patients without infection.

Conclusions: This analysis suggests risk of superficial, deep, and general infections within 30 days following spinal fusion increases with a 10-minute increase in ORT. A larger sample size is needed to confirm the associations observed and develop recommendations on reducing ORT to potentially decrease these post-operative infection rates.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4770 | Evaluation of the association between 30-day post-operative infection and change in operation room time by spinal anatomy

Katherine Corso[1], Zhenna Huang[1], Chantal Holy[1] and John Prayck[2]
[1]*Johnson & Johnson, New Brunswick, NJ;* [2]*Johnson & Johnson, Raynham, MA*

Background: The association between operation room time (ORT) and post-operative infections among patients undergoing spinal fusion surgery has been evaluated, with higher risks for infection paralleling increases in ORT.
Objectives: This study sought to further understand the incidence of 30-day post-operative infections and incremental changes in ORT among patients who underwent thoracic or lumbar versus thoracolumbar fusion.
Methods: Through data partnership with Mercy Technology Services, adult patients who underwent multi-level fusions of the thoracic and/or lumbar anatomic regions of the spine were extracted from 2011-2018 Mercy electronic health records. To evaluate incidence of 30-day post-operative infections by 10-minute changes in ORT, a binary logistic regression model was fitted. To evaluate the association between any infection type and 10-minute changes in ORT, a multinomial logistic regression model was fitted; the outcome variable was presence of superficial, deep, general or no infection. Models included an interaction term between ORT + anatomic region and covariates included patient characteristics.
Results: A total of 556 patients were evaluated. The incidence of any 30-day infection was 16.8% (66/392) and 17.7% (29/164) for patients that had thoracic or lumbar fusions and concurrent thoracic and lumbar (thoracolumbar) fusions, respectively. When compared to patients without infection (no infection-infection), the mean difference in ORT was -35.1 (94.5) minutes, thoracic or lumbar, and -43.1 (110.0) minutes, thoracolumbar. With a 10-minute increase in ORT, the odds for any infection increased similarly for both anatomy categories: thoracic or lumbar, 3.0% (adjusted Odds ratio (aOR), 1.03, 95% Confidence Interval (CI), 1.00-1.06), and thoracolumbar, 2.5% (aOR, 1.02, 95% CI, 0.99-1.06) compared to no infection. The odds differed by infection type and anatomy; with a 10-minute increase in ORT, the odds for thoracic or lumbar were 5.2%, 2.1%, and 2.0%, and for thoracolumbar, 1.2%, 4.8%, and 2.5%, superficial, deep and general, respectively, compared to no infection.
Conclusions: The risk of post-operative infection type and increase in ORT may differ due to regional spinal anatomy. Evaluation of these trends with a larger sample size is needed.

4802 | Issues during the insertion of intrauterine devices reported in the EURAS-LCS12 study

Christine Hagemann, Anja Bauerfeind, Jens Lange and Klaas Heinemann
ZEG Berlin, Berlin, Germany

Background: Intrauterine contraceptive methods, such as Mirena and CU-IUDs, have a high contraceptive efficacy and are commonly used. However, the insertion procedure can be difficult, and several issues like multiple insertion attempts, failed insertions or relevant complications can occur.
Objectives: To identify insertion related issues reported in the "European Active Surveillance Study on LCS12" (EURAS-LCS12) among users of intrauterine devices in ten European countries (Austria, Czech Republic, Finland, France, Germany, UK, Poland, Spain, Italy, and Sweden).
Methods: Large, prospective, controlled, non-interventional, long-term cohort study with active surveillance of approximately 60,000 study participants in ten European countries. Women are enrolled by their HCP after the insertion. HCPs and participating women complete a baseline questionnaire including information on insertion related procedures and issues. Patients receive up to 5 follow-up questionnaires within 3 years. All patient-reported outcomes of interest are validated with the treating physician.
Results: Until end of August 2019, 55,793 women were enrolled by the prescribing HCPs, thereof 5,988 (11%) Jaydess, 26,183 (47%) Mirena, 3,671 (7%) Kyleena and 18,840 (34%) CU-IUD users. Users of the smaller hormonal IUDs were considerably younger (Jaydess users: mean age 26,9 years, Kyleena mean age 27.8 y) than Mirena (35.9 y) and CU-IUD (30.5 y) users. The insertion failed in 78 (0,1%) of 55,793 women, thereof 5 cases with uterine perforation during the insertion attempt. In women with anatomical abnormalities of the cervix or uterus, the proportion of failed insertion was 5-fold higher than in women without specific anatomical findings. Multiple insertion attempts were necessary in 496 (0.9%) of women, thereof 220 (44.4%) due to anatomical problems such as tight cervix canal or uterine fibroids. Relevant complications were reported in 348 (0.3%) of 55,793 women. Most commonly were circulatory problems (202 of 348 women, 58%) or pelvic pains (52 of 348 women, 15%). There were no differences observed between the cohorts except for a slightly higher proportion of multiple insertion attempts in CU-IUD users (1.3% vs. 0.6% in Jaydess, 0.2% in Kyleena and 0.7% in Mirena users).
Conclusions: In the EURAS-LCS12 study, the number of insertion related issues is low in all cohorts, and no substantial differences were observed between the cohorts so far. Women with anatomical findings such as tight cervical canal were more likely to face problems such as multiple insertion attempts or failed insertion.

4898 | Changes in healthcare use and cost associated with catheter ablation among patients with paroxysmal and persistent atrial fibrillation

Daniel Friedman[1], Michael Field[2], Motiur Rahman[3], Laura Goldstein[4], Qun Sha[5], Sidharth M[6], Rahul Khanna[3] and Jonathan Piccini[7]
[1]*Yale New Haven Hospital, New Haven, CT;* [2]*Medical University of South Carolina, Charleston, SC;* [3]*Johnson and Johnson, Medical Device Epidemiology, New Brunswick, NJ;* [4]*Johnson and Johnson, Franchise Health Economics and Market Access, Irvine, CA;* [5]*Biosense Webster, Irvine, CA;* [6]*MuSigma, Bengaluru, India;* [7]*Duke University Medical Center, Durham, NC*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Catheter ablation [CA] effectively reduces atrial fibrillation [AF] symptoms and improves health-related quality of life. Little is known regarding the impact of CA on changes in healthcare use and cost among patients with paroxysmal AF [pAF] and persistent AF [PsAF].

Objectives: To compare 6-month pre- and 18-month post-ablation healthcare use and costs among pAF and PsAF patients.

Methods: Patients (aged ≥ 19 years) undergoing CA for pAF or PsAF between April 2016 - December 2017 were identified using the Optum Clinformatics database. Patients needed to be continuously enrolled throughout the 6-month pre- and 18-month post-ablation period. Study outcomes included inpatient admissions, emergency department [ED] visits, outpatient visits, office visits, inpatient length of stay [LOS], cardioversion, and healthcare costs. Mean changes in per-patient-per-month (PPPM) healthcare utilization and costs were compared for the 6-month period before and 18-month period after CA using Wilcoxon signed-rank test.

Results: A total of 2,608 pAF and 1,754 PsAF patients were included. Among both pAF and PsAF patients, a significant reduction in mean AF-related inpatient admission (pAF: -82%, PsAF: -81%), AF-related ED visits (pAF: -83%, PsAF: -77%), AF-related outpatient visits (pAF: -49%, PsAF: -52%), AF-related office visits (pAF: -39%, PsAF: -40%), cardioversion (pAF: -71%, PsAF: -76%), and AF-related inpatient LOS (pAF: -83%, PsAF: -83%) PPPM were observed in the 18-month post- vs. 6-month pre-CA period (p<.0001). A significant decrease in mean (reported as mean and standard deviation [SD]) AF-related inpatient admission cost (-65% for pAF: $223 [±$1,454] vs. $78 [±$531]; -63% for PsAF: $304 [±$1,087] vs. $112 [±$727]), AF-related ED visit cost (-86% for pAF: $99 [±$341] vs. $14 [±$86]; -80% for PsAF: $79 [±$327] vs. $16 [±$112]), AF-related office visit cost (-51% for pAF: $84 [±$91] vs. $41 [±$42]; -52% for PsAF: $91 [±$94] vs. $44 [±$41]), and cardioversion cost (-76% for pAF: $207 [±$1,473] vs. $51 [±$265]; -74% for PsAF: $410 [±$1,013] vs. $106 [±$360]) PPPM were also observed (p<.0001). The mean AF-management cost decreased by 35% PPPM for pAF patients ($828 [±$1,695] vs. $540 [±$1,229], p<.0001) and 34% for PsAF patients ($1,061 [±$1,647] vs. $701 [±$1,414], p<.0001). The average AF-related outpatient cost increased by 4% PPPM among pAF patients ($353 [±$743] vs. $366 [±$1,038] p<.0001).

Conclusions: In comparison to the pre-CA period, a significant decrease in healthcare utilization and cost were observed in the post-CA period for patients with pAF and PsAF.

4903 | A machine learning approach for sentiment analysis of breast implant recipients using social media data

Safa Saifudeen[1], Shimonee Shah[1], Paul Coplan[2], Jennifer Wood[2], Subhadeep Debnath[1] and Shubham Gupta[1]

[1]*Mu Sigma, Bangalore, India;* [2]*Johnson & Johnson, New Brunswick, NJ*

Background: Reports from breast implant recipients about a diverse set of symptoms has led to the use of the term "breast implant illness" (BII), though no precise clinical definition has been established. Understanding the complaints reported by breast implant recipients can help to clarify a BII clinical definition.

Objectives: To classify positive and negative sentiments among breast implant recipients from posts on social media forums using Machine Learning (ML).

Methods: User posts between 2010-2019 from three breast implant patient support websites were scraped using the Python library *Selenium*. Text was preprocessed to remove duplicates, special characters, html tags, emojis, extra white spaces and stop words. Subsequently, posts were tokenized, where the text was split into different words to eliminate unnecessary details. Lemmatization was performed, which is a word normalization technique that takes the inflected form of words and returns the base word. For instance, 'replacement' becomes 'replace'. During feature generation, term frequency - inverse document frequency (tf-idf) was used to convert the posts into vectors. Tf-idf is a numeric statistic that describes the importance of each word in the post. Classification of data into positive, negative and neutral posts was done using five supervised ML techniques - Logistic regression, Random Forest, XG Boost, support vector machines, and Naïve Bayesian - and results were compared. To create the training dataset for the classification model, 3360 posts were manually tagged as positive, negative or neutral based on the sentiment expressed - with 838 positive, 748 negative and 1774 neutral posts. The tagged posts were randomly split into training and testing datasets in an 80:20 ratio. SMOTE (Synthetic Minority Oversampling Technique) was used to oversample the data and reduce the effects of class imbalance.

Results: With the entire corpus of 331,868 user posts, the model classified 89% of posts as neutral, 7% as negative and 4% as positive. Random forest with SMOTE gave the best results with an accuracy of 63%, precision of 62% and recall of 63%.

Conclusions: Patient experience can be ascertained by social media analysis and classified into positive, negative, and neutral sentiments by using ML techniques.

4926 | Long-term healthcare use and cost comparison pre-and-post ablation treatment among patients with heart failure and atrial fibrillation

Michael E. Field[1], Motiur Rahman[2], Laura Goldstein[3], Sonia Maccioni[4], Abhishek Srivastava[5], Rahul Khanna[2], Jonathan P. Piccini[6] and Daniel J. Friedman[7]

[1]*Medical University of South Carolina, Charleston, SC;* [2]*Johnson and Johnson, New Brunswick, NJ;* [3]*Johnson and Johnson, Irvine, CA;* [4]*Johnson and Johnson, Irvine, CA;* [5]*MuSigma, Bangalore, India;* [6]*Duke University Medical Center, Durham, NC;* [7]*Yale School of Medicine, New Haven, CT*

Background: Recent studies have demonstrated catheter ablation (CA) to be an effective treatment for patients with atrial fibrillation (AF) and heart failure (HF). However, little is known regarding long-term healthcare utilization and cost differential before and after CA among patients with AF-HF.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To compare one-year pre- and three-year post-ablation healthcare utilization and costs among patients with AF-HF.

Methods: Patients (aged ≥ 19 years) undergoing CA with a primary or secondary diagnosis of AF and HF between 2012-2016 were identified using the Optum Clinformatics Datamart, Extended - Date of Death database. Patients needed to be continuously enrolled throughout the one-year pre- and three-year post-ablation period. Patients with a prior history of AF-ablation, surgical ablation, valvular procedure, or left atrial appendage occlusion were excluded. Outcomes of interest included inpatient admission, emergency department (ED), outpatient, and office visits, inpatient length of stay (LOS), cardioversion, and costs. Mean changes in the healthcare utilization and costs per-patient-per-month (PPPM) were compared for the one-year period before and three-year period after CA using Wilcoxon signed-rank test.

Results: A total of 378 patients met the study criteria. A 78% reduction in mean AF-related inpatient admission, a 68% reduction in mean AF-related ED visit, a 39% reduction in mean AF-related outpatient visit, a 27% reduction in mean AF-related office visit, a 67% reduction in cardioversion, and a 76% reduction in AF-related inpatient LOS PPPM were observed in the three-year post- vs one-year pre-CA period (p<.0001). Mean changes in the HF-related outcomes did not emerge significant. A 62% decrease in mean AF-related inpatient admission cost (reported as mean and standard deviation) ($374 [± $926] vs. $142 [±$811], p<.0001), 73% decrease in mean AF-related ED visit cost ($61 [±$395] vs. $16 [±$93], p=0.009), 37% decrease in mean AF-related office visit cost ($57 [±$53] vs. $36 [±$35], p<.0001), and 74% decrease in mean cost for cardioversion ($319 [± $919] vs. $84 [±$326], p<.0001) PPPM were observed. The mean AF-management cost decreased by 36% ($850 [±$1,160] vs. $546 [± $1,210], p<.0001) PPPM.

Conclusions: A significant reduction in PPPM healthcare utilization and cost was observed among AF-HF patients in the three-year post-ablation period versus one-year pre-ablation period.

4981 | A methodology to characterize breast implant illness using social media

Shimonee Shah[1], Paul Coplan[2], Safa Saifudeen[1], Jennifer Wood[2], Subhadeep Debnath[1] and Shubham Gupta[1]

[1]*Mu Sigma, Bangalore, India;* [2]*Johnson & Johnson, New Brunswick, NJ*

Background: Reports about a diverse set of symptoms from breast implants recipients has led to use of the term "breast implant illness" (BII), though no precise clinical definition has been established. Social media data was leveraged to capture experiences of women with breast implants and to characterize BII.

Objectives: To develop a methodology to identify symptoms and illnesses reported by women with breast implants using social media data.

Methods: User comments between 2010-2019 from three breast implant patient support websites were scraped using the Python library *Selenium*. Text was cleaned to remove duplicates, special characters, html tags, emojis, extra white spaces and stop words and processed via lemmatization, tokenization and N-gram. Posts included ≥1 complaint. Additionally, an exhaustive list of complications of interest was compiled, using FDA listed complications for breast implants, and the list of suspected symptoms for BII. Synonyms along with results from fuzzy matching (used to identify spelling variations, eg. exhausted' matched to 'exhaustion') and text-to-vector (used to identify semantically similar words - eg. 'muscle sore' matched to 'muscle pain') were added to the list. Counts of complications from the posts were obtained by performing direct text matching against the list of complications, using string functions in R. Validation was performed using cTAKES (Clinical Text Analysis and Knowledge Extraction System), a Natural Language Processing (NLP) system. It combines rule-based and machine learning techniques to extract clinical information from unstructured or free-text. It uses UMLS (Unified Medical Language System), which is a comprehensive thesaurus and ontology of biomedical concepts.

Results: Results obtained via the applied methodology i.e. text preprocessing and text processing by fuzzy matching, word to vector, and direct text matching were found to be similar to the results obtained by validation via cTAKES. Thus, complications expressed by breast implant recipients in social media posts were identified and were found to differ by implant type (saline, silicone), surface type (smooth, textured), and surgery (reconstruction, augmentation).

Conclusions: Using NLP techniques, BII can be characterized by type, surface of implants, and surgery, from social media posts. Results could be improved by expanding preprocessing steps to reduce noise in the input data. Additional systems can be used to further validate the results. Insights generated from unstructured data present on social media platforms can prove valuable towards providing direction to further RWE studies.

4984 | Evaluation of two severity scores and three comorbidity measures in an administrative claims database to predict outcomes after treatment with intramedullary nailing in femur fractures

Abhishek Chitnis[1], Bidusee Ray[2], Mollie Vanderkarr[3] and Chantal Holy[1]

[1]*Johnson and Johnson, New Brunswick, NJ;* [2]*Mu Sigma, Bangalore, India;* [3]*DePuy Synthes, West Chester, PA*

Background: The New Injury Severity Score (NISS) and Injury Severity Score (ISS) have been used as indicators for anatomical injury severity in trauma patients. The three commonly used comorbidity measures, Charlson Comorbidity Index (CCI), Elixhauser Comorbidity Index (ECI) and Functional Comorbidity Index (ECI) have been used as risk-adjustment tools in quality and safety data. The value of these tools to predict outcomes following fracture repair with intramedullary nails is unknown.

Objectives: To evaluate the discriminative ability of the NISS, ISS, CCI, ECI and FCI for predicting extended length of stay (LOS),

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

infections, and reoperations after intramedullary nailing (IMN) for treatment of femur fractures.

Methods: Patients who underwent IMN for femur fractures between 2007-2018 in IBM® Marketscan® Commercial claims database were identified. The outcomes of interest were (1) extended LOS, defined as >5days of stay for index IMN admission (2) infection within three months post-index, (3) reoperations within three months post-index. For each outcome, six multivariable logistic regression models were constructed. One base model that included age, gender and fracture type and five models with the variables in the base model plus one of the following: NISS, ISS, CCI, ECI or FCI. The predictive performance of the NISS, ISS, CCI, ECI and FCI was assessed using the area under the receiver operating characteristic curve (AUC) derived from these regression models.

Results: A total of 13,828 patients were identified. The mean (SD) age of the cohort was 40.1 (18.8) years and most were males (57.1%). For extended LOS, AUC of base, NISS, ISS, CCI, ECI and FCI models were 0.603 (95% CI, 0.593-0.611), 0.669 (95% CI, 0.660-0.678), 0.712 (95% CI, 0.704-0.721), 0.622 (95% CI, 0.612-0.631), 0.626 (95% CI, 0.617-0.636) and 0.617 (95% CI, 0.608-0.627), respectively. For infection, AUC of base, NISS, ISS, CCI, ECI and FCI models were 0.625 (95% CI, 0.594-0.656), 0.627 (95% CI, 0.597-0.658), 0.650 (95% CI, 0.620-0.680), 0.639 (95% CI, 0.608-0.670), 0.654 (95% CI, 0.622-0.686) and 0.658 (95% CI, 0.627-0.690), respectively. Finally, for reoperations, AUC of base, NISS, ISS, CCI, ECI and FCI models were 0.619 (95% CI, 0.600-0.639), 0.625 (95% CI, 0.605-0.645), 0.638 (95% CI, 0.618-0.658), 0.619 (95% CI, 0.599-0.639), 0.620 (95% CI, 0.600-0.639) and 0.619 (95% CI, 0.600-0.639), respectively.

Conclusions: Of the five severity and comorbidity measures, the ISS had greatest discriminative ability for extended LOS and reoperations.

4993 | Discriminative ability of two severity scores and three comorbidity measures in an administrative claims database to predict outcomes after treatment with intramedullary nailing in tibial fractures

Abhishek Chitnis[1], Bidusee Ray[2], Mollie Vanderkarr[3] and Chantal Holy[1]

[1]Johnson and Johnson, New Brunswick, NJ; [2]Mu Sigma, Bangalore, India; [3]DePuy Synthes, West Chester, PA

Background: The New Injury Severity Score (NISS) and Injury Severity Score (ISS) have been used as indicators for anatomical injury severity in trauma patients. Three commonly used comorbidity measures, Charlson Comorbidity Index (CCI), Elixhauser Comorbidity Index (ECI) and Functional Comorbidity Index (ECI) have been used as risk-adjustment tools in quality and safety data. The value of these tools to predict outcomes following fracture repair with intramedullary nails is unknown.

Objectives: To evaluate the discriminative ability of the NISS, ISS, CCI, ECI and FCI for predicting extended length of stay (LOS), infections, and reoperations after intramedullary nailing (IMN) for treatment of tibial fractures.

Methods: Patients who underwent IMN for tibial fractures between 2007-2018 in IBM® Marketscan® Commercial claims database were identified. The outcomes of interest were (1) extended LOS defined as >5days of stay for index IMN admission (2) infection within three months post-index, (3) reoperations within three months post-index. For each outcome, six multivariable logistic regression models were constructed. One base model that included age, gender and fracture type and five models with the variables in the base model plus one of the following: NISS, ISS, CCI, ECI and FCI. The predictive performance of the NISS, ISS, CCI, ECI or FCI was assessed using the area under the receiver operating characteristic curve (AUC) derived from these regression models.

Results: A total of 10,232 patients (mean age =37.8 years and males=62.2%) were identified For extended LOS, AUC of base, NISS, ISS, CCI, ECI and FCI models were 0.641 (95% Confidence Interval [CI], 0.627-0.654), 0.729 (95% CI, 0.717-0.741), 0.750 (95% CI, 0.738-0.763), 0.650 (95% CI, 0.637-0.663), 0.656 (95% CI, 0.643-0.669) and 0.653 (95% CI, 0.640-0.662), respectively. For infection, AUC of base, NISS, ISS, CCI, ECI and FCI models were 0.649 (95% CI, 0.622-0.676), 0.648 (95% CI, 0.621-0.675), 0.654 (95% CI, 0.627-0.680), 0.667 (95% CI, 0.641-0.693), 0.675 (95% CI, 0.649-0.700) and 0.669 (95% CI, 0.643-0.695), respectively. Finally, for reoperations, AUC of base, NISS, ISS, CCI, ECI and FCI models were 0.578 (95% CI, 0.555-0.602), 0.583 (95% CI, 0.559-0.606), 0.594 (95% CI, 0.570-0.618), 0.585 (95% CI, 0.562-0.609), 0.583 (95% CI, 0.559-0.606) and 0.585 (95% CI, 0.562-0.608), respectively.

Conclusions: Of the five severity and comorbidity measures, the ISS models had greatest discriminative ability for extended LOS and reoperations.

5011 | Comparison of discriminative ability of two severity scores and three comorbidity measures in an administrative claims database to predict outcomes after treatment with intramedullary nailing in humerus fractures

Abhishek Chitnis[1], Bidusee Ray[2], Mollie Vanderkarr[3] and Chantal Holy[1]

[1]Johnson and Johnson, New Brunswick, NJ; [2]Mu Sigma, Bangalore, India; [3]DePuy Synthes, West Chester, PA

Background: The New Injury Severity Score (NISS) and Injury Severity Score (ISS) have been used as indicators for anatomical injury severity in trauma patients. Three commonly used comorbidity measures, Charlson Comorbidity Index (CCI), Elixhauser Comorbidity Index (ECI) and Functional Comorbidity Index (ECI) have been used as risk-adjustment tools in quality and safety data. The value of these tools to predict outcomes following fracture repair with intramedullary nails is unknown.

Objectives: To evaluate the discriminative ability of the NISS, ISS, CCI, ECI and FCI for predicting extended length of stay (LOS) and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

reoperations after intramedullary nailing (IMN) for treatment of humerus fractures.

Methods: Patients who underwent IMN for humerus fractures between 2007-2018 in IBM® Marketscan® Commercial claims database were identified. The outcomes of interest were (1) extended LOS defined as >5days of stay for index IMN admission (2) reoperations within three months post-index. For each outcome, six multivariable logistic regression models were constructed. One base model that included age, gender and fracture type and five models with the variables in the base model plus one of the following: NISS, ISS, CCI, ECI or FCI. The predictive performance of the NISS, ISS, CCI, ECI and FCI was assessed using the area under the receiver operating characteristic curve (AUC) derived from these regression models.

Results: A total of 921 patients underwent treatment with IMN for humerus fractures. The mean (SD) age of the cohort was 45.4 (17.5) years and most were females (57.2%). For extended LOS, AUC of base, NISS, ISS, CCI, ECI and FCI models were 0.611 (95% CI, 0.567-0.654), 0.736 (95% CI, 0.695-0.777), 0.788 (95% CI, 0.750-0.825), 0.678 (95% CI, 0.638-0.718), 0.642 (95% CI, 0.600-0.684) and 0.631 (95% CI, 0.588-0.674), respectively. For reoperations, AUC of base, NISS, ISS, CCI, ECI and FCI models were 0.578 (95% CI, 0.505-0.652), 0.597 (95% CI, 0.526-0.668), 0.585 (95% CI, 0.513-0.657), 0.585 (95% CI, 0.514-0.657), 0.583 (95% CI, 0.512-0.655) and 0.603 (95% CI, 0.533-0.674), respectively.

Conclusions: Of the five severity and comorbidity measures, ISS for extended LOS and FCI for reoperations had greatest discriminative ability for IMN in humerus fractures. All AUC <0.8 suggests only including demographic and severity or comorbidity measures are not enough to distinguish those with and without outcome in this population.

5022 | Reoperations and risk factors after intramedullary nail fixation of tibial fractures

Abhishek Chitnis[1], Mollie Vanderkarr[2], Bidusee Ray[3], Chantal Holy[1], Suzanne Hughson[2] and Michael Blauth[4]

[1]Johnson and Johnson, New Brunswick, NJ; [2]DePuy Synthes, West Chester, PA; [3]Mu sigma, Bangalore, India; [4]DePuy Synthes, Zuchwil, Switzerland

Background: Intramedullary nailing (IMN) is a widely used method for treating tibial fractures. Reoperations after IMN surgical procedures are associated with a significant healthcare burden.

Objectives: This study evaluated the frequency of reoperation within one-year of initial intramedullary nail fixation for patients with tibial fractures and assessed the risk factors associated with reoperations.

Methods: This retrospective cohort study used patient-level data from the IBM® Marketscan® Commercial database. All patients between 18-64 years who underwent fixation with an IMN for a tibial fracture between 2007-2018 were included. Reoperations were defined as presence of a second tibial surgery with known and unknown laterality within one-year of initial intramedullary fixation. Reoperations associated with non-union were also reported. The Multivariable Cox proportional hazards model was used to evaluate the factors associated with reoperations.

Results: A total of 6,082 patients that underwent IMN for tibial fractures were included in the analysis. The mean age (standard deviation) of the cohort was 37.6 (15.4) years with 37.9% female. Thirty-four point four percent of patients had a functional comorbidity score ≥1. A second tibial surgery within one year after the IMN procedure was performed in 1,463 (24.1%) patients of which 449 (7.4%) patients had records for ipsilateral reoperations and 337 (5.5%) had reoperations associated with non-union. The most common conditions for reoperations were removal of implant, complications with the implant, pain, non-union and infection. The significant risk factors associated with reoperations were age (odds ratio, OR [95% confidence interval, 95% CI], 1.21 [1.07-1.38] for age 31 to 45 years vs 18 to 30 years), region (OR [95% CI], 0.83 [0.72-0.96] for North Central vs West; OR [95% CI], 0.71 [0.60-0.84] for Northeast vs West; OR [95% CI], 0.75 [0.66-0.85] for South vs West), functional comorbidity index (OR [95% CI], 1.10 [1.03-1.17]), injury severity score (OR [95% CI], 1.20 [1.00-1.44] for 9-16 vs 1-8; OR [95% CI], 1.56 [1.27-1.91] for 17-75 vs 1-8), metastatic cancer (OR [95% CI], 2.30 [1.14-4.65]), and open fractures (OR [95% CI], 1.27 [1.07-1.51]) (All P<0.05).

Conclusions: A high proportion of patients (24%) required a second tibial surgery after initial fixation with an IMN. The significant risk factors for reoperations included age, region, comorbidity and severity scores along with certain clinical factors. Novel tibial nailing systems that would reduce the need for reoperation are warranted.

5039 | New injury severity score: Does it independently predict the treatment with intramedullary nailing in tibial fractures?

Abhishek Chitnis[1], Mollie Vanderkarr[2], Bidusee Ray[3], Chantal Holy[1], Zhenna Huang[1] and Charisse Sparks[2]

[1]Johnson and Johnson, New Brunswick, NJ; [2]DePuy Synthes, West Chester, PA; [3]Mu Sigma, Bangalore, India

Background: Intramedullary nailing (IMN) is a widely used method for treating tibial fractures. New injury severity score (NISS), a measure of trauma severity, has been used to predict mortality.

Objectives: This study evaluated NISS as an independent predictor for treatment with an intramedullary fixation in tibial fractures.

Methods: This retrospective cohort study used patient-level data from the IBM® Marketscan® Commercial database. All patients between 18-64 years with tibial fractures between 2007-2018 who either underwent fixation with an IMN or did not receive any surgical procedure within three-months of tibial fracture were included. Mean (standard deviation, SD) NISS for the patients with and without IMN was reported. NISS was then categorized into three groups for easier clinical decision making based on the frequency distribution. A multivariable logistic regression was developed to evaluate categories of NISS as independent predictors for treatment with an IMN surgery controlling for demographic and clinical factors.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: A total of 20,997 patients that underwent fixation with an IMN for tibial fractures were identified. The mean (standard deviation, SD) age of the cohort was 38.8 (17.3) years with 41.8% female and 39.2% with Elixhauser score >0. Mean (SD) NISS was 14.9 (7.2) for IMN group, while it was 11.6 (8.9) for no surgery group. As the NISS score increased the mean hospital length of stay (LOS) was longer. For the NISS groups 1-8 and 9-16, the LOS was 4.9 days while for 17-75 group, the LOS was 8.2 days. Adjusted logistic model (c-statistic-0.90) showed that the patients in higher NISS group have statistically significantly higher odds (odds ratio, OR [95% confidence interval, 95% CI], 1.82 [1.65-2.01] for 9-16 vs 1-8; OR [95% CI], 1.21 [1.05-1.39] for 17-75 vs 1-8, all P<0.05) for treatment with an intramedullary fixation as compared with lowest NISS group. Other significant factors included age (OR [95% CI], 1.02 [1.02-1.03]), open fractures (OR [95% CI], 3.35 [2.95-3.79]), shaft fractures (OR [95% CI], 33.62 [30.21-37.43]) and lower end fractures of tibia (OR [95% CI], 3.10 [2.65-3.63]).

Conclusions: This study found that NISS is an independent predictor for treatment with an intramedullary fixation in tibial fractures.

5052 | Is a superficial infection an independent predictor for a later deep incisional infection in total knee arthroplasty?

Abhishek Chitnis[1], Deepak Krishnan[2], Chantal Holy[1] and John Wright[3]

[1]Johnson and Johnson, New Brunswick, NB; [2]Mu Sigma, Bangalore, India; [3]DePuy Synthes, Raynham, MA

Background: Superficial and mostly deep incisional infections after primary total knee arthroplasty (TKA) are associated with significant burden on hospital and the health care system. Risk of deep incisional infection is associated with multiple comorbid conditions and socio-economic factors.

Objectives: This study evaluated superficial infection as an independent risk factor to predict a later deep incisional infection in TKA.

Methods: This retrospective cohort study used the electronic health records (EHR) from the Optum Pan-Therapeutic database (2007-2018) to identify TKA patients. The EHR data were available for a geographically diverse population of 80 million patients from more than 700 hospitals and 7,000 clinics. The main independent variable was a record for superficial infection (yes/no) within six-months post-TKA. The superficial infection was required to precede deep incisional infection to be included. The dependent variable was presence of a deep incisional infection (yes/no) within 12-months post-TKA. A multivariable logistic regression was developed to evaluate superficial infection as an independent predictor for a later deep incisional infection controlling for demographic and clinical factors.

Results: A total of 238,773 patients with primary TKA were identified. Mean (standard deviation, SD) age of the cohort was 66.6 (10.4) years, 62.8% were females and 88.9% patients were Caucasian. Mean (SD) Charlson Comorbidity Index (CCI) was 1.2 (1.6). Over the 12-months post-TKA, 2.5% patients developed deep incision infection and the median time to infection was 53 days. Adjusted model showed that the patients with superficial infection have statistically significantly higher odds (odds ratio [95% Confidence Interval], 5.00 [4.46-5.60], P<0.0001) of developing deep incisional infection as compared to those without superficial infection. Other significant factors included age, gender, race, CCI, insurance type, body mass index.

Conclusions: This study found that superficial infection is an independent predictor of deep incisional infection in TKA; patients with superficial infection have five times higher odds of developing a deep incisional infection than those without.

5065 | Overall cancer risk from exposure to cobalt alloys in orthopedic implants or cobalt in occupational settings: A systematic review and meta-analysis of published epidemiologic studies

Shumin Zhang[1], Chantal E. Holy[1], Gary Eichenbaum[1], Laura E. Perkins[2], Laurence B. Katz[3], Jason R. Brown[4], Luca Orlandini[5], Gion Fessel[5], Behrooz Nasseri-Aghbosh[6], Natalie S. Egnot[7], Meijia Zhou[1], Richard Beech[1], Stephen R. Marcello[1] and Paul M. Coplan[1]

[1]Johnson & Johnson, New Brunswick, NJ; [2]Abbott Vascular, Santa Clara, CA; [3]LifeScan, Malvern, PA; [4]Medtronic, Minneapolis, MN; [5]Smith +Nephew, Baar, Switzerland; [6]Stryker, Elstree, United Kingdom; [7]Cardno ChemRisk, Pittsburgh, PA

Background: The European Chemicals Agency announced at the end of 2019 that it will adopt the up-classification of cobalt metal as a Category 1B hazard, based primarily on two inhalation carcinogenicity studies in rats and mice with metallic cobalt. The assessment did not evaluate the hazard or risk of cancer from exposure to cobalt alloys in medical devices, which have different properties than metallic cobalt, and it was not a thorough systematic epidemiologic cancer hazard/risk assessment of cobalt alloys in medical devices.

Objectives: To perform a systematic review and meta-analysis of published epidemiologic studies evaluating the association between overall cancer risk and exposure to orthopedic implants containing cobalt alloys or cobalt particulates from occupational settings. These study types were chosen as they represent possible long-term and high-level exposure routes.

Methods: A search of the literature published up to December 2019 with primary data was performed in PUBMED and by checking references in relevant publications. Two researchers reviewed relevant papers identified, extracted data, and graded the quality. Study-specific estimates (including standardized incidence ratio, standardized mortality ratio, or other ratios) were pooled using random effects models. A total of 20 implant studies and 10 occupational cohort studies, which consisted of approximately 1 million patients, were included in overall and/or subgroup analyses.

Results: The summary estimate for overall cancer was 1.00 (95% confidence interval, 0.96-1.04) in the meta-analysis that included all study types. The results were similar in analyses stratified by data sources (registry, database, or occupational cohort), comparator types (national vs regional general population, or metal-on-metal [MoM] vs

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

non-MoM implants), cancer outcome types (incidence or mortality), the average follow-up duration, and the measure of study precision.

Conclusions: Meta-analysis of peer-reviewed epidemiologic publications found no association between cobalt exposure through orthopedic implants or from occupational settings and overall cancer risk. This includes an analysis of studies directly comparing MoM vs non-MoM implants. These findings suggest that cobalt alloys in medical devices are not associated with overall cancer risk in humans.

5067 | Medical devices-induced harm in Peruvian patients

Yesenia Rodríguez, Elisa Gálvez and Gisela Pecho
Institute of Health Technology Assessment and Research (IETSI) ESSALUD, Lima, Peru

Background: Medical Devices use is expanding in Latin America and a strong post-marketing monitoring regulation is needed. According to the Pharmacovigilance and Technovigilance System of EsSalud, an Adverse Incident (AIMD) is defined, from a clinical perspective, as the harm possible related to the use of a medical device. Problems of device malfunction is included in the definition of AIMD.

Objectives: To characterize medical devices-induce harm in patients of Security Social of Peru

Methods: Reports of Adverse Incidents related to medical devices (AIMD) during the period January 2018 until December 2019 were retrieved from the Technovigilance DataBase of EsSalud. We performed a retrospective and descriptive analysis of AIMD reports. Characteristics of patients (age and gender), medical devices (type, risk class, country of manufacture) and characteristics of AIMD (severity and causality assessment) were analyzed

Results: 203 AIMD were identified, involving adults (79%), infants (17.7%) and adolescents (n=2.9%). Thirty-eight medical devices were found to be related to AIDM. Colostomy bag was the most reported (22%) followed by Closed-*circuit endotracheal* suctioning (12%) and Chromic catgut suture (10%). Regarding the risk class, the most involved were Class 2 (medium risk) medical device. There were 50 cases of AIMD related to Class 4 (high risk) medical device being the biological aortic valve prosthesis one the most reported in this group (29%). Medical devices manufactured in Peru were the most reported (30%) followed by those from China (20.1%) and from India (12.3%). The vast majority of AIMD were moderate (58.1%) and only 7.4% of the AIMD were serious. Thrombocytopenia and death were the most frequent serious AIMD. Almost 60% of AIMD was device malfunction.

Conclusions: Low quality of medical devices assessed in this study was considered the main cause of AIMD. Since there is an increasing number of medical devices that do not undergone clinical trials to be authorized, strong regulatory and clinical strategies focused on medical devices vigilance must be implemented. Reporting AIMD is essential to prevent harm at the earliest possible timepoint.

5103 | Using social media to characterize adverse events: A case study of breast implant illness

Paul Coplan[1], Safa Saifudeen[2], Shimonee Shah[2], Jennifer Wood[1], Subhadeep Debnath[2], Jesse Berlin[1] and Shubham Gupta[2]
[1]*Johnson & Johnson, New Brunswick, NJ;* [2]*Mu Sigma, Bangalore, India*

Background: Reports from recipients of breast implants about a diverse set of symptoms has led to the use of the term "breast implant illness" (BII), though no precise clinical definition of a symptom complex has been established. Breast implant types differ in implant surface (textured, smooth) and content (saline, silicone).

Objectives: Using social media analysis, to qualitatively characterize patients' experience of complications with breast implants to assist in defining BII, and to evaluate if complaints differs by implant type.

Methods: Posts were identified from 3 websites for breast implant patient support between 2010-2019. Using natural language processing (NLP), the posts were searched for symptoms from FDA's list of suspected BII symptoms, such as redness, skin rash, fatigue and any other mentioned complications. Posts were stratified by saline smooth, saline textured, silicone smooth, and silicone textured implant. Posts included ≥1 complaint.

Results: There were 5,470 posts mentioning silicone, of which 240 contained 'smooth' and 199 contained 'textured', and 2,518 mentioning saline implants, of which 137 contained 'smooth' and 39 contained 'textured'. Redness/Bruising/Skin Rash was the most common complaint for smooth implants (silicone smooth 29%, silicone textured 16%, saline smooth 18%, saline textured 21%). Wrinkling/Rippling was the most common complaint for textured implants (silicone smooth 13%, silicone textured 25%, saline smooth 15%, saline textured 36%), and more common for textured than smooth. The 3rd and 4th most common complaints were more common for smooth than textured: inflammation/irritation (silicone smooth 13%, silicone textured 8%, saline smooth 11%, saline textured 5%) and capsular contracture (silicone smooth 7%, silicone textured 5%, saline smooth 8%, saline textured 3%). Rupture was more common for saline than silicone (silicone smooth 5%, silicone textured 8%, saline smooth 10%, saline textured 13%). Complaints thought to be common in BII, eg, brain fog, trouble concentrating and not thinking clearly were infrequent (<1%).

Conclusions: In this social media analysis using NLP, wrinkling/rippling appeared more common for textured than smooth implants, while inflammation/irritation and capsular contraction appeared more common for smooth than textured implants. However, multiple factors other than implant may influence differences. Social media analysis may be useful to understand patients' experience and qualitatively characterize complex complaints.

5130 | Comorbidities and complications associated with hernia repair using surgical mesh in the United States

Qiheng Zhou[1], Christina DeFilippo Mack[2], Deb Casso[3] and Susan A. Oliveria[4]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]IQVIA, Cambridge, MA; [2]IQVIA, Durham, NC; [3]IQVIA, Seattle, WA; [4]IQVIA, New York, NY

Background: Hernia has a high rate of recurrence, and surgeons often use surgical mesh during the hernia repair process to reduce the rate of recurrence. Since the 1980s, there has been an increase in mesh-based hernia repair, although complications have been reported.
Objectives: To compare risk of complications and hernia recurrence for patients who underwent laparoscopic hernia repair with surgical mesh compared to those with open hernia repair with surgical mesh.
Methods: Using PharMetrics Plus, a U.S. commercial claims database, we identified patients who received either laparoscopic or open repair surgery with hernia mesh implantation between 2007-2018. Baseline demographics and clinical characteristics are described by surgery type; risk of surgical site infections, pain conditions, other complication and hernia recurrence is compared between device recipients with laparoscopic vs. open repair surgeries.
Results: A total of 217,289 and 120,097 patients were identified in the laparoscopic and open hernia mesh cohort, respectively. The number of laparoscopic patients increased from 4,087 in 2007 to 23,437 in 2018 while the open patients had a downward trend with 12,712 in 2008 and 6,803 in 2018. The laparoscopic cohort was 62.1% inguinal hernia and 74.6% male, compared to 16.1% inguinal hernia and 50% male for open repair, with slightly younger patients (55 vs. 58 years of age). The open cohort had a higher risk (1.5%) of surgical site infections within 7 days after the surgery compared to laparoscopic (0.2%). Pain conditions within 1 year after surgery were also more common in the open cohort (abdominal pain: 31.6%, pain in joint: 19.4%, chest pain: 13.4%, and pain in limb: 13.3%) than laparoscopic cohort (23.3%, 16.8%, 9.5%, and 9.9%, respectively). Within 1 year after surgery, 19.8% of open and 5.3% of laparoscopic patients experienced hernia recurrence. Compared to laparoscopic patients, open patients were slightly more likely to have prior physical and mental health conditions within 1 year before surgery, including diabetes (20.0% vs 11.8%), hypertension or hyperlipidemia (60.6% vs 51.0%), and depression (16.1% vs 11.7%).
Conclusions: Patients undergoing open hernia repair with surgical mesh are more likely to experience post surgery conditions and hernia recurrence compared to laparoscopic repair with mesh. Further research to examine risks by hernia type and by device implanted will be a key next step in understanding implications of surgical approach.

Methods in pharmacoepidemiology -> Analytical methods - e.g., marginal structural models, instrumental variables, sensitivity analyses

2448 | Applying sufficient-cause principle to estimate risks of adverse events in the general indicated patient population should a new drug is used

Chuntao Wu, Lin Li and Juhaeri Juhaeri
Sanofi, Bridgewater, NJ

Background: In drug development, it is of interest to assess the risk of an adverse event (AE) in the general indicated patient population using the data from clinical development. Suppose that in the randomized placebo-controlled clinical trials of Drug A, the incidence proportions of an AE of interest are IP(1) in the treatment arm and IP(0) in the placebo arm, and IP(1) is greater than IP(0). We denote the background incidence proportion of the AE of interest in the general indicated patients as IP(b0). The incidence ratio (IR=IP(1)/IP(0)) and incidence difference (ID=IP(1) - IP(0)) based on the data in the clinical trials are commonly used to estimate the incidence proportion of the AE of interest in the general indicated patients if Drug A is used as IP(b1)=IP(b0)*IR and IP(b1)=IP(b0) + ID, respectively. These two approaches usually yield different results, which cause confusion.
Objectives: Using the sufficient-cause principle, we propose a new approach to estimate the risk of an AE in the general indicated patients should a new drug is used.
Methods: In clinical trial data, we define IP(0) as the proportion of patients with sufficient causes resulting in AE of interest, absent of drug A. Thus, 1 - IP(0) is the proportion of patients without any sufficient causes for the AE, i.e., free of event. We define ID/(1 - IP(0)) as the additional sufficient-cause completion rate when Drug A is used, and denote it as CR (completion rate). Suppose Drug A yields the same additional sufficient-cause completion rate in the general indicated patients, the estimated incidence proportion of the AE when Drug A is used in the general indicated patients is calculated as IP(b0) + CR * (1 - IP(b0)), in which IP(b0) is the proportion of patients with sufficient causes for the AE in the background, without drug A; and 1 - IP(b0) is the proportion of patients without any sufficient causes for the AE.
Results: In a hypothetical example of clinical trial, IP(1) and IP(0) of an AE are 0.3 and 0.1, and the background incidence proportion in the general indicated patients is IP(b0) = 0.25. Using IR (0.3/0.1=3) and ID (0.3-0.1=0.2), the expected incidence proportions in the indicated patients using drug A are estimated as 0.75 (0.25 * 3) and 0.45 (0.25 +0.2), respectively. Using our approach, the estimated incidence proportion is calculated as 0.25 + [0.2/(1-0.1)]* (1-0.25)=0.42.
Conclusions: The proposed approach avoids conflicting results from applying IR and ID, and the estimated incidence proportion is bounded between 0 and 1. This approach can be expanded to incidence rate measures and to that a study drug reduces the risk of an AE.

2506 | A weighting method to remove bias from within-subject exposure dependency in case-crossover studies

Kiyoshi Kubota[1], Lan Kelly[2], Tsugumichi Sato[3], Nicole Pratt[2], Libby Roughead[2] and Takuhiro Yamaguchi[4]
[1]*NPO Drug Safety Research Unit Japan, Tokyo, Japan;* [2]*Quality Use of Medicines Pharmacy Research Centre, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia;* [3]*Department of Pharmacy, Tokyo University of Science, Chiba, Japan;* [4]*Division of Biostatistics, Tohoku University Graduate School of Medicine, Miyagi, Japan*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: The case-crossover design with more than one control period may be biased from within-subject exposure dependency and/or time trends when analyzed by standard conditional logistic regression.

Objectives: We propose a weighting method to remove bias from within-subject exposure dependency, with or without a time trend, by extending the method of Vines and Farrington in 2001.

Methods: We modified Greenland's formula for case-crossover likelihood by weighting the exposure probability in the case period. This probability is estimated from cases when no time trend exists but from cases and time-controls if a time trend exists. The method was applied to real-world data from Japan and Australia. The Japanese study used claims data of corporate type health insurance plans. We selected 311 cases prescribed celecoxib who had peripheral edema (defined by new use of furosemide) and 1,555 time controls during 84, 168, and 336 day time windows. The Australian study used the Australian Department of Veterans' Affairs administrative claims database. We re-analyzed case-control data on psychoactive medicines and hip fracture (Pharmacoepidemiol Drug Saf 2015; 24:576-82). We selected 1,316 cases prescribed selective serotonin reuptake inhibitors with hip fracture and 3,948 time-controls during a 180-day time window. Time windows were divided into 2 to 336 periods in the Japanese study and 2 to 180 periods in the Australian study. The data were analyzed by standard conditional logistic regression and our proposed weighting method, with and without time-controls.

Results: The odds ratio (OR) estimated by the usual case-control design was 2.26 (95% confidence interval: 1.75-2.92) in the Japanese study and 1.32 (1.15-1.53) in the Australian study. After adjusting for time trends, standard conditional logistic regression in the case-crossover study overestimated the OR and bias increased with longer time windows. The ORs were overestimated as 4.74 (3.34-6.71) and 7.16 (5.27-9.74) with and without time-controls, respectively, with 1 day periods and a 336 day time window in the Japanese study. The ORs were overestimated as 1.75 (1.46-2.11) and 2.02 (1.71-2.37) with and without time-controls, respectively, with 1 day periods and a 180 day time window in the Australian study. Our proposed weighting method produced an OR close to the case-control OR which was stable when the exposure period or time window varied (1.88 to 2.40 Japan; 1.29 to 1.35 Australia).

Conclusions: Using our method, case-crossover studies can be used for pharmacoepidemiology studies when exposure periods are autocorrelated or time trends exist.

2516 | Two-stage G-computation: Estimating effects of treatment policies from observational data when treatment information is missing

Tiffany L. Breger, Jessie K. Edwards, Stephen R. Cole, Daniel Westreich, Brian W. Pence, Michele Jonsson Funk and Adaora A. Adimora

University of North Carolina, Chapel Hill, NC

Background: Linkages of data sources is a common approach to constructing a cohort in pharmacoepidemiologic studies. However, analyses are often restricted to the subset of individuals with linked records (i.e., complete case analysis), which can lead to substantial bias.

Objectives: We propose new two-stage g-computation estimators that leverage valuable covariate information in unlinked records, and we use simulation to illustrate bias variance tradeoffs for existing and newly proposed estimators.

Methods: In a simulation study, we evaluated our developed two-stage inverse-probability weighted g-computation and exposure imputation g-computation estimators. We considered a hypothetical scenario in which the research goal was to estimate the effect of a policy to shorten the duration of initial opioid prescription to <7 days on 12-month risk of emergency room visit among an HIV+ cohort. Prescription duration was only observed in a subset with linked records. To evaluate estimators, we simulated a cohort of 1623 HIV+ individuals motivated by the Women's Interagency HIV Study, and varied the percentage of the cohort with linked opioid data. Risk differences were estimated using two-stage estimators as well as the naïve g-computation estimator fit to complete cases. Bias, standard error (SE), root mean squared error (RMSE), and 95% confidence limit (CL) coverage were estimated from 10,000 simulation experiments.

Results: The true 12-month risk of emergency room visit was set at 20% under a practice in which the full (linked and unlinked) cohort received short duration prescriptions initially, and 31% under the natural course in which only 40% received short duration prescriptions (RD: -11.1%). In our primary example in which 30% of the cohort had linked opioid information, the risk difference was -3.7% when estimated with the complete case approach (bias: 7.4; SE: 2.3; RMSE: 7.8; 95% CL coverage: 0.09), -10.6% when using inverse-probability weighted g-computation (bias: 0.6, SE: 3.4; RMSE: 4.7; 95% CL coverage: 0.94) and -10.6% when using exposure imputation g-computation (bias: 0.5; SE: 3.3; RMSE: 4.5; 95% CL coverage: 0.94). Two-stage approaches leveraging unlinked records were less biased than the naïve g-computation estimator across all scenarios in which complete data ranged from 10-90%.

Conclusions: Increasing access to fragmented, real-world observational data provides more opportunities to evaluate optimal treatment policies. While missing data threaten validity and precision, our developed two-stage g-computation approaches can overcome these challenges.

2581 | Covariate missingness, complete case analysis, and transportability, oh my!

Michael Webster-Clark and Jessie K. Edwards

University of North Carolina, Chapel Hill, NC

Background: Interest in transporting study results to external target populations is increasing. While work has addressed differing distributions of effect measure modifiers (EMM), little attention has been paid to missing EMM data. The appropriateness of complete case analysis

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

may depend on whether missingness is completely at random (MCAR), at random with respect to observed covariates (MAR), or not at random with respect to EMM value (MNAR).

Objectives: We sought to identify cases when complete case analysis would induce bias in estimates by adding known missingness to real trial and target population data.

Methods: We assessed performance of inverse odds of sampling weighting to estimate effects of dabigatran vs warfarin on stroke in real-world patients when data on EMM were missing. Specifically, we reweighted Randomized Evaluation of Long-Term Anticoagulation trial participants to resemble new users of oral anticoagulant therapy (specifically, warfarin new users) in a random sample of US Medicare patients. We then estimated intention-to-treat hazard ratios in the weighted trial. Next, we added missingness to trial or target populations in history of transient ischemic attack (TIA), an EMM, and re-estimated treatment effects. Missingness was a logit-linear function of age and past warfarin use (if MAR) and TIA (if MNAR), evaluated in 21 scenarios with differing model coefficients. We report the medians (confidence limits: 2.5th, 97.5th) of 1000 bootstraps.

Results: We used data from 15,132 trial participants over age 65 and 74,891 warfarin initiators in Medicare. We estimated a hazard ratio (HR) of 0.656 (95% confidence interval [CI] of 0.41, 1.08 and confidence limit ratio [CLR] of 2.65) after reweighting the trial data to resemble Medicare warfarin initiators. Complete case analysis in the presence of trial MCAR, MAR, and MNAR resulted in estimates with substantially increased variance (largest CLR of 4.55) but minimal bias (most biased HR = 0.635) compared to our full data estimate, even with strong associations between covariates and missingness. Complete case analysis in the presence of MAR and MNAR covariate data in Medicare with the same coefficients for missingness appeared capable of adding more bias (most biased HR=0.709) but less variance (largest CLR: 2.81).

Conclusions: When transporting estimates from randomized trials to external populations, using trial complete cases may be acceptable if the study population is large even if covariate data is MAR or MNAR. Taking complete cases in the target population, however, may add some bias if data is MAR or MNAR because the distribution of EMM can differ from the full target.

2609 | Using multiple random index dates for each patient improves precision of prescription durations estimated with the reverse waiting time distribution

Katrine Bødkergaard Nielsen[1], Randi Marie Selmer[2], Jesper Hallas[3], Lars Jøran Kjerpeseth[2], Anton Pottegård[3], Eva Skovlund[2] and Henrik Støvring[1]

[1]*Aarhus University, Aarhus, Denmark*; [2]*Norwegian Institute of Public Health, Oslo, Norway*; [3]*University of Southern Denmark, Odense, Denmark*

Background: Prescription durations can be estimated using the reverse Waiting Time Distribution (rWTD) as the time within which 80% of the current users have redeemed a new prescription. When there is seasonal variation in redemption rates, rWTD estimates vary with the chosen index date, which can be mitigated by using individual random index dates. However, using a single index date for each patient is statistically inefficient.

Objectives: Using more than one random index date for each patient to efficiently utilize the information in the data and hence improve the precision of the estimates.

Methods: First, we select a one-year sample window supplemented with a preceding period of equal length. Second, for each patient we uniformly sample multiple random index dates within the sample window and identify the last prescription, if any, within one year prior to the index date. Based on time from the last prescription to the index date, prescription durations are estimated using the rWTD with robust variance estimation to account for the non-independence of observations from the same patient. We conducted a simulation study with log-normal distributed prescription durations both with and without seasonal variation in redemption rates. We generated 1,000 datasets such that on average 5,000 patients had prescriptions each year, of whom 25% ended treatment. We analyzed the simulated datasets with the rWTD (log-normal) after sampling 1, 5, 10 or 20 random index dates for each patient and estimated the relative bias and coverage probability of nominal 95% confidence intervals. We finally applied the method to Danish data on warfarin redemptions from 2013-2015.

Results: In the simulation study without seasonal variation, the relative bias was negligible (-0.41 to -0.20%) whether sampling 1 or 5 times. The coverage probability was slightly lower when sampling 5 times (89.0 to 93.9%) as compared to 1 (92.4 to 93.6%). When durations varied seasonally, bias was higher whether sampling 1 or 5 times (-0.73 to 6.71%). Consequently, the coverage probability was lower and decreased with the number of sampled index dates. Patterns continued with more random index dates (10 and 20). The estimated durations of warfarin prescriptions in Denmark were 93.4 (91.8; 95.0) and 93.8 (92.9; 94.8) days with 1 and 5 index dates, respectively.

Conclusions: Precision improves with the number of random index dates, but it does not reduce bias due to misspecification, e.g. with seasonal variation in redemption rates. Given misspecification, the improved precision lowered coverage probability.

2628 | Estimating vaccine effects: A comparison of causal methods

Alexander Breskin[1], Anne M Butler[2], John Sahrmann[2] and M. Alan Brookhart[1,3]

[1]*NoviSci, Durham, NC*; [2]*Washington University in St Louis, St Louis, MO*; [3]*Duke University, Durham, NC*

Background: Estimating the effects of vaccine schedules on important health outcomes remains a challenge due to missing or delayed vaccine administration. Modern causal inference methods that account for informative non-adherence may be useful in such settings, but

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

each method requires different statistical assumptions which may impact performance. For instance, inverse probability weighting (IPW) requires properly specified weighting models. Augmented inverse probability weighting (AIPW) takes both outcome and weighting models as inputs and is consistent if at least one of the input models is correctly specified, a property known as double robustness.

Objectives: Using IPW and AIPW estimators, we compared the 2-year risk of acute gastroenteritis (AGE) - related emergency department (ED) visits between infants who received 0 versus 3 doses of the 3-dose RotaTeq® rotavirus vaccine (RV).

Methods: Using the IBM MarketScan® Commercial database (2007-2015), we identified 1433925 infants who received a diphtheria-tetanus-acellular pertussis (DTaP) vaccine between 38 and 92 days of age. Follow-up began on the date of the first DTaP dose and continued for a maximum of 720 days. The data were setup so that there were two copies of each infant record. In the first copy, representing no vaccine, infants were censored on the date of rotavirus vaccine receipt. In the second copy, representing full adherence to the 3-dose RV schedule, infants were censored on the date of nonadherence to the 3-dose RV schedule. Within each group, Cox proportional hazard models were fit to estimate risk of protocol nonadherence and AGE-related ED visits conditional on patient-, provider-, and insurance plan-level covariates. The fitted models were used to construct weights and outcome predictions for the IPW and AIPW estimators.

Results: Using IPW, the 2-year risks of AGE-related ED visits with no vaccine was 4.46%. With the fully adherent 3-dose RV schedule, the risk was 3.29%, for a risk difference of -1.17% (95% CI: -1.34%, -1.01%). Using AIPW, the risks were 5.01% and 3.51% for no vaccine and the fully adherent schedule, respectively, for a risk difference of -1.50% (95% CI: -1.67%, -1.34%).

Conclusions: Using both IPW and AIPW, we found that adherence to the 3-dose rotavirus vaccine schedule prevented AGE-related ED visits, though the AIPW estimate was larger in magnitude than the IPW estimate. Notably, the AIPW double robustness property came with no loss of precision. Given the improved robustness with no precision loss, AIPW may be preferred for estimating the effects of vaccine schedules, or more generally any treatments or protocols that require adherence over time.

2673 | Differential cancer screening during follow-up as a source of bias in pharmacoepidemiology

Sophie E Mayer[1], Jessie K Edwards[1], Jesper Hallas[2], Jennifer L Lund[1] and Til Stürmer[1]

[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC;* [2]*University of Southern Denmark, Odense, Denmark*

Background: Certain medications are associated with receipt of cancer screening through health-seeking behavior, comorbidity, and healthcare access and quality. In these settings, screening after the start of follow-up acts as an intermediate to cancer detection and may result in the appearance of non-causal relationships between medication use and cancer risk.

Objectives: Evaluate the impact of screening during follow-up in pharmacoepidemiologic studies of cancer risk using simulation.

Methods: We simulated 200 cohorts of 100,000 women in which "high healthcare access" impacted both treatment initiation and screening; true disease risk was independent of treatment and healthcare access (odds ratios [ORs]: 1.0). Disease detection within 5 years of drug initiation was affected by true disease status and ever-receipt of screening, with screening conferring a higher probability of cancer detection than through clinical surfacing (85 vs. 40%). For the purposes of this study, we assumed 100% screening specificity, and varied the associations between healthcare access and treatment or screening (ORs: 1.0, 2.5, 10.0). We also varied the marginal screening prevalence in the population between 10, 25, 50, 75, and 90%. We calculated observed 5-year risks and risk ratios (RRs) based on detected cases only, and computed mean bias.

Results: In total, 45 scenarios were simulated. Because both screening and clinical surfacing had <100% sensitivity, marginal cancer risk estimates were consistently lower than true cancer risks, with greater bias observed at lower screening prevalence. There were no notable differences in the proportion screened and therefore no bias in the observed RR when healthcare access was not associated with either treatment or screening. In scenarios where healthcare access was associated with both treatment and screening, the differences in the proportion screened between treatment groups ranged from 1.7-25.5 percentage points, in line with literature supporting the existence of differential screening in some clinical settings (e.g., glucose-lowering drugs, statin adherence). The resulting mean bias in the ln(RR) ranged from 0.012 to 0.183; the greatest bias was consistently observed in scenarios with a marginal screening frequency of 50%.

Conclusions: In the setting of a null treatment effect, strong associations between healthcare access, treatment, and post-initiation screening generated notable bias in the observed RR. The presence of shared predictors of treatment and outcome detection in observational research should be assessed and considered in the interpretation of study findings.

3700 | Analysing patient level data from Norwegian registries: Challenges and considerations

Sophie Graham[1], Dimitra Lambrelli[1], Anna Schultze[1,2], Robert Donaldson[1], Waleed Ghanima[3,4], Robert Carroll[5] and Maria Ulvestad[6]

[1]*Evidera Ltd, London, United Kingdom;* [2]*London School of Hygiene and Tropical Medicine, London, United Kingdom;* [3]*Østfold Hospital, Oslo, Norway;* [4]*University of Oslo, Oslo, Norway;* [5]*Bristol-Myers Squibb, London, United Kingdom;* [6]*Bristol-Myers Squibb, Lysaker, Norway*

Background: The Norwegian patient and prescription registries provide linked data without dates of event occurrences. Instead, the dataset contains so-called "difference days", which represent the difference between an event date and a random date. Although the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

difference days from event occurrences are provided, difference days from known event dates such as the end of study follow-up are not included.

Objectives: To investigate the impact of absent information on patients' end of follow up on a treatment pattern analysis in the Norwegian registries.

Methods: Patients were identified with a venous thromboembolism (VTE) diagnosis that occurred between 2013 and 2017, and a dispensation of an oral anticoagulant within 30 days after VTE diagnosis. Treatment discontinuation was defined as no new dispensation of oral anticoagulation during the days' supply of the previous prescription + 30-day grace period. Kaplan Meier (KM) methods were used to assess time to treatment discontinuation. Patients were censored at the earliest of death or at their last 'known' date in the data. The last 'known' date was either the last dispensation date or last encounter (outpatient or inpatient) that was identified in the patient's record. In the absence of date of end of follow up, it was not possible to determine whether patients initiating treatment in 2017 had discontinued treatment or reached the end of follow up. Therefore, a sensitivity analysis was conducted to assess the discontinuation rates in all treatment groups excluding patients who initiated treatment in 2017.

Results: In the main analysis, 3,557 warfarin, 3,088 apixaban and 5,828 rivaroxaban patients were identified. Warfarin patients were younger than apixaban (median [IQR]: 64 [26] vs. 66 [24] years; p=0.0045), but older than rivaroxaban (61 [24]; p<0.0001). The median (IQR) months to treatment discontinuation was 6.4 (3.7-15.9), 6.3 (3.4-10.6) and 6.0 (3.9-9.2) for apixaban, warfarin and rivaroxaban patients, respectively. In the sensitivity analysis, the median (IQR) months to treatment discontinuation was 6.3 (3.7-13.8), 6.3 (3.5-10.6) and 5.9 (3.9-8.9) for apixaban, warfarin and rivaroxaban patients, respectively.

Conclusions: A treatment pattern analysis in the Norwegian registries can be conducted by censoring patients at their last 'known' encounter in the data. Excluding the final calendar year (sensitivity analysis) had little impact on the results, however, further analysis using different methodologies is recommended to more accurately address this issue.

3858 | Causal estimands in survival analysis with competing events: An application to breast cancer screening

Xabier Garcia de Albeniz[1], John Hsu[2,3] and Miguel A Hernán[4]
[1]*RTI-HS, Barcelona, Spain;* [2]*Massachusetts General Hospital, Boston, MA;* [3]*Harvard Medical School, Boston, MA;* [4]*Harvard T.H. Chan School of Public Health, Boston, MA*

Background: The presence of competing events poses challenges for the interpretation of effect estimates. In an analysis that censored individuals at death from causes other than breast cancer (BC), the hazard ratio (95% CI) of BC death was 0.78 (0.63 to 0.95) for continuing breast cancer screening vs. stopping among women aged 70-74 years, and was 1.00 (0.83-1.19) among women aged 75-84 years. However, censoring at death is only one possible way to deal with competing events.

Objectives: To estimate two causal estimands for the effect of mammography screening on BC deaths: (1) the total effect of BC screening on BC mortality, which quantifies the effect through all causal pathways, including those possibly mediated by any competing event and (2) the direct effect of BC screening on BC mortality, which quantifies the effect that is not mediated by competing events.

Methods: We emulated a (hypothetical) target trial to compare the effect of two BC screening strategies (continue annual screening vs. stop screening) on the 8-year risk of BC mortality in 1,058,013 Medicare beneficiaries who were 70 to 84 years, had a life expectancy of at least 10 years, no previous diagnosis of BC, and had received screening at baseline between 1999-2008. We censored women when they deviated from their assigned strategy and adjusted for time-varying confounders via inverse probability weighting. We estimated the total effect of "continue screening" vs. "stop screening" as the difference in the 8-year risks (cumulative incidences) of BC mortality, that is, deaths from other causes were included in the denominator of the risk (cumulative incidence). We estimated the direct effect as the difference in the 8-year risks after censoring women when they died for causes other than BC and estimating additional inverse probability weights for this censoring.

Results: During follow-up, there were 61,586 deaths (1533 due to BC, 2.5%) under the "continue screening" strategy and 76023 deaths (1304 due to BC, 1.7%) under the "stop screening" strategy. Among women aged 70 to 74 years, the total and direct effects were -1.01 (-2.3 to 0.09) and -1.17 (-2.5 to 0.01) BC deaths per 1000 women respectively. Among women aged 75-84 years, the total and direct effects were 0.11 (–0.93 to 1.3) and 0.022 (–0.99 to 1.1) BC deaths per 1000 women respectively.

Conclusions: The estimates of the total effect of BC screening on BC mortality were similar to the estimates of the direct effect in each age group. This finding is consistent with the hypothesis that differences in the effect of BC screening by age group are not explained by competing events.

3875 | Comparing inverse probability of treatment and standardized mortality ratio weights in a small sample setting

Leah J. McGrath[1], Alexander Breskin[1], Bradley Saul[1], Ying Yu[1], Michael Kelsh[2], Kara Kilpatrick[2], Carrie M. Nielson[2] and M. Alan Brookhart[1,3]
[1]*NoviSci, Durham, NC;* [2]*Amgen Inc., Thousand Oaks, CA;* [3]*Duke University, Durham, NC*

Background: Propensity score (PS) based methods are commonly used to account for confounding in observational studies. For instance, the average treatment effect (ATE) can be estimated using inverse probability of treatment weighted (IPW) estimators, and the average treatment effect in the treated (ATT) is estimated using standardized mortality ratio weighted (SMR) estimators. In small sample

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

settings, IPW estimators of the ATE may not achieve balance, as both the weighted treated and untreated groups must represent the entire study population. However, it may be possible to estimate the ATT, because only the untreated group is weighted to represent the treated group.

Objectives: We aimed to assess the performance of IPT and SMR weights in terms of covariate balance, PS overlap, and estimator variability in a rare disease setting.

Methods: Adults with primary immune thrombocytopenia (ITP) were identified using electronic health record data from hematology clinics (Flatiron Health, Inc.) linked with MarketScan® health insurance claims data (IBM Watson) from 01/01/11-06/30/17. We included patients with ITP for ≤1 year, a platelet count of ≤30 x 10^9/L, and prior ITP therapy. We compared patients initiating romiplostim to those initiating standard of care (SOC). PS models with baseline potential confounders were fit using logistic regression under various specifications. IPT and SMR weights were constructed and covariate balance was assessed using standardized mean differences (SMD). The maxima of the weights were compared, and PS overlap was visually assessed.

Results: We identified 23 romiplostim-treated and 201 SOC-treated patients. Even in a reduced model (4 terms), IPT weighting caused the SMD for some variables to increase (e.g. age, unweighted = 19.8%, weighted = 25.4%) and had a higher maximum weight in the romiplostim group (maximum = 16.7) compared with SOC (1.5). SMR weighting resulted in adequate balance (e.g. age, unweighted = 19.8%, weighted = -3.4%) and yielded comparable PS distributions between groups. With SMR weights, we were able to include additional covariates (16 terms) in the PS model without negatively impacting balance.

Conclusions: In our example, IPT weights did not adequately balance covariates and were highly variable, suggesting a possible problem with positivity. In contrast, SMR weights resulted in sufficient covariate balance and permitted us to construct larger PS models. Although IPT weights result in an estimate that generalizes to the overall population, SMR-weighted estimates of the ATT may be less biased in a small sample setting.

3884 | Random effects modelling compared to logistic regression for treatment effect estimation in medical device safety: A simulation study

Mike Du[1], M. Sanni Ali[2], Victoria Y. Strauss[1] and Daniel Prieto-Alhambra[1]

[1]University of Oxford, Oxford, United Kingdom; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Surgeons influence both treatment choice and outcome in medical device epidemiology. This creates challenges in observational medical device studies due to surgeon-related confounding (eg surgeon expertise) and/or instrumental variable effects.

Objectives: To estimate the performance (bias and accuracy) associated with logistic regression (LR) compared to random effects modelling (REM) for treatment effect estimation for various surgeon effect scenarios, ranging from weak (OR close to 1) to strong (OR 1.5) confounding.

Methods: Multi-level Monte Carlo simulations (1,000 iterations) with patients nested under surgeon and sample size of n=10,000 were conducted. Different scenarios were created with fixed treatment effect 1.5 odd ratio (OR), five patient confounders, one patient risk factor, one patient instrumental variable all based on Bernoulli distribution; surgeon level cluster effect (both effect on treatment allocation and outcome) based on a normal distribution (mean = 0, standard deviation = 0.5), and one surgeon confounder (equivalent to eg surgeon expertise) based on uniform distribution. The latter was generated with OR on outcome ranging from 1.01 to 1.5. The number of surgeons ranged from 4 to 500, and patients per surgeon 20 to 2,500 respectively. Propensity scores were estimated using logistic regression including all 5 patient-level confounders, but no surgeon covariates. Two modelling strategies were tested for treatment effect estimation: 1.LR ignoring surgeon clusters, and 2.REM with surgeon effect as cluster. Absolute (%) bias, mean square errors (MSE) of treatment effect, and average standardised absolute mean difference (ASMD) for all confounders were computed after stabilized inverse probability weighting (IPW).

Results: Bias increased as number of surgeons increased: for example, for an OR of 1.5 for surgeon confounding, % bias went from 8.4% in LR with 4 surgeons to 15.6% in LR with 500 surgeons. REM modelling reduced bias, much more so in scenarios with strong surgeon confounding effect: in the examples above, REM resulted in 2.3% and 12.0% bias respectively. MSE decreased dramatically in REM compared to LR modelling in all the generated scenarios.

Conclusions: Ignoring surgeon effect/s leads to bias and inaccuracy in medical device safety studies, with higher bias seen in high surgeon effect scenarios and where the number of surgeons included is large. Using REM to account for surgeon clustering reduces bias and improves accuracy and confounder balance compared to LR modelling.

3971 | Random effects modelling vs logistic regression for the inclusion of surgeon covariates in propensity scores for medical device epidemiology: A simulation study

Mike Du[1], M Sanni Ali[2], Victoria Y Strauss[1] and Daniel Prieto-Alhambra[1]

[1]University Of Oxford, Oxford, United Kingdom; [2]London School of Hygiene and Tropical Medicine, LSHTM, London, United Kingdom

Background: Surgeon covariates like experience or volume can be relevant confounders in medical device epidemiology. This creates challenges in propensity score (PS) estimation due to the multi-level nature of the resulting data, with a variable number of patients operated by a same surgeon

Objectives: To estimate the performance (bias and accuracy) of random effect modelling (REM) compared to logistic regression (LR) for PS estimation in different surgeon-level effect scenarios.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: Treatment choice and outcome effect for 10,000 patients were generated using Monte Carlo simulations with multi-level mechanisms (patients nested within surgeons). Five patient confounders, one instrumental variable and one risk factor were generated, all binary. True treatment effect was fixed at Odds ratio (OR) 1.5. A surgeon-level confounder was generated with Pois(2), with an OR = 2 association with treatment, and an OR ranging from 1.5 to 5 for effect on outcome. Two different PS were estimated using: LR including both patient- and surgeon-level confounders; and REM including patient confounders and with surgeon effect as cluster. Inverse probability weighting (IPW) with non-parametric marginal estimator was used for treatment effect estimation. The resulting treatment effects were compared to the true effect, and % bias and mean square errors (MSE) estimated.

Results: LR-based PS result in lower bias and MSE than REM-based ones in all simulated scenarios. For example for an OR of 1.5 for surgeon confounding, % bias and MSE was 9.2% and 0.006 for LR compare to 16.4% and 0.009 for REM. Bias and MSE increased in scenarios with stronger surgeon effect on outcome for both LR and REM PS models.

Conclusions: Using REM for propensity score does not reduce bias compare to plain LR-based propensity scores including surgeon-level confounders. More research is needed on alternative solutions for multi-level PS estimation, and on guidance for their use in medical device epidemiology.

3972 | The impact of including surgeon covariates in propensity score estimation in medical device epidemiology: A simulation study

Mike Du[1], M Sanni Ali[2], Victoria Y Strauss[1] and Daniel Prieto-Alhambra[1]

[1]University of Oxford, Oxford, United Kingdom; [2]London School of Hygiene and Tropical Medicine, LSHTM, London, United Kingdom

Background: Surgeons potentially influence both treatment choice and outcome risk in medical device epidemiology. This creates challenges in propensity score (PS) estimation for medical device studies due to confounding and/or instrumental variable effects.

Objectives: To estimate the bias and accuracy associated with the inclusion of surgeon-level covariates in logistic equations for PS estimation in different scenarios of surgeon effect/s on outcome.

Methods: Data were generated for 10,000 patients using Monte Carlo simulations with multi-level mechanisms (20 patients nested per 500 surgeons). Patient covariates included five confounders, one instrumental variable and one risk factor, all binary. True treatment effect was fixed at Odds ratio (OR) 1.5. Surgeon covariates were generated with Pois(2), and included a fixed OR = 2 for treatment allocation, and a varying effect on outcome ranging from OR 1.01 (no effect on outcome and therefore equivalent to instrumental variable) to OR 5 (strong effect on outcome, equivalent to surgeon-level confounding). PS was estimated using two methods: a. Logistic regression (LR) including only patient-level confounders and b. LR including both patient and surgeon-level covariates. Inverse probability weighting (IPW) with non-parametric marginal estimator was used for treatment effect estimation. Methods (a and b) were compared in terms of % bias and mean square errors (MSE) of treatment effect.

Results: When surgeon effect on outcome was negligible (OR=1.01), the inclusion of surgeon covariates in the PS equation (model b) increased bias compared to PS based on patient-level confounders only (model a), with % bias of 8.5% and 2.8% respectively. Conversely, adding surgeon covariates in PS reduced bias when surgeon effects on outcome are present: % bias dropped from 21.6% in model a to 8.1% in model b vs a when surgeon effect OR is 1.25, and from 55.0% to 24.0% when OR for surgeon effect is 5.0. MSE was consistently lower in model b.

Conclusions: Incorporating surgeon features in PS estimation leads to increased bias when direct surgeon effects on outcome are negligible, equivalent to an instrumental variable scenario. Conversely, adding surgeon variables to the PS equation reduces bias in scenarios with strong surgeon effect on outcome), which would otherwise result in surgeon-level confounding. More research is needed to provide guidance on the use of PS in medical device epidemiology.

4038 | Estimation of treatment effects in registry data: Informative patient visits require careful modeling

Thomas P. A. Debray[1], Massimiliano Copetti[2], Robert W. Platt[3], Carl de Moor[4] and Fabio Pellegrini[5]

[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [3]Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada; [4]Biogen Inc, Cambridge, MA; [5]Biogen International GmbH, Baar, Switzerland

Background: Multiple sclerosis (MS) is a chronic progressive disorder that affects approximately 2.3 million people worldwide. There is a growing demand for real-world evidence on MS treatments, yet, beyond the well-known concerns about exposure-related bias, the analysis of non-randomized routine care data may be prone to bias due to informative missingness of relevant patient outcomes.

Objectives: To evaluate existing and develop new methods for estimating comparative treatment effects from routine care registry data when outcomes are assessed at irregular visit schedules.

Methods: We conducted an extensive simulation study where we generated individual MS disease trajectories for MS patients from multiple practices. Patient outcomes were expressed as Expanded Disability Status Scale (EDSS), a standard reference scale to assess progression of MS disease, and generated for distinct months using multilevel normal distributions correlated over time. To mimic the irregular visit times in clinical practice, we censored patient outcomes according to an informative missingness procedure. For each simulated dataset, we estimated the treatment effect (with respect to no treatment) in terms of time to confirmed EDSS progression at 6 months, as defined in clinical practice. **Setting:** Simulation study

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

mimicking routine clinical practice **Exposures:** MS disease-modifying therapies **Main outcome measures:** Time to confirmed EDSS progression at 6 months. **Statistical analysis:** For each simulated dataset, missing EDSS scores were imputed using (i) last observation carried forward (LOCF), (ii) rounding to the closer regular visit schedule (RND), and (iii) advanced mixed effects models accounting for patient clustering and autocorrelation. Subsequently, time to confirmed EDSS progression at 6 months treatment effects were estimated using Cox regression.

Results: Imputation using LOCF or RND leads to substantial bias in confirmed EDSS progression and consequently in treatment effect estimates, particularly when patient visits are scarce and highly dependent on patient characteristics. EDSS scores imputed using multilevel models were much more accurate to estimate confirmed EDSS progression and improved the [bias and precision] of treatment effect estimates.

Conclusions: Studies analyzing real world effectiveness of medical interventions should account for informativeness of patient visits. Methods such as LOCF and RND should be avoided when patient visits are infrequent; instead, advanced statistical models should be used to impute missing patient outcomes and account for their uncertainty.

4050 | The performance of instrumental variables in medical device epidemiology: A simulation study of non-normally distributed continuous outcome data based on real world post-operative PROMs

Albert Prats-Uribe[1], M Sanni Ali[2], Victoria Y Strauss[1] and Daniel Prieto-Alhambra[1]

[1]University of Oxford, Oxford, United Kingdom; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Patient reported outcomes (PROMs) are often used in surgical RCTs for comparative efficacy studies. UTMOST, a cohort study assessing the comparative effectiveness of partial and total knee replacement was able to replicate an RCT using propensity scores. However, instrumental variables (IV) based on surgeon's preference failed to emulate the trial, yielding implausible estimates.

Objectives: To estimate bias and power of IV analyses of non-normally distributed continuous outcome data based on a PROM.

Methods: Different scenarios of outcome distributions and violation of IV assumptions were explored. We simulated data (n=130,000) using the distributions: gamma distributed (0.3,3) IV truncated at 1 and binarised at median to mimic UTMOST's IV; binary treatment based on a logit function of IV and 3 confounders; outcome as a linear function of IV, treatment effect of 2 (same as the RCT effect), and the 3 confounders. Different strengths of IVs (IV-Treatment correlation, with β ranging from 0 to 10^-9, equivalent to OR 1 to 20), and distributions of outcome (rounded normal (30,8) and truncated rounded normal (30,8)) were considered. We tested different scenarios of patient eligibility for treatment (50% to 100%), treatment prevalence (10% to 50%), and IV violations, introducing a direct effect of the IV on the outcome (β 0 to 20). Two-stage least squares regression was used to estimate treatment effects, and relative bias and mean standard error (MSE) were calculated.

Results: In scenarios with low IV strength, IV estimates were extremely biased and inaccurate (high MSE and up to 1,000% bias). Conversely, bias was low (<2%) when IV was independent of outcome satisfying the assumption, and remained reliable with minor violations: bias was low (<5%) when IV strength β was >10,000-fold the IV-outcome correlation β. Exposure prevalence did not affect bias, nor did patient eligibility. Analyses of a truncated normal outcome yielded systematically lower estimates compared to non-truncated normal. Binarization of the IV did not introduce bias compared to continuous IV use.

Conclusions: IVs should be used with caution when dealing with non-normally distributed and/or truncated continuous outcomes, e.g. PROMs. Bias increased in the presence of weak IVs. Violation of IV assumptions introduced bias, except when the IV was very strong yet slightly correlated with outcome. More research including multilevel simulations are needed to further understand the reliability of IV methods for medical device epidemiology.

4109 | Replicating the findings of a medicare study on stroke, and bleeding risk in patients using NOACs for atrial fibrillation in the sentinel system

Marie C. Bradley[1], Emily C. Welch[2], David J. Graham[3], Efe Eworuke[1], Rongmei Zhang[4], Elande Baro[5] and Mayura Shinde[6]

[1]FDA, Silver Spring, MD; [2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [3]FDA, Silver Spring, MD; [4]FDA, Silver Spring, MD; [5]FDA, Silver Spring, MD; [6], Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: A recent FDA study in Medicare concluded that among older patients (65+ years) rivaroxaban had a less favorable benefit-harm profile compared to other nonvitamin K oral anticoagulants (NOACs). However, limited data exist for younger users.

Objectives: As a prelude to studying the comparative safety and effectiveness of individual NOACs in younger patients within the Sentinel system, we sought to use Sentinel modular programs to replicate the findings of a previous FDA Medicare study that compared the safety and effectiveness of individual NOACs in older patients.

Methods: Patients, aged 65 years and older initiating NOACs between 10/19/2010 and 9/30/2015 in the Sentinel Medicare data partner only, were identified. Propensity score matching (1:1) was used for each pairwise NOAC-NOAC comparison instead of propensity score weighting used in the reference Medicare study. Cox proportional hazards regression was used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the outcomes of thromboembolic stroke (stroke), intracranial hemorrhage (ICH), major extracranial bleeding (MEB), and GI bleeding (GIB) comparing each NOAC with each other NOAC.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Overall, the risk estimates were largely similar in the Medicare and Sentinel studies. For example, there was no difference in the risk of stroke with rivaroxaban compared with dabigatran [Medicare HR (95% CI) 0.90 (0.76-1.06) and Sentinel 0.89 (0.74-1.07)]. Similarly, rivaroxaban use was associated with an increased risk of ICH compared to apixaban in both studies-Medicare HR (95% CI) 1.21 (0.94-1.55)) and Sentinel 1.28 (0.99, 1.67). Despite using a modified algorithm for identification of GI bleeding events in the Sentinel study the results were also largely similar: risk of MEB with rivaroxaban compared to apixaban in Medicare and Sentinel studies was HR (95% CI) 2.70 (2.38-3.05) and 2.29 (2.06-2.55)respectively and risk of GIB was 2.83 (2.47-3.25) and 2.32 (2.07-2.59) respectively.

Conclusions: We were able to successfully replicate the findings of a previous FDA Medicare study in the Sentinel Medicare data partner using a modified analytic approach. Going forward we will use the Sentinel system to compare the safety and effectiveness of individual NOACs in younger users.

4179 | Replication of protocol-based analyses of saxagliptin and sitagliptin using sentinel modular programs

Christian Hampp[1], David J. Graham[1], Rongmei Zhang[2], Yandong Qiang[1], Laura Hou[3], Sheryl Kluberg[3], Sengwee D. Toh[3] and Justin Bohn[3]

[1]U.S. Food and Drug Administration, Silver Spring, MD; [2]U.S. Food and Drug Administration, Silver Spring, MD; [3]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: Since the publication of protocol-based assessments (PBAs) of acute myocardial infarction (AMI) and hospitalized heart failure (hHF) among users of saxagliptin or sitagliptin in FDA's Sentinel system, the capability of semi-automated modular programs in Sentinel has expanded greatly.

Objectives: We aimed to evaluate the performance of Sentinel modular programs in replicating the previous PBAs for saxagliptin and sitagliptin, using similar study design, parameters, and data.

Methods: This cohort study included health plan members from up to 17 Sentinel Data Partners enrolled between 2006 and 2015. We matched new users of saxagliptin or sitagliptin to each other and to new users of three comparator agents (pioglitazone, second-generation sulfonylureas, long-acting insulin) using propensity scores. Cox proportional hazards models assessed the hazard ratios (HRs) of AMI and hHF. We compared 14 assessments from the PBAs with results from two modular program analyses: the primary "replication" analysis mirrored, as closely as possible, every study parameter and data from the PBAs, and a secondary "updated" analysis included data not available at the time of the PBAs.

Results: Each pairwise replication analysis included at least 40,831 matched initiators of saxagliptin or 126,432 matched initiators of sitagliptin. More than twice as many patients were identified in the updated analysis. Covariate distributions were comparable to those in the PBA and well-balanced after matching. HRs for AMI comparing saxagliptin to sitagliptin were 0.96 (95% CI, 0.77-1.18), 0.96 (0.77-1.22), and 0.93 (0.85-1.03) in the PBA, replication, and updated analysis, respectively. HRs for hHF comparing saxagliptin to sitagliptin were 0.93 (0.75-1.15), 0.91 (0.73-1.15), and 0.90 (0.83-0.96) in the PBA, replication, and updated analysis, respectively. Of all 14 replication comparisons, 43% of HR point estimates were within 5%, 79% within 10%, and 93% within 20% of their reference estimate from the PBA. Qualitatively, all replication analyses yielded HR point estimates on the same side of the null as the PBA, although 3 out of 14 comparisons differed from the PBA in their statistical significance. Findings were similar across subgroups by sex, age, and prior cardiovascular disease history.

Conclusions: Sentinel modular programs were able to replicate findings of prior PBAs, which did not indicate an increased risk of AMI or hHF associated with saxagliptin or sitagliptin exposure. An updated analysis with additional data yielded similar findings.

4195 | A marginal structural model to evaluate the association between statins and the risk of developing hepatocellular carcinoma in patients with diabetes

Yi-Chun Yeh[1,2], Pei-Chun Chen[2] and Yen-Yu Chen[1,3]

[1]Research Education and Epidemiology Center, Changhua Christian Hospital, Changhua, Taiwan; [2]Department of Public Health, China Medical University, Taichung, Taiwan; [3]Department of Neurology, Changhua Christian Hospital, Changhua City, Taiwan

Background: Observational studies showed that statin was associated with a reduced risk of hepatocellular carcinoma (HCC). Marginal structural model (MSM) is a weighted repeated measures approach to deal with time-dependent confounders that are also mediators in longitudinal studies.

Objectives: The aim of the study was to evaluate the association between statin use and the incidence of HCC in patients with diabetes using a MSM.

Methods: The retrospective cohort study included 244,344 patients with type 2 diabetes who were new users of lipid-lowering drugs identified using the claims data of Taiwan's National Health Insurance Program. Statin exposures and follow-up of HCC was divided into monthly intervals. Chronic liver disease and insulin were both time-dependent confounders and affected by past exposures of statins. Pooled logistic regressions were used to calculate the stabilized weights (SW) and estimate the hazard ratios (95% confidence intervals, CIs) of HCC in relation to statins exposures using the weighted sample.

Results: The median follow-up was 4.29 years, generating 1,141,673 person-years of follow-up. The hazard ratio for HCC was 0.82 (95% CI: 0.60, 1.12), comparing statin with non-statin using MSM approach. The results were similar in the sensitivity analysis, where the truncated SW and lagging exposure were applied. However, statin use was associated with a decreased risk of HCC (HR=0.73, 95% CI: 0.57, 0.95) in the analysis that did not take into account for time-dependent confounders.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Statin use is not associated with the incidence of HCC among patients with diabetes treated with lipid-lowering drugs after adjusting for time-dependent confounders affecting by previous exposures using MSM.

4206 | Comparing three signal identification methods with self-controlled designs

Judith C. Maro[1], Shirley V. Wang[2], Inna Dashevsky[1], Joshua J. Gagne[2], Sai Dharmarajan[3], Esther H. Zhou[3], Sandra DeLuccia[1], Elande Baro[3], Monica Munoz[3], Danijela Stojanovic[3], Jesper Hallas[4], G. Niklas Norén[5], Martin Kulldorff[2] and Michael D. Nguyen[3]
[1]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [2]Harvard Medical School and Brigham and Women's Hospital, Boston, MA; [3]U.S. Food and Drug Administration, Silver Spring, MD; [4]University of Southern Denmark, Odense, Denmark; [5]Uppsala Monitoring Centre, Uppsala, Sweden

Background: Post-market signal identification - detecting unexpected potential associations between medical product exposures and adverse outcomes - is an important part of protecting public health.
Objectives: To compare three self-controlled signal identification methods - Bernoulli tree-based scan statistics (TreeScan), Information Component Temporal Pattern Discovery (ICTPD), and Sequence Symmetry Analysis (SSA) - using the same datasets to assess variation in findings.
Methods: We identified adult new users of two study drugs, lamotrigine and levetiracetam, in IBM MarketScan Research Databases from 2010-2015. We assessed incident outcomes as first in 400 days using groupings of 8,000+ ICD-9-CM codes. We identified elevated occurrences in a risk window 1-28 days post-exposure relative to each of three 28-day comparison windows, occurring pre- or post-exposure. For TreeScan, "alerts" were recorded at the p=0.01 level when using a post-exposure comparison window. For ICTPD, alerts were recorded when elevated occurrences were observed relative to two pre-exposure comparison windows at the lower bound of a 99% credibility interval. SSA does not use thresholds so associations were ranked by risk differences.
Results: We identified 180,228 new lamotrigine users and 102,404 new levetiracetam users. In lamotrigine, TreeScan produced 8 alerts compared to 80 for ICTPD with 5/8 observed in both. Many ICTPD alerts (~35%) were due to small cell counts. When observing the top 10 ranked alerts, all methods (including SSA) were reasonably aligned in identifying labeled serious skin conditions (e.g., Stevens-Johnson syndrome), and non-specific adverse drug reactions. For levetiracetam, TreeScan had 16 alerts compared to 20 in ICTPD with no specific overlap. Many alerts were related to post-operative complications as levetiracetam is dispensed prophylactically post-neurosurgery and for traumatic brain injury. The top 10 ranked alerts were dispersed across methods, and there were strong temporal patterns in overall outcome counts in the study period, indicative of greater time-varying confounding.
Conclusions: Signal identification methods using self-controlled designs are appropriate when time-varying confounding is low. These methods have tuning parameters to define alerts that create tradeoffs in type I and II error rates. The larger number of alerts observed with ICTPD versus TreeScan is likely due to lack of direct multiplicity adjustment in ICTPD. Some alerts with small cell counts are related to rare and important outcomes, but many more are likely to be spurious.

4384 | Use of external data in pharmacoepidemiology

Til Stürmer[1], Michele Jonsson Funk[1], Olaf Klungel[2], Kaatje Bollaerts[3]
[1]UNC, Chapel Hill, NC; [2]University of Utrecht, Utrecht, Netherlands; [3]P95 Pharmacovigilance and Epidemiology, Leuven, Belgium

Background: Limitations of available data is one of the principal problems in pharmacoepidemiology. Multiple methods have been proposed to mitigate bias due to uncontrolled confounding, exposure, and outcome misclassification. Some of the most effective tools leverage external data.
Objectives: The symposium will provide an overview of methods related to external data, orient the audience to existing tools/resources available to incorporate external data, and generally encourage the audience to use external data to improve study validity.
Description: Three 15' - 20' presentations followed by 5' Q&A each followed by ~20' podium discussion.
1. "Validation studies and data linkages" Administrative claims and other routinely collected data provide the foundation for many drug utilization, safety, and effectiveness studies. These databases provide a rich source of timely health care information on large, well-defined populations yet lack potentially important information. The increasing ability to link data sources provides researchers with opportunities to add clinical detail to well defined cohorts. The presentation will cover issues related to ongoing linkages of US Medicare claims with electronic health records (EHR) and provide examples on how such linked data can be used to address a variety of issues, including uncontrolled confounding.
2. "Methods to control for unmeasured confounders based on validation data" The presentation will provide an overview of commonly used methods to address unmeasured confounders in the design and analysis phase and provide recommendations for proper application in pharmacoepidemiology. Methods that utilize additional information on confounders collected in a validation study (e.g., external adjustment, propensity score calibration, two-stage sampling, and multiple imputation) will be discussed highlighting the importance of using both statistical evidence and substantial clinical knowledge for the interpretation of study results.
3. "Multiple-bias analysis based on parameters assessed in external data" The use of quantitative bias analyses is advocated by several key-opinion leaders and international health authorities including regulatory agencies. Such bias analyses involve bias parameters for which the values can be chosen to be either wide-ranging and hypothetical ('Which bias levels are needed to reach a certain value?') or evidence-based ('Which result would be obtained given a certain realistic level

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of bias?'). Traditional deterministic bias analyses can be improved by randomly sampling from the distributions of multiple bias parameters to obtain a distribution of the adjusted effect measure.

4462 | Machine learning for causal inference in a realistic prescribing scenario

Alexander Breskin[1] and Paul N Zivich[2]
[1]NoviSci, Durham, NC; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Commonly used causal inference methods for observational data require correct models for nuisance parameters. These parameters are not of primary interest but are used to estimate the target quantity. For instance, the propensity score is the nuisance parameter for inverse probability weighted estimators. Methods that rely on a single nuisance model, like inverse probability weighted estimators, are said to be singly-robust. More recent doubly-robust methods, such as augmented inverse probability weighted estimation (AIPW) and targeted maximum likelihood estimation (TMLE) are consistent as long as either the treatment or outcome nuisance model is correct. These methods also allow the use of machine learning for nuisance model fitting. However, this property requires additional smoothness conditions. Cross-fitting, or fitting the nuisance models on a subset of the data and making predictions in a different subset, has been proposed as a way to avoid the need for these additional conditions.

Objectives: To assess the performance of AIPW and TMLE with machine learning in a realistic setting.

Methods: Datasets of 3000 individuals were simulated from a data generating mechanism based on current statin prescribing guidelines for the primary prevention of atherosclerotic cardiovascular disease (ASCVD). The true propensity score and ASCVD distributions included log-transforms, polynomial terms, and discontinuities. AIPW and TMLE were used to estimate the effect of statin prescribing on ASCVD in each simulated dataset. For each estimator, the nuisance models were fit with parametric main-effects generalized linear models as well as a stacked ensemble of machine learners.

Results: With parametric models, the root mean squared errors (RMSE) of AIPW and TMLE were 0.026 and 0.025, respectively, with 95% confidence interval (CI) coverages of 84% and 85%. In this scenario, both methods were biased for the true effect. With machine learning, the RMSEs were 0.020 and 0.020, and the CI coverages were 91.1% and 89.5%. Notably, both methods were unbiased when machine learning was used.

Conclusions: Both methods performed poorly when the underlying parametric nuisance models were misspecified. When machine learning was used for the nuisance models, both AIPW and TMLE had improved performance, but neither attained nominal confidence interval coverage. Doubly robust methods with machine learning may be preferred over traditional estimators to avoid bias from statistical model misspecification, but further enhancements, such as crossfitting, may be needed for valid confidence intervals when machine learning is used.

4483 | Trajectories of care in patients with chronic obstructive pulmonary disease

Sandrine Henri[1], Ronald Herrera[1], Alain Vanasse[2,3], Amélie Forget[1,4] and Lucie Blais[1,4,5]
[1]University of Montreal, Montreal, QC, Canada; [2]University of Sherbrooke, Sherbrooke, QC, Canada; [3]Research Center of the Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada; [4]CIUSSS du Nord-de-l'île-de-Montréal, Montréal, QC, Canada; [5]AstraZeneca Pharmaceutical Chair in Respiratory Health, Montréal, QC, Canada

Background: Individuals with chronic obstructive pulmonary disease (COPD) navigate the healthcare system (HCS) in many ways in Quebec, Canada. A better understanding of COPD patients' trajectory of care (ToC) could help clinicians and policymakers optimize the delivery of care and resource allocation.

Objectives: To identify and characterize ToCs in individuals with COPD in Quebec and to assess their associations with mortality.

Methods: A retrospective COPD cohort was built by linking Quebec administrative databases and Quebec respondents to the Canadian Community Health Survey (CCHS). CCHS, available from 2007 to 2013, provided data on participants' characteristics and offers representative data of the population. Administrative databases provided data on ambulatory medical visits, emergency department visits, and hospitalizations from 1996 to 2016. Participants included had a diagnosis of COPD recorded in the administrative databases in the 7 years before CCHS completion, were 40 years old or more at the COPD diagnosis, and were alive during the 2 years following survey completion. ToCs were measured in the 2 years following CCHS, patients entered the cohort after this period and were followed until death or up to 5 years. ToCs were identified through sequence analyses, an emerging statistical method which regroups patients based on their use of HCS. Chi-squared and V tests were used to identify patients' characteristics that differ between ToCs. A Cox regression model was used to evaluate the association between ToCs and mortality.

Results: The cohort contains 3309 COPD patients: mean age of 68 yo and 54% women. Five ToCs were identified: 1) low use of HCS (51%), 2) average use of HCS predominantly with specialists (16%), 3) high use of HCS predominantly with family physicians (20%), 4) high use of HCS predominantly with specialists (16%), and 5) high use of HCS predominantly in acute care (5%). patients' characteristics that best distinguished ToCs were age, comorbidity index and perceived health. Patients in ToCs 5 and 3 had the highest mortality hazard (HR=2.10; 95% CI: 1.63-2.71 and HR=1.34; 95% CI: 1.06-1.68, respectively) compared to patients in the first ToC.

Conclusions: Sequence analysis revealed that most patients were treated in ambulatory care and that only 5% of patients' ToC was characterized by acute care. Moreover, COPD patients followed by specialists did not have a higher mortality rate than those followed by family physicians. This could indicate that patients' follow-up by specialists is more adequate and that specialists base their care on objective data such as pulmonary function tests.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4501 | A novel approach to quantitatively synthesize subgroups findings from multiple trials

Devon Boyne, Paul Arora and Darren Brenner
Cytel, Toronto, ON, Canada

Background: The identification of characteristics that stratify patients according to the likelihood of treatment response is a key goal of precision medicine research. Within randomized trials, effect modification is typically examined through subgroup analyses or the inclusion of an interaction term(s) in a multivariable regression model. To date, systematic reviews of such findings have relied upon qualitative summaries or subgroup-specific meta-analyses. Such approaches are problematic because they do not quantify the magnitude or the degree of uncertainty in the difference in the treatment effects between subgroups.
Objectives: To develop an approach that can be used to quantitatively pool subgroup findings from multiple trials.
Methods: Our procedure is focused on the estimation of the pooled difference between the subgroup-specific treatment effects within a two-stage meta-analysis. In the first stage, the magnitude and standard error of the difference between the subgroup-specific treatment effects is estimated for each study. When studying relative effect measures, this difference can be estimated on the log-scale, e.g., study-specific difference = log(RRsubgroup A) - log(RRsubgroup B). The standard error of this difference can then be estimated using subgroup-specific 95% CIs. A meta-analysis of the study-specific differences is then conducted. When the differences are estimated on the log-scale, the pooled quantity can be re-expressed as the ratio of the subgroup specific ORs, RRs, or HRs whereby a ratio equal to 1.00 indicates that the subgroup-specific estimates are equal in magnitude.
Results: Case-studies and empirical simulations highlighting the application of our approach will be presented. Potential extensions of this methodology will also be discussed. Such extensions include the use of dose-response models to address subgroup categories of a continuous variable and the inclusion of three or more treatments within a network meta-analysis.
Conclusions: This method may help to quantify the presence and degree of heterogeneity in subgroup differences across trials, particularly in settings where the number of participants within each trial is limited.

4580 | Using patient-level data from electronic health records to replicate the control arm of the IMblaze370 trial in metastatic colorectal cancer

Michael T. Bretscher[1], Marcus Lawrance[2], Shivani K. Mhatre[3], Carsten Schröder[1], Christelle Lenain[1], Marta Pereira[2] and Irmarie Reyes-Rivera[1]
[1]F. Hoffmann-La Roche AG, Basel, Switzerland; [2]Roche Products Limited, Welwyn, United Kingdom; [3]Genentech, Inc., South San Francisco, CA

Background: In recent years FDA has approved oncology drugs on the basis of single-arm trials for patients with very limited treatment options. External controls (EC) derived from electronic health records (EHR) can provide context to single-arm clinical trials. Carrigan et al 2019 showed that properly selected control arms from contemporaneous EHR data could be used to replicate trial control arms in advanced non-small cell lung cancer, using overall survival (OS) as an endpoint. The present study extends this work to metastatic colorectal cancer (mCRC).
Objectives: To assess how well an EC derived from EHRs can approximate the control arm of the IMblaze370 trial (NCT02788279).
Methods: To create an EC arm, a patient cohort receiving regorafenib in 3rd line or later was selected from the US based Flatiron Health EHR-derived, de-identified database of patients with mCRC by applying the relevant enrolment criteria of IMblaze370. EHR-derived and trial control arms were compared in terms of confirmed baseline prognostic variables age, gender, race, and Eastern Cooperative Oncology Group (ECOG) performance score. Covariate imbalances between the arms were adjusted by propensity score-based weighting of data points. Log rank test and Cox regression models were used to obtain effect estimates for OS comparing trial control arm against EC arm.
Results: A cohort of 251 patients treated with regorafenib met inclusion criteria. These were on average slightly older, had higher (worse) ECOG, and had received more previous lines of treatment compared to the trial patients. Median OS was 8.5 (IQR 6.4-10.7) months in the IMblaze370 regorafenib arm, compared to 7.4 (IQR 6.7-8.7) months (unadjusted) and 9.9 (IQR 8.1, 12.4) months (with covariate adjustment) in the EHR-derived data. Both log-rank test (p=0.18) and Cox-regression (HR: 1.02, 95%CI: 0.66-1.47) indicated no significant OS difference between the two arms.
Conclusions: The EC derived from real-world data aligned closely with the IMblaze370 control arm. This is encouraging for the prospect of further testing and eventually applying prospective external control arms in similar mCRC populations to help interpret results from single-armed trials.

4622 | Using a random forest model to identify demographic and clinical characteristics that predict pain within a cohort of rheumatoid arthritis patients in the US

Harriet A Dickinson[1], Daniel C Gibbons[2] and Jolyon Fairburn-Beech[2]
[1]GSK, Stevenage, United Kingdom; [2]GSK, Uxbridge, United Kingdom

Background: Rheumatoid arthritis (RA) is characterized by the chronic inflammation of the synovium of joints, and may result in joint damage and pain. Little is known about the key drivers that predict pain in RA patients, and the synergistic effects of each of these factors further complicates the study of these relationships. Random forests (RFs) are a form of ensemble machine learning that generates a large 'forest' of random decision trees that can be used to classify cases within a dataset. An advantage of RFs is a reduced likelihood of overfitting, through leverage of bootstrap aggregation ('bagging') and the selection of a random subset of features at each tree branch point. RFs are trained on a subset of the input dataset, with its accuracy assessed against 'held out' data.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To classify incident RA cases into predicted pain categories and explore which features are most closely associated with pain, though estimation of variable importance within the generated RF model.

Methods: An incident cohort of 1,866 RA patients in the Optum integrated database was used (74.5% female, mean age 63.6 years). A 1 year lead in period was used to identify incident RA status, and a 1-3 year gap was allowed between index RA diagnosis and a valid patient-reported pain score (recorded between 2014-2015 inclusive). Patients with evidence of discordant inflammatory markers were excluded. Data was accumulated on 32 features including demographics, selected comorbidities, medications and lab tests in the period between index and pain score. Pain was dichotomised into the presence or absence of pain, according to a pain VAS of > 0 or 0 respectively. 30% of patients were held out as the testing set. 10,000 trees were grown, features were centered and scaled, and hyper-parameters were tuned via grid search. This work was funded by GSK.

Results: The RF model had a precision of 0.72 and a recall of 0.55 (with an F1 of 0.63). Scaled to the most important feature (age at index RA diagnosis, 100.0%), the five next most important features were: years from index diagnosis to pain score (68.0%), number of encounters for RA (67.7%), any use of opioids (55.5%), any use of nonsteroidal anti-inflammatory drugs (54.8%) and a diagnosis of fibromyalgia (51.1%).

Conclusions: Whilst this prediction could be further improved, this study indicates there are several features that could be important in driving pain in RA patients. Further work may be done to investigate the relationship of these features with pain or this model could be applied to another dataset to understand if similar features are deemed important.

4708 | Simulation of pharmacological treatments for metabolic disorders

David Bernotas
University of Washington, Seattle, WA

Background: We present an overview of the design and application of digital simulations to estimate the impact of drug interventions. The results of these simulations can inform research and investment decisions as well as policies and treatment guidelines.

Objectives: To use computer based simulations and population level data to estimate the benefit of drug interventions for treatment of disease.

Methods: The computer simulations are individual based, meaning we track each person in the simulated population over the relevant time period, recording the person's health state and behavior at predetermined time steps. Simulants are initialized using data from the Global Burden of Disease and other sources. These data provide information on the initial health state of each simulated person. Since these models use simulated participants, the setting is limited only by data availability. Any population, location, age group, intervention, treatment criteria and health outcome can be simulated. The examples presented focus on metabolic disorders - obesity, hypertension, hyperlipidemia - and the results estimate the impact on mortality and morbidity given various hypothetical treatment scenarios. Consider the impact of drug adherence - if patients took their medication more often, how would the disease specific outcomes change? If adherence increased by 22% after the introduction of a single pill, multi-drug therapy, what is the expected reduction in SBP in China over the next 10 years - and how many lives would be saved due to the induced decline in hypertension related ischemic strokes during this 10 year period? Which age groups benefit most from the intervention? What if the change in adherence was 18% instead? Simulation is a flexible tool to answer these questions, providing valuable insight into treatment design.

Results: The simulation methodology, when applied to specific case of the impact on adherence due to introduction of a combination therapy for metabolic disorders, estimates that mortality and morbidity related to the these risks will fall by several percent - simply by combining two drugs into a single pill. These models simulated populations of one million people from multiple locations, and compared several intervention scenarios simultaneously.

Conclusions: These results are illustrative of how useful simulation can be in pharmacological research. The ability to select populations and parameter values provide robust sensitivity analyses and enable exploration of multiple intervention designs simultaneously.

4738 | Combining primary care electronic health record data from multiple sources: A systematic review of observational studies

Daniel Dedman[1,2], Melissa Cabecinha[3], Rachael Williams[1], Stephen J. W. Evans[2], Krishnan Bhaskaran[2] and Ian J. Douglas[2]
[1]Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]University College London, London, United Kingdom

Background: Real world data from primary care electronic health record (EHR) databases are particularly valuable due to their longitudinal nature and richness. Individual databases are often relatively small, but their growing availability means they are increasingly used in multi-database studies. Establishing best practice for combining primary care EHR databases would be of clear benefit, and an important preliminary step is to describe current practice. As yet there is no comprehensive summary of studies which used two or more primary care EHR databases, and the methods for combining them.

Objectives: To identify observational studies which used data from two or more primary care electronic health record (EHR) databases, and summarise key characteristics including: objective and rationale for using multiple data sources; methods used to manage, analyse, and (if applicable) combine data; and approaches to assess and report heterogeneity between databases.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: Systematic review of observational studies published between 2000-2018 which included at least 2 primary care EHR databases. Studies were identified by searching Pubmed and Embase databases with a list of named primary care EHR databases, plus hand searches of reference list of studies retained after initial screening.

Results: 6054 studies were screened and 109 were selected for review, the majority published between 2014-2018. Included studies used 38 different primary care EHR data sources. There were 76 pharmacoepidemiology studies (70%), and 47 (43%) were descriptive studies comparing patterns and trends in different populations (37 [34%]), or in different databases from the same populations (10 [9%]). Of 62 analytical studies, 22 (36%) presented separate results from each database, and did not combine them; 29 (48%) combined individual patient data in a 1-stage meta-analysis; 21 (34%) combined estimates from each database using 2-stage meta-analysis; and 10 (16%) used both 1- and 2-stage methods. Discussion and exploration of heterogeneity was inconsistent across studies.

Conclusions: Describing trends and variation in different populations or databases were common objectives. When combining results using meta-analysis, reporting separate results from each database is helpful for interpretation. This information was often missing, particularly for studies using 1-stage approaches, which also often lacked details of statistical adjustment for heterogeneity and/or clustering. For 2 stage meta-analysis a clear rationale should be provided for using fixed effect (FE), random effects (RE) or other models.

4856 | Evidence of distinct censoring dynamics across treatment groups and impact on censoring weight model specification: The example of anticoagulation in atrial fibrillation

Liliya Sinyavskaya[1], Alexis Matteau[1], Jason Robert Guertin[2], Mireille Schnitzer[3], Christel Renoux[4] and Madeleine Durand[1]

[1]*Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada;* [2]*Centre de Recherche du CHU de Québec – Laval University, Montreal, QC, Canada;* [3]*Université de Montréal, Montreal, QC, Canada;* [4]*McGill University, Montreal, QC, Canada*

Background: Inverse probability of censoring weighting is a popular method to reduce bias due to informative censoring. However, failing to recognize distinct censoring dynamics between exposure groups will not provide adequately adjusted estimates.

Objectives: We explored the impact of two censoring weight models on the estimates of safety and effectiveness in a cohort of patients prescribed warfarin or direct oral anticoagulants (DOACs) for stroke prevention after the diagnosis of atrial fibrillation.

Methods: Using the Québec administrative healthcare databases, we formed a cohort of patients newly dispensed warfarin or a DOAC between 2010-2016. One-to-one matching was done on age, sex, cohort entry date and propensity score. The primary outcome was a composite of stroke, major bleeding or death. Follow-up was censored at the time of treatment switch or discontinuation. Unstratified and exposure-stratified pooled logistic regressions were used to calculate the censoring weights ($IPCW_1$ and $IPCW_2$, respectively). Unweighted, $IPCW_1$, and $IPCW_2$ -weighted Cox proportional hazards regression models were used to estimate hazard ratios (HR) of the composite outcome in warfarin- versus DOACs-treated patients.

Results: The study cohort included 22,241 matched pairs. A significant proportion of patients (70% for warfarin and 36% for DOAC group) were censored due to switch or discontinuation of therapy. When modelling censoring weights stratified by exposure, distinct covariates were associated to censoring in the warfarin vs. DOACs treated patients. For example, males, those with comorbid heart failure, chronic renal failure, and acute kidney injury had higher odds of being censored from the DOAC group, but lower odds of being censored from the warfarin group. In the unweighted analysis, exposure to warfarin compared to DOACs was associated to a HR of 1.35, (95%CI: 1.28-1.42) for the composite outcome. In $IPCW_1$-weighed cohort, the HR was very similar (HR:1.37; 95%CI:1.30 - 1.44). However, in $IPCW_2$-weighed cohort, the HR was lowered to 1.27 (95% CI:1.20 - 1.34).

Conclusions: Failing to account for distinct censoring dynamics when modelling weights led to larger HR estimate in a cohort of patients initiating warfarin or DOACs for stroke prevention. Simulation studies are needed to explore the best way to build weights when censoring dynamics differ by exposure.

5005 | Development and validation of a prediction model for 1-year risk of thromboembolism in hemodialysis patients with atrial fibrillation

Sapna Rao[1], Abhijit V Kshirsagar[2], M Alan Brookhart[1], Alexander Keil[1], Laura Loehr[1], Michele Jonsson Funk[1] and Charles Poole[1]

[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC;* [2]*University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Hemodialysis (HD) patients with atrial fibrillation (AF) are at an increased risk of stroke and thromboembolism (TE) compared to AF patients with normal kidney function. The most commonly used CHA2DS2-VASC score was developed in the general population with AF not on any anti-coagulation therapy. Validation studies have shown poor performance in the HD population. While some risk scores incorporate the contribution of kidney disease, no risk score to date has been developed specifically in the HD population.

Objectives: To develop and validate a claims-based prediction model for 1-year risk of TE and ischemic stroke in HD patients with AF and compare it to the CHA2DS2-VASC model.

Methods: A retrospective study of HD patients diagnosed with AF (2007 - 2016) was conducted using the United States Renal Data System (USRDS). Adult patients with continuous Medicare part A, B and D enrollment, in-center dialysis and no anticoagulant use during the 6-month baseline period prior to AF diagnosis were included. Primary outcome was defined as hospitalization or death from TE. Secondary outcome was hospitalization or death from ischemic stroke. Patients

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

were followed for outcomes from AF diagnosis date (index date) to the earliest of the following: death, loss of Medicare part A, B or D coverage, transplant, discontinuation of HD or administrative censoring on December 31, 2016. Predictors of TE and stroke were selected in a 70% training dataset using a regularized logistic regression model with LASSO method and 10-fold cross-validation. The final model for each outcome was tested in the 30% validation dataset. Performance of the LASSO model in validation dataset was assessed using area under curve (AUC) receiver operating characteristic (ROC) and compared with the CHA2DS2-VASC score.

Results: We identified 42,069 anticoagulant naïve patients with AF and follow-up for at least 1 year (mean age: 65 years, 47% female). There were 6,784 TE events and 3,622 ischemic stroke events within 1 year of AF diagnosis. Median predicted probability of 1-year risk of TE and ischemic stroke was 14.8% and 7.8% respectively. In the validation sample, the C-statistic for the LASSO and the CHA2DS2-VASC model was 0.616 (95%CI 0.603, 0.623) and 0.609 (95%CI 0.596, 0.623) for TE and 0.613 (95%CI 0.595, 0.630) and 0.612 (95%CI 0.595, 0.629) for ischemic stroke.

Conclusions: Performance of the claims-based LASSO model was identical to the CHA2DS2-VASC model for TE and ischemic stroke. More predictive indicators of TE risk specific to the HD population, such as those from dialysis clinics, may provide better prediction.

Methods in Pharmacoepidemiology -> Clinical Trial Methodology - Including pragmatic trials, cluster/sub-analyses of RCTs

3945 | Frequency and characteristics of uncontrolled long-term extensions to randomized controlled trials

Ching-Yu Wang[1], Joan Gretenkord[1], John D Seeger[2], Kourtney J Davis[3], Michelle R Iannacone[4], Wei Zhou[5], Nancy Dreyer[6], Almut G Winterstein[1], Nancy Santanello[7], Barry Gertz[8] and Jesse A Berlin[9]
[1]Center for Drug Evaluation & Safety, Gainesville, FL; [2]Optum, Boston, MA; [3]Janssen R&D, Titusville, NJ; [4]Food and Drug Administration, Silver Spring, MD; [5]Merck & Co. Inc., Kenilworth, NJ; [6]IQVIA Real World Solutions, Cambridge, MA; [7]Pharmacoepidemiology Consultant, New Hope, PA; [8]Blackstone Life Sciences, Boston, MA; [9]Johnson & Johnson, Titusville, NJ

Background: Long Term Extensions (LTEs) implemented after randomized control trials (RCTs) are often used to assess long-term drug safety and effectiveness. However, some LTEs are Uncontrolled (UC)-LTEs which lack comparison groups, limiting the ability to draw valid inferences. Real-world data or data from other RCTs are a potential source for external comparators for UC-LTEs. Information on the frequency and types of UC-LTEs and the use of external comparisons are lacking.

Objectives: To identify and characterize UC-LTEs to Phase II and III RCTs, including use of external comparisons.

Methods: A systematic search was conducted in clinicaltrials.gov spanning 2009 to 2019. Search terms included "extension" and "continuation". Only LTEs to Phase II and III RCT without internal controls were included (UC-LTEs). UC-LTEs of single-arm parent RCTs and of dose-ranging parent trials (without control group) were excluded. Trials were screened by a single primary reviewer for consideration and in cases of uncertainty, three secondary reviewers evaluated trial eligibility for inclusion. Counts of eligible UC-LTEs are reported by year and the following study characteristics were extracted and summarized: therapeutic area, phase of parent RCT and presence of different dosing arms, and sample size. "External" and "historical control" were used to search for UC-LTEs with external controls. Counts of UC-LTEs with external controls and their respective data sources were reported.

Results: Among 216,944 registered studies, 3,262 met search criteria, and 1,142 UC-LTEs were included, originating primarily (60%) from phase III RCTs. Distributions of disease areas were diverse with: 358 (31.3 %) in neuroscience, 287 (25.1%) in autoimmune/inflammatory disease, 134 (11.7%) in metabolic/endocrinologic disease, 114 (10.0%) in hematology/oncology. The majority of UC-LTEs (82%) had only one arm without different dosing comparisons. The sample size of these UC-LTEs was right-skewed; ranging from 0 (for ongoing trials) to 27,395 with a median of 150 participants per UC-LTE study. The number of UC-LTEs increased over time (slope=5.3 additional UC-LTEs per year), but other characteristics remained stable. Only 4 UC-LTEs were identified that indicated using external controls; 2 UC-LTEs did not report data sources; 1 reported using the placebo arm of a previous RCT; and 1 reported using a registry.

Conclusions: Since 2009, the use of UC-LTEs has increased but limited consideration has been given to designs that include external comparisons groups. Future studies examining the methods of employing external controls are needed.

4107 | Quantitative bias analysis for external comparator studies

Christen M. Gray, Fiona Grimson, Deborah Layton and Joseph Kim
IQVIA Ltd, London, United Kingdom

Background: External comparators added to single arm trials are becoming more prevalent in regulatory decision-making. Given the challenge of combining observational data from routinely healthcare sources with clinical trial data, additional rigor must be integrated into planning and analytical execution that includes careful feasibility assessment of data source, study design, covariate balance and quantitative bias analysis (QBA). QBA is the practice of modelling sources of bias, using deterministic or probabilistic models, which may impact results of research. Existing publications focus exclusively on QBA applications in epidemiology, such as case-control and cohort studies.

Objectives: To describe the potential application of QBA within the context of an evaluation framework for real world data (RWD) external comparator studies.

Methods: Three biases of highest impact in RWD studies were identified (selection bias, unmeasured confounding and information bias

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

i.e. misclassification error, measurement error, and error from missing data). For each bias, we explored how QBA can be applied for each situation specifically for RWD external comparator studies.

Results: Three motivating case examples applying QBA are presented for (a) uncontrolled confounding due to selection bias; (b) outcome misclassification in the external comparator arm; and (c) differential error in time-to-event analysis due to active vs passive reporting of the event. For example (a) and (b) we demonstrate how use of categorical analysis using bias factors can be adapted to this setting. For (c) we demonstrate the power of probabilistic modelling in forecasting the extent of the impact of reasonable assumptions of bias.

Conclusions: Where external comparator studies are being used to support regulatory decision making there is increased demand for bias assessment. Using these motivational examples, we provide insights into how QBA can be adapted for use in this context. However further work is needed to make a robust assessment of the utility of QBA when compared to other bias analyses that may have been performed for regulatory approvals of products on the basis of uncontrolled studies.

4356 | A picture is worth 1000 words: Visual tools to guide transport of trial results to real-world populations

Jennifer L. Lund, Michael A. Webster-Clark, Til Sturmer, Daniel Westreich, Hanna K. Sanoff and Alexander P. Keil
University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Increasingly, quantitative methods are being used to transport treatment effects from trials to real-world populations. The first step in these analyses is identifying relevant patient populations (target populations) and select sets of variables (i.e., effect measure modifiers) to include in transport models.

Objectives: We introduce a set of visual plots to help characterize alternative target populations and select a set of variables to transport treatment effects to a given target population.

Methods: We generated three visualizations. We plotted coefficients from multivariable models for the independent associations between each patient characteristic and (1) trial enrollment on the x-axis and (2) the outcome on the y-axis for each target population of interest to help researchers identify potential effect measure modifiers for each specific target population. Next, we plotted distributions of trial enrollment probabilities estimated from the transport model for a given target population, similar to plotting propensity score distributions, to illustrate overall differences between populations. Finally, we plotted trial participant transport weights to identify extreme weights and influential observations. As a case study, we used a trial of chemotherapy (FOLFOX vs 5FU) for stage II-III colon cancer (MOSAIC) and target population data from a community oncology network (US Oncology) from 2008-19. We included: (1) all trial-eligible US Oncology patients with stage II-III colon cancer; (2) the subgroup of those treated with FOLFOX; and (3) the subgroup of untreated patients. Patient characteristics included age, sex, stage, body mass index (BMI), and performance status. The primary outcome was mortality.

Results: There were 2246 MOSAIC participants and 9935 US Oncology patients. As expected, cancer stage, performance status, and age were strongly associated with trial enrollment in all targets and mortality. Surprisingly, BMI and sex distributions differed between MOSAIC and the targets but were not independently associated with mortality. Trial enrollment probability distributions for MOSAIC and US Oncology patients were most similar for FOLFOX-treated target patients and least similar for the untreated target patients. In general, older individuals with good performance status received large weights, with the most extreme weights observed when targeting the untreated.

Conclusions: These visual tools serve as a methodologic bridge to guide researchers in model selection when transporting treatment effects from trials to specific clinical practice populations.

4537 | contextualizing background safety rates using comparable historical clinical trials

Hu Li[1], Antoniu Fantana[1], Matthew Connelly[1], Thomas S Hilzinger[2] and Manas Singh[3]
[1]Eli Lilly and Company, Indianapolis, IN; [2]PricewaterhouseCoopers, LLP, Chicago, IL; [3]PricewaterhouseCoopers, LLP, Mumbai, India

Background: Understanding the context for drug related adverse events (AEs) is crucial in clinical development. If safety signals remain elusive until unblinding phase, the delayed risk mitigation strategy could cause potential patient harm and/or result in a negative benefit risk profile. However, to our knowledge there has been no widely accepted methodology on how to generate background rates.

Objectives: To establish a process of generating background rates for the most frequently reported serious AEs in a newly approved acute migraine medication (lasmiditan)

Methods: The historical data were obtained from clinical trials of a chronic migraine drug (galcanezumab) that was approved in 2018. A three-step process was established: 1) inclusion and exclusion (I/E) summaries and structured demographics data collected from clinicaltrials.gov of galcanezumab and lasmiditan trials were compared using SciBite, a natural language processing engine. Subjects were pooled together from trials with similar scores; 2) to confirm comparability of the two patient sets, individual patients' characteristics (demographic, comorbidity, concomitant medication and behavior) were then compared using Kullback Leibler Divergence, t-test and weighted difference in prevalence; 3) incidence rate and prevalence rate of top 25 most frequently reported serious safety events were calculated among placebo patients from galcanezumab trials.

Results: Eight galcanezumab trials were identified to meet I/E of lasmiditan trials. Based on the distribution of demographics, medical history, and concomitant medication, 1305 placebo subjects from galcanezumab trials were determined to be comparable to lasmiditan subjects, which constructed a “virtual cohort”. The most frequently

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

reported SAEs using System Organ Class, High-Level Group Terms, Preferred Terms for galcanezumab placebo subjects were gastrointestinal disorders, infections and upper abdominal pain with incidence rate of 6.79, 5.69 and 2.13 per 1000 patient years and the prevalence rate was 5.75, 4.6, 1.73 per 1000 patients respectively. Additional frequently reported serious adverse events (SAEs) (top 25) will be disclosed at the presentation.

Conclusions: The study illustrated a three-step process to generate background safety rates among a "virtual cohort" obtained from historical clinical trials. Despite the limitation in the sample size, the study demonstrated the value in understanding reasonably anticipated SAEs, contextualizing safety profiles, and the potential benefit to conduct proactive safety monitoring in clinical development.

4841 | Lessons learned from replicating clinical trials with real-world data

Solomon Iyasu[1], David Martin[2], Sebastian Schneeweiss[3], William Crown[4], Thomas Jemielita[5]

[1]Merck and Co., West Point, PA; [2]FDA, Silver Spring, MD; [3]Harvard T.H. Chan School of Public Health, Boston, MA; [4]Optum Labs, Cambridge, MA; [5]Merck and Co., Kenilworth, NJ

Background: With multiple initiatives attempting to replicate clinical trials with real-world data (RWD) beginning to report findings, the collective wisdom gathered from the exercises will help provide insights regarding

1) what research questions that may be best answered by clinical trial data or RWD;

2) factors that may contribute to the incomparability between RWD and clinical trials; and

3) approaches that may help increase the comparability between the two different kinds of data sources in a systematic way.

Objectives: 1. To summarize general patterns observed in various exercises of replicating clinical trials, focusing on:

(a) Critical factors that can affect the feasibility of replication;

(b) Research questions that may be better answered by RWD vs those by clinical trials

2. To discuss pharmacoepidemiologic and statistical methodologies that were employed in the replication exercises, focusing on:

(a) Scenarios that may warrant specific type(s) of methodology;

(b) Accounting for the clinical inclusion/exclusion criteria.

3. To discuss applications of the learnings from the replication exercises

Description: The symposium will start with a brief introduction of the panelists, background, objectives, and the various exercises of replicating clinical trials with RWD (Solomon Iyasu, 5 minutes), followed by review of findings and lessons learned from the first 8 trials replicated as part of RCT DUPLICATE (Sebastian Schneeweiss, 20 minutes) and from OPERAND (Bill Crown, 20 minutes), focusing on summarizing specific patterns/scenarios in which the feasibility is high vs. low, and if there are corresponding methodologies to help enhance the comparability. In addition, replication results of cancer trial(s) and methodologies designed to enhance the effective sample size of RWD in clinical settings with stringent clinical inclusion/exclusion criteria, along with broad replication considerations and challenges based on real clinical examples, will also be discussed (Thomas Jemielita, 20 minutes). Applications of the learnings in future considerations of using RWE supporting regulatory submission will be considered and discussed (David Martin, 20 minutes). The symposium will then end with a brief summary and conclusion (Solomon Iyasu, 5 minutes).

Methods in Pharmacoepidemiology -> Confounding/Bias - Methods to avoid bias and confounding, including confounder summary scores (e.g., propensity scores, disease risk scores)

77 | Caliper considerations for propensity score matching

Elizabeth M. Garry, Wesley Eddings, Aditya Rajan, Amanda R. Patrick and Nicolle M. Gatto

Aetion, Inc., Boston, MA

Background: When using propensity scores (PS) to match initiators of a referent treatment to those initiating the exposure, a maximum caliper should be specified to allow for variation of the PS within each match. Although recommendations have been made previously for calipers 0.20-0.25 the standard deviation of the logit of the PS, the methods used to make these recommendations may have limited generalizability in regulatory settings. As tighter calipers yield closer matches, a conservative absolute caliper of 0.01 is frequently used in practice without strong precedent, but may exclude more exposed patients who are unable to be matched.

Objectives: Evaluate changes to covariate balance and effectiveness estimates when the absolute caliper for PS is systematically varied.

Methods: We used IBM Marketscan commercial claims data 2014-2018 to create cohorts 1:1 PS-matched without replacement to evaluate comparative effectiveness using a previously established example comparing systemic stroke or embolism among initiators of rivaroxaban versus warfarin. We started with the frequently used caliper of 0.01 and then increased the caliper by increments of 0.05. At each interval, we confirmed covariate balance (no standardized difference values ≥0.1 for any dichotomous covariates included in the PS model) and whether the regulatory decision would likely be the same based on the hazard ratio [HR] falling within the confidence interval of the previously published ROCKET trial that concluded that rivaroxaban was noninferior to warfarin (0.88 [0.74-1.03]).

Results: Among the 3102 rivaroxaban and 4128 warfarin initiators, the unadjusted HR was 0.71 [0.53-0.95]. When a caliper of 0.01 was used for PS matching, 81.5% of exposed patients were matched in the analytic cohort, covariate balance was achieved, and the HR was 0.90 (0.63, 1.27). With calipers of 0.10, 0.15, 0.20, 0.25, and 0.30, covariate balance continued, the number of matched exposed patients increased to 93.2%, and the HR moved further from the null (0.89 [0.63-1.25], 0.87 [0.62-1.23], 0.85 [0.61-1.19], 0.83 [0.59-1.15], and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

0.80 [0.58-1.11], respectively). At a caliper of 0.35, the HR was 0.80 (0.58-1.10) and we began to see covariate imbalance.

Conclusions: In this example, covariate balance was achieved using a caliper as high as 0.30, which allowed for most exposed patients to be matched and yielded an estimate that would lead to the same noninferiority regulatory decision. These findings suggest a need to further explore increases to the caliper used for PS matching to minimize the exclusion of exposed patients who might otherwise be unable to match without impacting the overall findings.

80 | Methodological considerations for pooling patient-level data (PLD) from noninterventional studies (NIS) and clinical trials (CT) in oncology

Francois-Xavier Lamy[1], Vivien Rothe[2], Caroline Foch[1], Regina Esser[1], Wenfeng Chen[3] and Diethelm Messinger[2]
[1]*Merck KGaA, Darmstadt, Germany;* [2]*Prometris GmbH, Mannheim, Germany;* [3]*Merck Serono, Shanghai, China*

Background: The present study, aimed to address the following research question with available PLD: in patients with *RAS* wild-type (wt) mCRC, is first-line treatment with cetuximab (CET) every 2 weeks (Q2W) in combination with chemotherapy noninferior to treatment with CET weekly (Q1W) in combination with chemotherapy in terms of overall survival (OS)? With a noninferiority margin hazard ratio (HR) of 1.25 and a power of 80% to reject the null hypothesis, 527 patients per arm were required. To achieve this sample size, pooling of CT and NIS was necessary. We included all non-registrational studies with available PLD at the time of design of this pooled analysis: 2 NIS and 3 CT, all based on primary data collection. Pooling of studies required specific considerations to account for differences in the nature of the data.

Objectives: To describe the methodological considerations for a study based on the pooling of PLD from CTs and NISs.

Methods: Propensity score (PS) methods were used to account for differences in baseline characteristics across all studies. In addition, depending on the outcome, subgroup analyses were considered. For OS (event: death), limited differences were expected across study types. A sensitivity analysis restricted to patients included in the NIS was conducted to assess the impact of the study type on the main outcome. Furthermore, in the NIS assessment, visits for tumor progression were not protocol-defined but took place according to practice at the site. A sensitivity analysis was conducted to account for missing responses. Similarly, for the progression-free survival time-to-event analysis (events: death or progression), the difference in frequency of assessment led to the use of a sensitivity analysis based on a logistic regression model rather than a survival model. Finally, for adverse events (AEs), only serious AEs were considered as the likelihood of these being reported in NIS was higher than for nonserious AEs. Recoding of AEs in NIS was necessary.

Results: After weighting on the PS, all the covariates included in the PS showed a standardized difference <0.1, and the PS distributions between Q1W and Q2W overlapped well. The HR (95% CI) for OS (Q2W vs Q1W) was 0.84 (0.72-0.96) in the main analysis and 0.73 (0.61-0.88) when restricted to NIS. Sensitivity analyses on other outcomes led to similar results in point estimates and identical conclusions as the main analyses.

Conclusions: Pooling data from different study types poses important challenges to standardize outcome definitions and relies on assumptions that can be tested through sensitivity analyses.

2582 | What quacks like a confounder and walks like an instrument?

Michael A. Webster-Clark, and Charles Poole
University of North Carolina, Chapel Hill, NC

Background: Directed acyclic graphs (DAGs) are potent tools for epidemiologists. Graphical rules for identifying minimally sufficient adjustment sets showed key exceptions to older definitions of confounders. That said, DAGs can be misleading when targeting specific populations. For example, researchers using propensity scores to estimate average treatment effects in the treated (ATT) may include variables associated with the outcome only in the treated (e.g. drug-drug interactions, hypersensitivity to drug components) in their models based on a DAG.

Objectives: We aimed to show that variables that are associated with the outcome only in the treated act like instruments for the ATT in that adjusting for them amplifies variance and unmeasured confounding.

Methods: We simulated populations with three independent binary variables (C_1, C_2, and C_3), a treatment X, and an outcome Y. The probability of receiving X was a linear function of C_1, C_2, and C_3. To make C_1 associated with the outcome only in the treated, the probability of experiencing Y was a linear function of C_2, C_3, and an interaction between X and C_1. We also explored the consequences of adding a weak main effect term for C_1 on the outcome.

Results: Adjusting for C_1 always amplified unmeasured confounding in and variance of ATT estimates. In one simulation with a true risk difference (RD) of 7.0%, the estimated RD after weighting the untreated to the treated based on C_1 and C_2 was 9.6% with a 95% confidence limit difference (CLD) of 2.8%, while the RD adjusting for C_2 alone was 9.1% (CLD of 2.4%); adjusting for C_1 thus amplified the confounding from C_3 by approximately 24%. In that same scenario, adjusting for all three confounders (C_1, C_2, and C_3) yielded an unbiased RD with a CLD of 3.4% while adjusting for only C_2 and C_3 yielded an unbiased and more precise RD with a CLD of 2.6%. These trends persisted when using outcome modeling and other adjustment methods. However, even a weak effect of C_1 on Y reversed these results.

Conclusions: Confounders like C_1 that are associated with the outcome only in the treated (including drug-drug interactions with or allergies to the treatment of interest) should not be included in propensity score or outcome models when estimating the ATT.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conversely, variables that are associated with the outcome only in the untreated act as instruments and should not be adjusted for when estimating the treatment effect in the untreated. The old adage-that confounders must be associated with the outcome in the untreated-bears out, as long as one is only looking at the ATT.

2614 | Application of quantitative bias analysis for unmeasured confounding in pharmacoepidemiology

Jeremy P. Brown[1], Clémence Leyrat[1], Nicholas Galwey[2], Kevin Wing[1] and Ian J. Douglas[1]

[1]*London School of Hygiene and Tropical Medicine, London, United Kingdom;* [2]*GlaxoSmithKline plc, Stevenage, United Kingdom*

Background: Confounding is a major concern in pharmacoepidemiological studies. Measured confounders can be accounted for through stratification, regression, or other methods. However, it is often unclear whether all confounders have been measured, and therefore it is not known to what extent associations observed are causal or due to unmeasured confounding.

Objectives: To apply and compare quantitative bias analysis methods for unmeasured confounding.

Methods: We applied two quantitative bias analysis methods, probabilistic bias analysis and e-value calculation, to a study we previously conducted where unmeasured confounding was considered likely. These methods quantify the potential impact of unmeasured confounders. In the cohort study conducted in the UK Clinical Practice Research Datalink, comparing new users of proton pump inhibitors (n=733,885) to new users of H2 receptor antagonists (n=124,410), we identified an increased risk of all-cause mortality associated with proton pump inhibitor prescription (adjusted hazard ratio 1.38, 95% CI 1.33-1.44). For the probabilistic bias analysis we repeatedly sampled (Monte Carlo sampling - 10,000 iterations) the prevalence of the putative unmeasured binary confounder (uniformly between 0.1 and 0.5), the strength of association between exposure and confounder (uniformly on log scale to obtain odds ratios between 1.0 and 6.0), and the strength of association between the confounder and outcome (uniformly on log scale for hazard ratios between 1.0 and 3.0). On each iteration we calculated a bias-adjusted hazard ratio using sampled parameters. We ran additional simulations increasing the number of unmeasured confounders (assuming independent multiplicative effects).

Results: Using the e-value formula, for an unmeasured confounder to fully account for the observed lower bound of the hazard ratio of 1.33, the confounder would need to be associated with both treatment and outcome by a risk ratio of at least 1.9. In probabilistic bias analysis, the median bias-adjusted hazard ratio (2.5^{th}, 97.5^{th} percentiles) was 1.27 (0.99, 1.38) with one unmeasured confounder, 1.22 (0.91, 1.36) with two unmeasured confounders, and 1.13 (0.80, 1.34) with three unmeasured confounders.

Conclusions: A single unmeasured confounder would need to be strongly associated with the exposure and outcome to fully account for the observed association, whereas multiple unmeasured confounders would only need be associated more weakly. Quantitative bias analysis deserves wider application in pharmacoepidemiology given the susceptibility of studies in the field to unmeasured confounding.

2624 | The impact of immortal time bias and the adjustment using modified Kaplan-Meier method and time-dependent cox proportional hazard model: A case study

Satoshi Onozawa[1], Masanori Ito[1] and Tomomi Kimura[2]

[1]*Astellas Pharma Inc., Tokyo, Japan;* [2]*Astellas Pharma US Inc., Northbrook, IL*

Background: Immortal time bias is well known, but often overlooked, in the analysis of time-varying exposure during the hospitalization. In our study, we tried to evaluate if the switching antibiotics from intravenous (IV) to oral can shorten the length of hospital stay (LoS) in hospitalized community-acquired pneumonia (CAP) patients, while maintaining clinical effectiveness.

Objectives: To calculate adjusted Kaplan-Meier estimates of time to discharge and death, the difference in median time to discharge and adjusted hazard ratios for time to discharge and death in CAP patients with and without switching to oral antibiotics.

Methods: Hospitalizations for adult CAP patients in 2010-2018 in a hospital-based administrative data were analyzed. CAP severity was determined by A-DROP score. Discontinuation of IV antibiotics followed by immediate start of oral antibiotics during the stay was defined as treatment switch, which was considered as time-varying exposure. Adjusted Kaplan-Meier estimates of time to discharge and death were estimated by modified Kaplan-Meier method in which the risk set of the time-dependent exposure is dynamically update over time. Also, adjusted hazard ratios for discharge and death were estimated with time-dependent Cox proportional hazard model. In addition, two sensitivity analyses were performed where death was treated as either a competing event or censor.

Results: In total, 210,314 hospitalizations were analyzed and median LoS (days) was 8 (mild CAP) to 16 (extremely severe CAP). After stratifying by CAP severity, unadjusted median time to discharge was similar between the switch and non-switch groups, while adjusted median time to discharge (days) was 6 to 15 days shorter in the switch group compared to the non-switch group. Unadjusted difference of Kaplan-Meier estimates of time to death between the switch and non-switch groups became wider as CAP severity worsened, while the differences shrank after the adjustment. Adjusted hazard ratios (95% confidence intervals) for time to discharge and death were 2.4 (2.3-2.4) and 0.7 (0.5-1.2) in mild, 1.9 (1.8-1.9) and 0.6 (0.5-0.6) in moderate, 1.7 (1.7-1.8) and 0.6 (0.5-0.6) in severe and 1.6 (1.5-1.7) and 0.6 (0.5-0.7) in extremely severe group, respectively. Sensitivity analyses showed robustness of the findings.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: The impact of immortal time bias was huge and appropriate analysis methods for retrospective database study are critical to assess the attribution of time-varying exposures.

2631 | Increasing the credibility of real world evidence: Identifying and reducing bias using negative controls

Alexander Breskin[1], Matthew Maciejewski[2], Leah McGrath[1], Vera Ehrenstein[3], Brian Bradbury[4], Gianmario Candore[5]
[1]*NoviSci, Durham, NC;* [2]*Duke University, Durham, NC;* [3]*Aarhus University, Aarhus, Denmark;* [4]*Amgen, Thousand Oaks, CA;* [5]*European Medicines Agency, Amsterdam, Netherlands*

Background: Common approaches for real world studies of comparative effectiveness and safety include covariate adjustment (e.g., with propensity score weighting, regression, or matching) and instrumental variable methods. Recently, negative control methods have been increasingly used as an approach to both detect and reduce bias when estimating causal effects. Negative control variables share the same unobserved confounding structure as the exposure-outcome association of interest. Unlike the exposure and outcome of interest, however, negative exposures do not have a causal effect on the outcome of interest, and negative control outcomes are not causally affected by the exposure of interest. Notably, the causal conditions underlying negative control methods are unique and different from those needed for covariate adjustment or instrumental variables. Thus, negative controls may also be useful in situations where other methods are infeasible.

Objectives: 1. To provide an introduction to the theory and concepts underlying negative control methods.

2. To demonstrate approaches to identifying negative control variables.

3. To describe analytical methods to detect and mitigate uncontrolled confounding using negative control variables.

4. To gain perspectives from industry and regulatory leaders on the potential for negative control methods to complement real world data analyses.

5. To benefit researchers involved in real world data analysis for comparative effectiveness and safety studies.

Description: The symposium will begin with Dr. Maciejewski introducing the theory and concepts underlying negative control methods. This will be followed with a case study by Dr. McGrath on selecting negative control outcomes, including the identification of novel negative controls using real world data. Next, Dr. Breskin will describe analytic methods for detecting uncontrolled confounding and calibrating estimates with negative controls, with an emphasis on the conditions required for their validity. Drs. Bradbury and Candore will then present industry and regulatory perspectives, respectively, on how negative control approaches can be used to complement and support comparative effectiveness and safety research. The symposium will conclude with reflections and an audience discussion guided by Dr. Ehrenstein regarding the potential uses of negative control methods in real world data analysis. Each presenter will be allotted 15 minutes.

2659 | Multi-level propensity scores in comparative effectiveness research on medical devices: A pragmatic example of partial vs total knee replacement using national joint registry data compared to RCT findings

Albert Prats-Uribe[1], M Sanni Ali[2], Victoria Y Strauss[1] and Daniel Prieto-Alhambra[1]
[1]*Centre for Statistics in Medicine, Botnar Research Centre, NDORMS, University of Oxford, Oxford, United Kingdom;* [2]*London School of Hygiene and Tropical Medicine, London, United Kingdom*

Background: Propensity scores (PS) are widely used in pharmacoepidemiology, but little is known about how surgeon-related confounders should be incorporated in PS in the study of implantable devices.

Objectives: To test the performance of different methods to account for surgeon level confounders to emulate the TOPKAT surgical RCT comparing partial (PKR) vs total knee replacement (TKR) [Beard D et al. Lancet 2019].

Methods: We identified trial eligible patients undergoing PKR or TKR in the UK National Joint Registry linked to hospital inpatients data and patient reported outcome measure. We calculated PS using four different strategies: a) Using 18 clinically defined patient confounders in logistic regression (LR), b) as A but adding surgeon volume in LR c) LR random effects model with surgeon pseudonymised id as a random intercept (REM), and d) like C but with both surgeon- and patient-level confounders included in the PS equation. We used the resulting PS to compute 4 different stabilized inverse probability weights. We used non-parametric marginal estimators to estimate post-operative Oxford Knee Scores (OKS) differences as treatment effects between PKR and TKR. We compared the resulting estimators to TOPKAT and specified four agreement criteria: I2<40%, Chi2 for a difference >0.05, full coverage of the estimate and 95CI, and statistical significance agreement.

Results: We identified 602 and 114,871 patients undergoing PKR and TKR, and 2,625 surgeons. Mean surgical volume in the previous year was 5 surgeries for PKR and 67 for TKR. PS based on patient variables (method a) resulted in a postoperative OKS difference of 0.87 95%CI (-0.20 to 1.94); PS using multilevel modelling (method c) resulted in 1.50 (-0.44 to 3.44). Adding surgeon volume in a LR-based PS (method b) resulted in an estimator of 1.41 (0.25 to 2.57), compared to 2.11 (0.16 to 4.06) for the REM-based PS including patient and surgeon variables (method d). Compared to TOPKAT (treatment effect 191 (0.20-3.62)), method b passed all four agreement criteria, followed by method d with 3/4.

Conclusions: Methods including surgeon-level confounders in the PS either in single level or multi-level models (methods b and d) are the preferable methods, indicating the importance of incorporating surgeon features in PS models for the study of implantable devices.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2669 | Addressing treatment implementation bias in the construction of high dimensional propensity scores

Nicolas H. Thurin, Jérémy Jové, Patrick Blin, Magali Rouyer, Stéphanie Lamarque, Pauline Bosco-Levy, Nicholas Moore and Cécile Droz-Perroteau

Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France

Background: Formally, covariate for propensity score (PS) construction are assessed before treatment onset. However differences occurring in patient journeys after the decision to treat and before the treatment onset may bias the score (e.g. pre-chemotherapy assessment).

Objectives: To address treatment implementation bias induced by differential patient journeys between the decision to treat and the treatment initiation.

Methods: A comparative effectiveness study was set to compare cancer treatments using the French nationwide healthcare database (SNDS). Successive high-dimensional PS (hdPS) were constructed to estimate the probability to be treated by an oral *versus* intravenous agent, aiming to minimize standardized differences (SD) >10% and C-statistic value, after 1:1 matching. All models included 100 empirical covariates and differed by the covariate assessment period length and extra fixed variables.

Results: Model 1 used a pre-exposure covariate assessment period of 1 year and showed 2 different patterns of hdPS distribution, leading to 273 matched patient-pairs out of 1213 potential (C-statistic =0.713). Model 2 excluded the month preceding treatment initiation from the covariate assessment period [-12; -1 months], leading to 830/1213 matched pairs (C-statistic =0.586; 12 independent variables with SD >10%). Model 3 extended the covariate assessment period [-24; -1 months], and included dispensing of previous anticancer agents as fixed variables. Cancer age and hdPS were used for matching, leading to 716/1213 patient-pairs (C-statistic =0.603; 5 independent variables with SD >10%).

Conclusions: Pre-exposure window should be routinely assessed and potentially excluded when constructing PS, especially when patients have followed distinct care pathways. Ideally, covariate assessment period should stop at the time treatments are decided upon and not yet started.

3756 | Adherence to statin therapy and the use of preventive health services: Cohort study using claims databases in Japan

Tsugumichi Sato[1], Yumiko Wakana[1], Motoyoshi Akiyama[1], Haruna Hasegawa[1], Moriya Ogino[1] and Kiyoshi Kubota[1,2]

[1]*Faculty of Pharmaceutical Sciences, Tokyo University of Science, Noda, Japan;* [2]*NPO Drug Safety Research Unit Japan, Tokyo, Japan*

Background: The healthy adherer bias can arise when patients who adhere to preventive therapy are healthier or more likely to be engaged in healthy behaviors than their non-adherent counterparts. Brookhart et al. reported that patients who adhere to statin therapy were more likely to seek out preventive health services, even after adjusted by various covariates.

Objectives: To investigate whether the healthy adherer bias arises in pharmacoepidemiology study associated with statin use in Japanese healthcare setting, we examined the association between adherence to statin therapy and the use of preventive health services using claims data.

Methods: We conducted a cohort study using claims data from two databases in Japan. We identified patients age ≥20 who newly started a statin between 2005 and July 2018. Adherers who filled two or more prescriptions and non-adherers who filled only one prescription for a statin during a 1-year ascertainment period were followed up to 365 days. The outcomes were the use of the following screening examinations: mammogram (MMG), prostate-specific antigen test (PSA), fecal occult blood test (FOBT), H. Pylori test (Pylori), gastroendoscopy (GE), and large bowel endoscopy (LBE). We estimated crude incidence rate ratios (IRRs) of adherers compared to non-adherers for those events by person-year method and hazard ratios (HRs) fully adjusted by covariates including age, sex, various comorbid conditions, number of days in the hospital, and Charlson Comorbidity Index as well as HRs adjusted by age only by Cox regression models.

Results: We identified 71,735 patients, 61,826 adherers and 9,909 non-adherers. Crude IRRs were 1.09 (95%CI: 0.94-1.27) for MMG, 1.78 (1.38-2.28) for PSA, 1.46 (1.09-1.97) for FOBT, 1.40 (1.18-1.66) for Pylori, 1.39 (1.26-1.54) for GE, and 1.37 (1.18-1.60) for LBE, respectively. The adjusted HRs got close to 1.0: HRs adjusted fully/by age only were 0.99 (0.96-1.02)/0.99 (0.96-1.03) for MMG, 0.99 (0.96-1.02)/0.99 (0.96-1.02) for PSA, 0.99 (0.97-1.01)/ 0.99 (0.97-1.02) for FOBT, 0.99 (0.97-1.01)/ 0.99 (0.97-1.01) for Pylori, 0.99 (0.97-1.01)/ 0.99 (0.97-1.02) for GE, and 0.99 (0.97-1.01)/ 0.99 (0.97-1.01) for LBE, respectively.

Conclusions: Our results suggest that although adherers to statin therapy are more likely to seek out preventive health services, the difference is mainly because adherers are older than non-adherers. For statin use, the healthy adherer bias, hard to adjust by routinely available covariates may not arise in Japanese healthcare setting.

3861 | A systematic review of how missing data is handled and reported in multi-database pharmacoepidemiology

Nicholas B. Hunt, Helga Gardarsdottir, Marloes T. Bazelier, Olaf H. Klungel and Romin Pajouheshnia

Utrecht University, Utrecht, Netherlands

Background: Pharmacoepidemiologic multi-database studies (MDBS) provide opportunities to better evaluate the safety and effectiveness of medicines compared to single database projects. However, data may be partially or systematically missing in one or more of the contributing databases. This could result in bias or loss of precision, so specialised methods are required to deal with this, especially in the case of distributed data networks.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To determine the extent to which missing data are reported and which methods are currently applied to account for missing data in MDBS.

Methods: We conducted a systematic literature search in PubMed for MDBS evaluating the safety or effectiveness of medicines published between 01-01-18 and 31-12-19. This was supplemented by searches for eligible studies from established database networks. Studies were considered MDBS if two or more distinct databases were used to capture information on the same variables in different populations. We extracted information on the general study characteristics, the strategies for executing a MDBS (e.g. general common data model, distributed analysis), the reporting of missing data (variables missing, number of patients with missing data) and the methods used to account for missing data.

Results: 2725 articles were identified, of which, 61 studies from 44 different journals were included in the analysis, with the majority using US (64%) and European (39%) data. Twenty-four (29%) used a common data model or common protocol, 19 (31%) carried out a distributed analysis and 10 (16%) shared raw data for a central analysis. Twenty-eight (46%) articles reported missing data, most of which were potential confounders such as lifestyle factors and 11 (18%) studies reported that this missing data could introduce bias. Eighteen (30%) studies addressed the missing data by using a complete case analysis (n=13, 21%), multiple imputation (n=3, 5%) or both methods (n=2, 3%).

Conclusions: Only 46% of MDBS published in the years 2018-19 report missing data and 30% reported applying methods to address it. The higher complexity of MDBS should be accompanied by an increased vigilance for database completeness and heterogeneity by reporting and addressing the missing data that could introduce bias.

3862 | The performance of different machine learning algorithms for data driven variable selection and propensity score estimation in the presence of multiple confounders and big sample size: A simulation study

Yuchen Guo[1], M Sanni Ali[2], Victoria Y. Strauss[1] and Daniel Prieto-Alhambra[1]

[1]University of Oxford, Oxford, United Kingdom; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Logistic regression informed by previous knowledge on causal structure and including prespecified confounder/s is traditionally used for propensity score (PS) estimation. Machine learning (ML) methods are promising alternatives for automatic, question-agnostic variable selection and PS estimation.

Objectives: We aimed to assess the performance of different ML methods for data driven variable selection and PS estimation compared to logistic regression in the presence of multiple confounders and big sample size.

Methods: Data (n=100,000) were generated using parametric Monte Carlo simulations, 700 iterations. Binary exposure with prevalence of 0.5 and binary outcome were generated via logistic distributions, assuming true exposure effect of an odds ratio of 1.49. 100 confounders, including 55 normal and 45 binomial distributed, and 10 binary instrumental variables were generated. ML-based PS are estimated without hyperparameter tuning: 1. Logistic regression including confounders only (reference method), 2. Logistic regression with LASSO (Least Absolute Shrinkage and Selection Operator) regularization, with regularization hyperparameter set to 0.01, 3. Random forest with 500 estimators, 4.ANN (Artificial Neural Network) with 2 hidden layers and each of them contains 64 neurons, and 5. Xgboost (eXtreme Gradient Boosting with 500 estimators. Absolute and relative bias (%), and average standardised absolute mean difference (ASAM) after PS matching and Area Under Curve (AUC) of Receiver Operating Characteristic (ROC) curve for PS vs treatment are calculated.

Results: The absolute and relative bias (%) is lowest at 0.07 (18.35%) for reference method, followed by 0.08 (20.16%) for ANN, 0.11 (27.76%) for Xgboost, and 0.12 (28.84%) for logistic regression with LASSO, 0.14 (34.33%) for random forest. ASAM is highest for ANN at 0.023 and lowest for random forest at 0.018. AUC ranged from 0.83 (reference method) to 0.99 (random forest).

Conclusions: ML methods are promising approaches for data-driven PS estimation with ANNs being the most reliable method, followed by Xgboost. Both of them yielded results comparable to standard ("clinically" informed) models including all confounders. Further research on hyperparameter tuning and the performance of these models in different scenarios is needed to guide the use of ML for data-driven PS estimation.

3904 | A neural-network driven longitudinal propensity score for evaluation of drug treatment effects

Jeremy A. Rassen

Aetion, Inc., New York, NY

Background: Insurance claims databases contain substantial information about a patient's longitudinal health status. While traditional propensity scores (PS) summarize covariates measured in aggregate over time (eg, "knee surgery in the 6 months prior to a cohort study's index date"), consideration of the patient's specific course of care over the multi-month period prior to index ("knee surgery 1 month prior to index, then office visits 2 weeks in a row") may yield a PS incorporating nuanced treatment patterns. A recurrent neural network (RNN) -- a machine learning technique using temporal sequences to predict an endpoint -- may be able to capture these patterns in ways that traditional PS estimation cannot.

Objectives: To assess whether an RNN-estimated PS leads to more complete confounding adjustment than a traditional PS in a comparative drug effectiveness question.

Methods: Using IBM's MarketScan Commercial and Medicare data, we identified 93,404 patients who initiated pain treatment with either celecoxib or diclofenac. We captured all insurance claims for each

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patient in the 180 days prior to the index exposure. We coded each type of observed diagnosis, medical procedure, and medication with a unique numeric token, and employed an RNN to predict a PS (probability of exposure to celecoxib) from each patient's token sequence. We matched on this PS and estimated relative risk (RR) of hospitalization for gastrointestinal (GI) bleed. We compared this effect estimate with a traditional PS estimated with logistic regression using 14 investigator-specified dichotomous covariates captured over the same period.

Results: Both methods yielded broadly overlapping PS distributions. The traditional matched PS analysis yielded an RR of 0.88 (0.56, 1.37), while the RR via RNN-based PS was 0.81 (0.41, 1.54), a point estimate more in line with the expectation set by clinical trials.

Conclusions: A longitudinal PS estimated with an RNN can account for patients' full course of care. This technique for capturing nuanced patterns from insurance claims, electronic healthcare records, or other longitudinal data may be considered to further minimize residual confounding.

3947 | Development of a Nordic frailty index based on hospital contacts and prescribed medications

Kasper Bruun Kristensen[1], Peter Bjødstrup Jensen[1], Mette Bliddal[1], Anne Broe[1,2], Lars Christian Lund[1], Emelie Rotbain[1,2], Per Damkier[1,2], Jacob Harbo Andersen[1], Daniel Pilsgaard Henriksen[1,2], Mikkel Højlund[1], Morten Olesen[1], Anton Pottegård[1], Lotte Rasmussen[1], Mette Reilev[1], Morten Rix Hansen[1], Martin Thomsen Ernst[1], Rikke Wesselhöft[1,2] and Jesper Hallas[1]

[1]University of Southern Denmark, Odense, Denmark; [2]Odense University Hospital, Odense, Denmark

Background: The Nordic countries all have universal tax-funded health care with long-standing nationwide registration of hospital contacts and prescribed medications. No generally accepted morbidity index leverages this wealth of data.

Objectives: To develop and test a morbidity index, optimized for the Nordic health care model and data infrastructure.

Methods: Based on a 10-percent sample of the Danish population aged 40 years or above, we analyzed predictors of five-year mortality in a cohort followed from 1 Jan 2014 until death, migration, or end of follow up 31 December 2018. We used a look-back period of five years for hospital contacts (3 digits of the ICD10 code) and six months for prescribed medications (4 digits of the ATC code) in order to reflect prevalent morbidity and drug use. Using clinical review of items coupled with data-driven variable selection, we developed a 50-item predictive model for 5-year mortality. The model was validated in a population separated in time, i.e. a 10-percent sample of the Danish population followed from 1 Jan 2008 until death, migration, or end of follow up 31 December 2012. Model performance was assessed using C-statistics for discrimination, the scaled Brier score, and calibration plots. We compared the discriminatory performance of the model with the two most commonly used existing comorbidity indices; the Charlson and Elixhauser comorbidity indices.

Results: The development cohort (n=284,666) had a five-year mortality rate of 8.9%. Examples of predictors with high weights included use of anti-dementia drugs, use of iron preparations, hospital admittance for dehydration, and a history of femoral fracture. The discriminatory power was good with a C-statistic of 0.838 (95% CI 0.836 to 0.841). The scaled Brier score was 0.229. When applied to the validation cohort (n=269,827, five-year mortality rate 9.7%), both discrimination and calibration was excellent. The C-statistic was 0.833 (95% CI 0.828 to 0.836), the scaled Brier score was 0.225, calibration-in-the-large was 0.14, the calibration slope was 1.025, and the calibration curve showed low miscalibration. The discriminatory performance of the model was markedly better than that of the Charlson comorbidity index (C-statistic 0.633, 95% CI 0.631 to 0.635) and the Elixhauser index (C-statistic 0.665, 95% CI 0.662 to 0.667).

Conclusions: Pending external validation in other Nordic countries, the model has promising performance exceeding that of commonly used existing indices and might have general utility in Nordic register-based epidemiological research.

3953 | Assessing techniques for quantifying the impact of bias due to an unmeasured confounder

Julie Barberio[1], Thomas P Ahern[2], Richard MacLehose[3], Lindsay J Collin[1], Deirdre Cronin-Fenton[4], Per Damkier[5], Henrik Toft Sørensen[4] and Timothy L Lash[1]

[1]Rollins School of Public Health, Emory University, Atlanta, GA; [2]The Robert Larner, M.D. College of Medicine, University of Vermont, Burlington, VT; [3]University of Minnesota, Minneapolis, MN; [4]Aarhus University Hospital, Aarhus, Denmark; [5]Odense University Hospital, Odense, Denmark

Background: Bias analysis methods that assume an unmeasured confounder is independent of controlled confounders likely overestimate the impact of bias.

Objectives: To evaluate whether methods used to assess the impact of an unmeasured confounder overestimate the magnitude of bias in an applied example.

Methods: We examined the association between cumulative milligrams of dibutyl phthalate [DBP] exposure and incident estrogen receptor [ER]-positive breast cancer in a Danish nationwide cohort. Cox regression models were adjusted for age and drugs contributing to DBP exposure (bisacodyl, budesonide, diclofenac, diclofenac combinations, lithium, mesalamine, multi-enzyme). We then estimated hazard ratios (HRs) that would have been observed if one of the DBP sources was "unmeasured" and not included in the regression. The strength of confounding was estimated by comparing this HR to the fully adjusted HR. E-values were calculated to assess the minimum strength of association the "unmeasured" variable would need to have with DBP and with incident ER-positive breast cancer to explain away the observed association. We then performed a quantitative bias

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

analysis to adjust for the "unmeasured" confounder, specifying the following bias parameters: the association between the unmeasured confounder and DBP (based on the United States National Health and Nutrition Examination Survey), the association between the unmeasured confounder and incident breast cancer (based on literature), and prevalence of the unmeasured confounder (based on Finnish statistics). Bounds on the bias due to the "unmeasured" confounder were estimated.

Results: The adjusted HR for incident ER-positive breast cancer among women with high-level DBP exposure (≥10,000 cumulative mg) compared to unexposed women was 2.12 (95% CI 1.12 to 4.05). Removing each DBP source in isolation resulted in negligible change of the HR (*i.e.*, relative bias due to confounding ranged from 0.95 to 1.00). E-values ranged from 3.46 to 3.68. Using the specified bias parameters, the estimated relative bias due to uncontrolled confounding ranged from 1.00 to 1.01. The maximum impact due to unmeasured confounding ranged from 1.01 to 1.51.

Conclusions: In this example, the impact of bias due to unmeasured confounding is negligible, in part because the unmeasured variable was not independent of controlled variables. When knowledge about a potential unmeasured confounder is available, we suggest quantitative bias is the most informative as to the impact from an uncontrolled confounder. E-values may best be reserved for situations in which an unmeasured confounder is unknown.

3973 | Use of sensitivity analyses to assess uncontrolled confounding in observational, head-to-head pharmacoepidemiologic studies: A systematic review

Chase Latour[1], Charles Poole[1], Jessie Edwards[1], Til Stürmer[1], David Martin[2], Jennifer L Lund[1], Nahleen Lopez[2] and Michele Jonsson Funk[1]

[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC;* [2]*Food and Drug Administration, Bethesda, MD*

Background: Understanding the likely direction and magnitude of uncontrolled confounding is critical in the context of real-world evidence based on analysis of non-randomized treatments. Many tools have been developed to assess this bias under various sets of assumptions, but it is unknown how and to what degree researchers are routinely using these methods.

Objectives: To summarize use of sensitivity analyses to assess uncontrolled confounding in observational, head-to-head comparison cohort studies of drugs and biologics published in high-impact, major medical journals.

Methods: We systematically reviewed articles in five high-impact, major medical journals published between January 1, 2017 and December 31, 2019. We initially identified candidate studies through title review of all original research articles, collecting any focusing on medical treatments. Based on abstract review, we included studies that implemented a head-to-head comparison cohort study design as a primary analysis to compare drugs or biologics. We read the full text of these articles and noted any methods used to evaluate uncontrolled confounding.

Results: Among 2,343 original research articles published in five selected journals, 43 head-to-head comparison cohort studies were identified. Of those, 28 (65%) implemented propensity score matching or weighting in primary analyses. Twenty-three (53%) articles conducted additional analyses that may inform judgements regarding uncontrolled confounding (e.g., estimating the treatment effect in a subset with additional covariate data, propensity score trimming). However, only 15 (35%) implemented 1+ sensitivity analyses using a previously published method specifically designed to assess this form of bias. The most common of these were the negative-control design (n=9) and the E-value (n=5). No studies reported effect estimates (with or without uncertainty intervals) directly adjusted (e.g. using quantitative bias analysis) for known or suspected uncontrolled confounders (e.g. BMI, smoking). Thirty-eight (88%) articles mentioned residual or uncontrolled confounding as a limitation.

Conclusions: Multiple methods have been developed to evaluate the potential impact of uncontrolled confounding. Despite this, often researchers note this as a limitation without formally evaluating the potential direction or magnitude of this bias. More rigorous assessment of potential bias due to uncontrolled confounding requires not only innovation in methods but also changing expectations.

4019 | Deep learning-based propensity scores for confounding control in comparative effectiveness research: A large-scale real-world data study

Janick Weberpals[1], Tim Becker[2], Jessica Davies[3], Fabian Schmich[1], Dominik Ruettinger[4], Fabian Theis[5,6] and Anna Bauer-Mehren[1]

[1]*Pharmaceutical Research and Early Development Informatics (pREDi), Penzberg/Munich, Germany;* [2]*xValue GmbH, Willich, Germany, on behalf Pharmaceutical Research and Early Development Informatics (pREDi), Penzberg/Munich, Germany;* [3]*F. Hoffmann-La Roche Ltd, Welwyn Garden City, United Kingdom;* [4]*Pharmaceutical Research and Early Development (pRED), Penzberg/Munich, Germany;* [5]*German Research Center for Environmental Health, Helmholtz Center Munich, Munich, Germany;* [6]*Technical University of Munich, Munich, Germany*

Background: Due to the non-randomized nature of real-world data, baseline confounders need to be balanced, which is often done by propensity scores (PS). However, the correct specification of the PS model in practice remains challenging.

Objectives: To investigate if autoencoders, which are unsupervised deep learning architectures, might be leveraged as a data-adaptive alternative to compute the PS.

Methods: Overall, patient-level data of 121,736 first-line treated patients with cancer were selected from the Flatiron Health EHR-derived de-identified database. An autoencoder architecture was trained to learn a latent non-linear patient representation reflecting a lower-dimensional embedding of the true data manifold. This embedding was used to compute the PS. To compare the performance of an

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

autoencoder-based PS this method was challenged against currently used approaches including investigator-defined (manual) variable selection and principal component analysis (PCA) within a plasmode simulation framework. To that end, 2700 datasets with each 20,000 patients and 27 different scenarios of confounding bias were simulated. The adjustment performance of each PS method was assessed using root-mean-square-errors (RMSE) and percent bias. To illustrate the application of the autoencoder-based PS, the study question of the 2015 published phase III PRONOUNCE trial was investigated as exemplary case study comparing the effectiveness of first-line carboplatin/pemetrexed vs. bevacizumab/carboplatin/paclitaxel followed by maintenance therapy in advanced non-small cell lung cancer patients.

Results: Overall, the autoencoder approach led to well balanced cohorts in each simulation scenario and yielded on average the lowest deviation of resulting hazard ratio (HR) estimates (RMSE 0.0276) as compared to manual variable selection (0.0651) and PCA (0.0605). The average bias was observed with 1.88%, 5.39% and 4.91% for autoencoder, manual variable selection and PCA, respectively. These results were consistent in each simulated scenario and in sensitivity analyses. In the case study, the autoencoder-based PS estimate was consistent with the published estimate from the PRONOUNCE trial ($HR_{autoencoder}$ 1.07 [95% CI 0.83-1.38] vs. $HR_{PRONOUNCE}$ 1.07 [0.83-1.36]).

Conclusions: Automated autoencoder-based PS computation was found to have a good performance in reducing bias from measured confounders.

4021 | Approaches to reduce the immeasurable time bias in cohort studies: A Monte Carlo simulation study and real-world example

In-Sun Oh[1], Han Eol Jeong[1], Hyesung Lee[1], Kristian B Filion[2,3,4] and Ju-Young Shin[1]

[1]Sungkyunkwan University (SKKU), Suwon, Republic of Korea; [2]McGill University, Montreal, QC, Canada; [3]McGill University, Montreal, QC, Canada; [4]Lady Davis Research Institute - Jewish General Hospital, Montreal, QC, Canada

Background: Immeasurable time bias may exaggerate drug benefits when in-hospital drug data are missing. However, the validity of approaches proposed to reduce this bias remains unclear in varying degrees of immeasurable time.

Objectives: To assess the validity and performance of approaches proposed to reduce immeasurable time bias in cohort studies in a Monte Carlo simulation and real-world example.

Methods: In our Monte Carlo simulation, we generated immeasurable time depending on factors related to hospitalization such as its duration, frequency, and timing. In total, 9 scenarios were created: 3 duration scenarios (empirical setting, ±30% of empirical setting) across 3 frequency scenarios (empirical setting, ±30% of empirical setting), where the empirical cohort distribution of hospitalization was used to simulate the 'timing'. For both our simulation and empirical study, we used Korea's healthcare database and a case example of β-blockers and mortality among patients with heart failure. Exposure was defined using a time-varying approach. We estimated the gold standard hazard ratio (HR) with 95% confidence intervals (CI) using both in- and outpatient drug data, and that of the pseudo-outpatient setting using outpatient data only. We assessed 12 approaches to restrict, stratify, and weight using measurable time (non-hospitalized time) to reduce the bias. Then, to determine the validity of the 12 approaches in the 9 different scenarios, we evaluated their performance using relative bias and mean squared error (MSE) compared to the empirical gold standard estimate across 1,000 bootstrap resamples.

Results: The empirical gold standard estimate (HR 0.93, 95% CI 0.86-0.99) was the reference estimate for both our simulation and empirical studies. In our simulation study, the approach of weighting by measurable time in a cohort restricted to those hospitalized <50% of the total follow-up had the smallest relative bias (-6.70%; range -6.70% to -7.35%) and MSE (0.004; range 0.004 to 0.005). Across all 9 scenarios and 12 approaches assessed, this approach generally produced the least biased estimate. For our empirical study, the immeasurable time bias overestimated drug benefits on mortality with a pseudo-outpatient estimate of 0.77 (0.71-0.84). The approach parallel to that of in our simulation study (0.89, 0.88-0.89) was also most effective at reducing the bias in our empirical study.

Conclusions: The approach of weighting by measurable time in a cohort of patients without extreme hospitalizations effectively reduced the immeasurable time bias in our simulation setting and real-world example.

4362 | Example of an over-fitting issue in a logistic regression estimating a high-dimensional propensity score

Caroline Foch, Michael Batech, Ulrike Gottwald-Hostalek, Patrice Verpillat and Emmanuelle Boutmy

Merck KGaA, Darmstadt, Germany

Background: If blood pressure (BP) is not controlled under monotherapy, European guidelines suggest switching toward a combination therapy of antihypertensive dugs rather than up-titrating the dosage.

Objectives: In hypertensive patients, to investigate if switching from a monotherapy amlodipine 5 mg toward a combitherapy bisoprolol 5 mg and amlodipine 5 mg (combi) is non-inferior to up-titrating toward amlodipine 10 mg (mono) in terms of change in systolic BP.

Methods: In the CPRD, hypertensive patients switching from amlodipine 5 mg toward either a combi or a mono, between 2000-2018, were included. The start of the combi or the mono exposure was defined as the index date. With a large numbers of covariates ascertained from CPRD to address confounding issues, a high-dimensional propensity score (hdPS) matching method was used, with a ratio of 1:5 (combi:mono). We specified 5 dimensions (drug, current diagnosis, medical history diagnosis, referral, and procedures),

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and for each retained the most 200 prevalent codes within the 181 days prior to the index date. Recurrence of codes was used to create 3 binary covariates if the code appeared once, more than the median or more than the 75th percentile. Based on the method described by Schneeweiss et al. (Epidemiology 2009;20(4):512-22), the top 500 covariates were then selected. Patients were then matched, without replacement, on exact age, sex, and the hdPS (caliper 0.01). (ISAC number 19_069)

Results: A total of 395 and 48,085 patients were included respectively in the combi and mono cohorts. Due to the very low number of patients in the combi cohort (0.82% of the total study size), the logistic regression estimating the hdPS did not fit the probability of being treated by the combi (median hdPS 0.04 (IQR, 0.01-0.21)). In order to reduce the sample size difference between the 2 cohorts, the size of the mono cohort was restricted based on a random sample of 25%, 20%, 15%, 10%, and 5% of the CPRD population. The hdPS was then computed on each of the x% sample of the mono cohort and on the full combo cohort. The model was then able to estimate a probability of being treated by the combi (median hdPS 0.32, 0.33, 0.47, 0.62, and 0.84, respectively with a random sample of 25%, 20%, 15%, 10%, and 5%).

Conclusions: In this context of a significant imbalance in the size of the two cohorts, computing the probability of being treated by one option or the other was not optimal, leading to overfitting errors in the regression coefficients and thereby underestimating the probabilities. Up to our knowledge, this over-fitting issue has been described extensively in the context of logistic regression but not of hdPS.

4395 | Machine learning to optimize and automate confounding control in studies using high-dimensional healthcare data

Xuerong Wen[1], Mark van der Laan[2], Richard Wyss[3], Robert W. Platt[4], Romin Pajouheshnia[5], Sebastian Schneeweiss[3]

[1]University of Rhode Island, Kingston, WA; [2]University or California, Berkeley, Berkeley, CA; [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [4]McGill University, Montreal, QC, Canada; [5]Utrecht Institute for Pharmaceutical Sciences, Kingston David de Wiedgebouw, Netherlands

Background: Using machine learning (ML) methods, including super learner, hybrid learner, and collaborative targeted maximum likelihood estimation (CTMLE), in high-dimensional confounding adjustment promises to reduce unmeasured confounding and optimize control in a given data set. However, concerns remain whether these methods can avoid bias amplification from inappropriate adjustment for instrumental variables or colliders.

Objectives: To provide an in-depth overview of recent advancements that expand the frequently-used high-dimensional propensity score (hdPS) framework with ML to help automate covariate identification and prioritization for improved causal effect estimation. Researchers working on high-dimensional real-world data, comprised of electronic health record, administrative, clinical, and other healthcare data, will benefit from attending this symposium.

Description: We will first describe how hdPS optimizes confounder identification and selection free of cognitive biases through automated feature generation and prioritization and why it may reduce bias from unmeasured confounding through proxy adjustment. Insight will be provided into the conditions under which an assumption of reduced unmeasured confounding is likely to hold, and whether this might outweigh the potential cost of adjusting for colliders or instrumental variables, which is known to potentially increase residual bias. Additional ML algorithms are thought to optimize covariate prioritization in the framework of causal inference. We will summarize recently proposed hdPS extensions that incorporate additional ML algorithms and their ability to address potential complications to causal interpretations of findings. The discussion around the pros and cons of these approaches will focus on: a) data structures in which the methods might perform similarly and/or differently; and b) cases of potential model misspecification due to investigator-driven variable selection approaches to propensity score estimation. Finally, we will introduce CTMLE that incorporates ML in estimation of both the treatment mechanism and the outcome regression, and provides statistically efficient estimations of target estimands in causal inference. The CTMLE framework and its cross-validation for selecting tuning parameters of the embedded ML algorithms will be discussed.

4604 | Mapping warfarin exposure in the clinical practice research datalink (CPRD)

Anneka Mitchell[1,2], Julia Snowball[1] and Anita McGrogan[1]

[1]University of Bath, Bath, United Kingdom; [2]University Hospital Southampton, Southampton, United Kingdom

Background: Misclassification can have a substantial impact on the results of studies when using prescription data to define exposure status. Warfarin is difficult to map as it does not have a fixed dosing schedule and doses vary widely between and within individuals over time due to clinical and genetic factors.

Objectives: To develop a method of mapping warfarin exposure in the CPRD using a combination of prescription, clinical and test data.

Methods: In the UK, prescriptions (Rx) for warfarin are issued as 0.5, 1, 3, and 5mg tablets and the patient's dose is determined by a blood test (INR). The CPRD contains details of prescriptions issued (date issued, quantity, strength, form) but not the dose recommended. A group of patients aged ≥75 years with atrial fibrillation and warfarin prescribed between 01/01/03 - 27/12/17 were identified. All warfarin Rx data were extracted and ordered by date. For each strength, the expected end date (EED) of the 1st Rx was defined as the day before the 2nd Rx issue date. EEDs for subsequent scripts were calculated using the median gap in days between all prior scripts of the same strength (capped at 1 year). Where there was a gap of more than twice the median between the EED of one Rx and the issue date of the next, the patient was defined as having discontinued that

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

strength; any subsequent Rx were classed as a new episode. Where episodes of the different strengths overlapped, patients were defined as continuously exposed. Test data were searched between Rx episodes for INR test results ≥ 2 which would suggest a patient was still exposed. Clinical data were searched for codes stating either warfarin was stopped or that the patient was still receiving warfarin when Rx mapping had defined them as unexposed: where these codes occurred, the stop date was amended.

Results: Rx mapping was done for 86 277 patients. Clinical codes indicating a patient was taking warfarin were present for 73% of patients. 53% had at least 1 clinical code suggesting they were still taking warfarin in a gap between prescriptions. Clinical codes indicating warfarin had been stopped were present for 15% of patients. At least one INR test result was recorded for 38% of patients and 15% of patients had an INR ≥ 2 after prescription mapping alone suggested warfarin had been discontinued.

Conclusions: Rx mapping is used to estimate drug exposure in electronic health databases. Drugs such as warfarin can be difficult to map as they do not have a fixed dosing schedule and doses can vary widely. Test results and clinical records are vital in improving prescription mapping algorithms to better estimate drug exposure in the CPRD thereby reducing misclassification in drug safety studies.

4612 | The use and quality of reporting of propensity score methods in multiple sclerosis literature

Mohammad Ehsanul Karim[1,2], Fabio Pellegrini[3], Robert W Platt[4,5], Gabrielle Simoneau[4], Julie Rouette[4,5] and Carl de Moor[6]

[1]School of Population & Public Health, University of British Columbia, Vancouver, BC, Canada; [2]Centre for Health Evaluation and Outcome Sciences, University of British Columbia, Vancouver, BC, Canada; [3]Biogen International GmbH, Baar, Switzerland; [4]Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada; [5]Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [6]Biogen Inc, Cambridge, MA

Background: Propensity score (PS) analyses are increasingly used in multiple sclerosis (MS) research, largely owing to the increasing availability of large observational cohorts and registry databases.

Objectives: This review evaluates the use and quality of reporting of PS methods in the recent MS literature.

Methods: We searched the PubMed database for articles published between January 2013 and July 2019. We restricted the search to comparative effectiveness studies of two disease-modifying therapies. We identified data elements from the PS literature and conducted the review using a pilot-tested form, refined over several iterations of the extraction process.

Results: Thirty-eight studies were included in the review, with most studies (61%) published within the past three years. All studies reported the list of covariates used for the PS model but only 21% of studies mentioned how those covariates were selected. Most studies used PS matching (71%), followed by PS adjustment (18%) and weighting (16%). Most studies using matching or weighting reported checking post-PS covariate imbalance (91%), although about 43% of studies relied on p-values for various statistical tests. Only 21% of studies using matching reported calculating robust standard errors for the PS analyses.

Conclusions: The quality of reporting of PS methods in the MS literature is sub-optimal in general, and in some cases, inappropriate methods are used. MS-specific guidelines are needed to improve the understanding and reporting of PS methods by MS researchers.

4754 | Divide and recombine approaches for propensity score matching in huge data: A case study using the Brazilian 100M cohort

Gabriela L Borges[1], M Sanni Ali[2,1], Mauricio Barreto[1], Dandara Ramos[3,1], Liam Smeeth[2,1] and Rosemeire L Fiaccone[3,1]

[1]Centre for Data and Knowledge Integration for Health - Fiocruz, Salvador, Brazil; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]Federal University of Bahia, Salvador, Brazil

Background: Due to an increase in the range of databases, the direct application of PSM to the entire data is either infeasible or impractical in terms of computing resources. In Divide & Recombine (D&R), the data is divided into subsets, an analytic method is applied independently to each subset, then the outputs are recombined. The use of multiple processors/cores simultaneously is easily applicable as ways to increase procedure's speed.

Objectives: To evaluate the performance of propensity score methods using "D&R" approaches in huge data to reduce bias of selection in a observational study of the 100M Cohort.

Methods: The 100M Cohort is derived from individual records of the Cadastro Único (CadUnico) that identifies low-income families applying for any of the several social protection programs. Applicants answer a detailed form that includes household characteristics and demographic, economic, and social information of the individual and each member of the family. We use the data to estimate the effect of a Brazilian cash-transfer program in childhood mortality. PSM was performed: 1) The data was split in k-samples; and 2) In each of the k-sample data PSM was performed with and without calliper using twelve cofounders such as race, cohort entrance, domiciliar density, living conditions and more; 3) The covariate balance was assessed using absolute standardized mean difference (SMD); 4) Results are recombined using weighted mean. Comparisons between the most common propensity score methods such stratification, inverse probability weighting and D&R matching were performed through covariate balance using SMD.

Results: In Baseline, there are huge differences between treated and untreated groups (SMD > 10% for all covariates). PSM analysis with the full dataset (about 18million observations) was infeasible in R and STATA. PSM with D&R approach gave the most balanced groups (SMD < 13% for all covariates), improved inclusively the covariate balance of cohort entrance covariate (87% in baseline vs 13% in PSM

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

with D&R). PS stratification with five quintiles resulted in SMD in the range from 1% to 26% and IPTW 1% to 52%.

Conclusions: It is important to note that the covariable balance implies a minor bias in the treatment effect. In general, PSM is the most restrictive method of propensity scores, resulting in more balanced treated and untreated groups. In huge data, the direct application of PSM is impossible but D&R shows an efficient alternative to implement PSM analysis with huge data without reducing its constraint and maintaining its level of covariate balance.

4775 | Impact of missing information recorded outside of study electronic health records on comparative safety and effectiveness studies

Kueiyu J. Lin[1,2], Joshua J. Gagne[1], Yinzhu Jin[1] and Sebastian Schneeweiss[1]

[1]*Brigham and Women's Hospital and Harvard Medical School, Boston, MA;* [2]*Massachusetts General Hospital and Harvard Medical School, Boston, MA*

Background: Electronic health records (EHR) discontinuity (i.e. receiving care outside of an EHR system) is associated with substantial misclassification of key variables when using EHR data for comparative effectiveness research (CER). We previously developed a prediction algorithm to identify patients with high EHR-continuity, but the impact of this algorithm has not been assessed in real-world comparative studies.

Objectives: To compare effect estimates in patients with high vs. low EHR-continuity in two studies: (1) sulfamethoxazole/trimethoprim vs. cephalexin on hospitalization with hyperkalemia in 2 weeks; and (2) nonsteroidal anti-inflammatory drugs vs. opioids on hospitalization with acute kidney injury in 1 year in patients with arthritis.

Methods: Study cohorts comprised patients aged ≥ 65 years in an EHR from 2 US provider systems (system "A" and "B") linked with Medicare insurance claims data from 2007/1/1 to 2014/12/31. We previously used System A for training and System B for validating the prediction model. Patients with high vs. low EHR-continuity were defined as having predicted EHR-continuity in the top 50% vs. lower 50%. We used Cox proportional hazards regression with new user design to adjust for potential confounding. The gold-standard estimates were based on linked EHR-claims data (to assess outcome and confounding variables) since claims data capture medical information recorded outside of study EHR. Comparing estimates based on only EHR (E_ep, error-prone) vs. linked EHR-claims data (E_gs, gold-standard), we calculated % bias [(E_ep - E_gs)/E_gs] and 95% confidence interval (CI) overlap [the intersection divided by union of the 95% CI of E_ep and E_gs]. We only used EHR to define user cohorts to ensure comparison was done in the same study population.

Results: For study 1, we identified 16,021 patients (201 events) and 11,997 patients (171 events) in systems A and B, respectively. For study 2, the corresponding numbers were 7,635 patients (448 events) and 6,306 patients (350 events). Similar patterns of results were observed in the two systems. In System A, for study 1, the % bias and 95% CI overlap of the hazard ratio (HR) was 0.1% and 95.0% in patients with high EHR-continuity and 48.3% and 37.8% in those with low EHR-continuity. For study 2, % bias and 95% CI overlap was 0.5% and 87.0% for high EHR-continuity and 16.7% and 72.7% for low EHR-continuity.

Conclusions: In 2 examples, we found that a previously developed prediction model may be useful for identifying patients with high EHR-continuity in which bias in adjusted estimates was meaningfully reduced.

4795 | Comparison of methods for incorporating test result information within the high-dimensional propensity score framework

John Tazare, Jeremy P. Brown, Liam Smeeth, Stephen J. W. Evans, Elizabeth Williamson and Ian J. Douglas

London School of Hygiene & Tropical Medicine, London, United Kingdom

Background: Laboratory test results are commonly available in electronic health records (EHRs) and can contribute to confounder adjustment. The optimal method for incorporating them in the high-dimensional propensity score (hd-PS) framework is unclear since the hd-PS creates binary covariates from the presence of codes. Applying this to test data ignores potentially large amounts of continuous data measured. Whilst binary categorisation offers a simple solution, concerns surrounding the loss of statistical power motivate the need for a more general solution.

We use a recent study where results strongly suggested residual confounding remained after hd-PS adjustment to illustrate various approaches.

Objectives: To propose and illustrate methods for incorporating laboratory test results when applying the hd-PS in EHRs.

Methods: We derived a cohort of proton pump inhibitor (PPI) and h2-receptor antagonists (H2RA) users from the UK Clinical Practice Research Datalink. All analyses estimated the hazard ratio (HR) of cause-specific mortality amongst PPI and H2RA users using a Cox model adjusting for confounders via hd-PSs; including 500 empirically-selected covariates. Initially test results were included using the established hd-PS assessment of code recurrence, since signs of increased healthcare utilisation were likely to be an important proxy for underlying health status. We further investigated semi-automated methods for incorporating the numerical test values within the hd-PS procedure. Hd-PS analyses incorporating clinical, referral and prescription dimensions were compared, with and without the addition of a test dimension.

Results: Our cohort consisted of 733,885 new users of PPIs and 124,410 new users of H2RAs. We focus on chronic obstructive pulmonary disease (COPD) specific mortality as the outcome; however similar trends were seen across other outcomes. Of PPI users, 7,846 (1.1%) had COPD-specific mortality versus 538 (0.4%) of H2RA users. Applying a standard implementation of hd-PS we obtained a HR of 1.36 (95% CI: 1.14 to 1.64), while incorporating test result data resulted in effect estimates closer to the expected null result (HR 1.24; 95% CI:

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

1.00-1.54). Of the 500 empirically selected covariates, 38% originated from the test dimension. Furthermore, test results contributed 53 of the top 100 covariates, as ranked by the Bross formula.

Conclusions: This study illustrates the potential for laboratory test result information to improve the ability of hd-PS approaches to minimise residual confounding in EHRs.

4824 | Transparency of high-dimensional propensity score analyses: Guidance for diagnostics and reporting

John Tazare[1], Richard Wyss[2], Jessica M Franklin[2], Liam Smeeth[1], Stephen JW Evans[1], Shirley V Wang[2], Sebastian Schneeweiss[2], Ian J Douglas[1], Elizabeth Williamson[1] and Joshua J Gagne[2]
[1]London School of Hygiene & Tropical Medicine, London, United Kingdom; [2]Brigham and Women's Hospital, Boston, MA

Background: The high-dimensional propensity score (hd-PS) is a semi-automated procedure for confounder identification, prioritization, and adjustment in large healthcare databases that requires investigators to identify data dimensions, prioritization strategy, and tuning parameters. Despite studies highlighting the sensitivity of results to these decisions, in practice, reporting is inconsistent. This can undermine the transparency, reproducibility and validity of results obtained. While recent reporting guidelines for pharmacoepidemiological research, for example the RECORD-PE statement, advocate for complete reporting of methods for high dimensional proxy adjustment, more detailed guidance is needed.

Objectives: To develop and illustrate guidance on diagnostics and reporting of hd-PS analyses.

Methods: We use examples from a diverse range of healthcare database studies where hd-PS had been previously applied to help illustrate the application of graphical tools and sensitivity analyses set out in our proposed guidance.

Results: We highlight relevant sensitivity analyses to explore the robustness of results to tuning parameter decisions made by the investigator, such as varying the number of covariates selected in the prioritisation step of the hd-PS. In the conventional propensity score setting there are a range of measures for assessing covariate balance. However, the extent to which these are suitable for high-dimensional settings is unclear, especially since matching on many weak confounders could reduce the balance on strong confounders. We recommend assessing the balance of the pre-defined variables before and after adjusting for the empirically-identified variables as a way to measure the potential impact on balance of including a particular number of hd-PS covariates. For reporting, we propose a framework describing key decisions made at each stage of the hd-PS algorithm. This includes the identification of data dimensions, method for code prioritisation and number of variables selected.

Conclusions: The potential benefits of the hd-PS approach have led to its popularity as a method for confounder adjustment in pharmacoepidemiological research. Reporting of these analyses in practice may be improved by the guidance and tools developed here and can be usefully applied to increase the transparency and reproducibility of results.

4833 | Propensity score approaches with multilevel data: A simulation study

Gabriela L Borges[1], Marisleane Moreira[2], M Sanni Ali[3,1], Mauricio L. Barreto[1], Liam Smeeth[3] and Rosemeire L Fiaccone[2,1]
[1]Centre for Data and Knowledge Integration for Health - Fiocruz, Salvador, Brazil; [2]Federal University of Bahia, Salvador, Brazil; [3]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Propensity score matching involves several implementation steps including estimation, selection of a matching algorithm, and estimation of the intervention effect in which it assumes that the observations are independent. In situations involving data with multilevel structure it is essential that the propensity score estimation takes into account the effects of observations of the different levels on the likelihood of treatment assignment as well as the estimation of the treatment effect.

Objectives: To explore the different approaches in calculating the propensity score taking into account the multilevel structure of the data in non-experimental or observational studies.

Methods: We used Monte Carlo simulations to generate 1.000 datasets with different sample sizes and treatment effects. Covariates were created using binomial, normal and multinomial distribution different according to its levels. The idea to incorporate the multilevel structure in propensity score has two perspectives: 1) taking into account multilevel structure in the matching and; 2) taking into account structure when calculating the propensity score. In the first approach, matching within the cluster (W) is used, preferably within the cluster (PW). In the second strategy, the multilevel structure considered in the calculation of the propensity score is performed by adjusting a model with a random intercept and also considering the structure of the cluster as a fixed effect.

Results: In most scenarios, the inclusion of level 2 variables in the propensity score models, in most scenarios, generated a smaller number of units excluded from the analysis, a better balance between the groups and a reduction in the relative bias of the ATT.

Conclusions: The results revealed that, when we included the level 2 variables in the propensity score estimation models, on average, it generated a reduction in the proportion of observations excluded from the analysis and a better balance between the treated and control groups.

4835 | Comparing optimization techniques and propensity scores for matching in observational studies of rare populations

Stephen Fortin, Stephen Johnston and Paul Coplan
Johnson and Johnson, New Brunswick, NJ

Background: In the setting of rare populations, the use of regression-based techniques for propensity score estimation to summarize large

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

numbers of matching covariates may be hindered by limited degrees of freedom or an insufficient number of observations per matching covariate (e.g. few treated patients per covariate). Cardinality matching (CM) uses recent advancements in optimization to find the mathematically-guaranteed largest matched sample size meeting prespecified balance criteria, by directly targeting the distributional balance of matching covariates; therefore, CM is not subject to the inherent limitations of regression-based propensity score estimation techniques.

Objectives: We compare the performance of propensity score matching (PSM) and CM while matching on progressively larger numbers of covariates in a rare population (patients undergoing total pancreatectomy); specifically, we match patients undergoing open surgery (OS) to those undergoing minimally-invasive surgery (MIS).

Methods: Retrospective, cross-sectional analysis of U.S. data from the Premier Healthcare Database. Included patients were aged ≥18 years undergoing total pancreatectomy between 10/1/2015-3/31/2019. PSM was performed through nearest-neighbor matching (1:1, caliper=0.15). CM was performed through 1:1 matching permitting a maximum SMD of 0.10 for matching covariates. We performed 3 separate matches: match1 included patient demographic and clinical characteristics (11 covariates, 24 levels); match2 added hospital and provider characteristics (18 covariates, 40 levels); match3 added select comorbidities from the Elixhauser comorbidity index (41 covariates, 63 levels). We compared PSM and CM on post-match sample size and number of imbalanced (e.g., SMD ≥0.10) matching covariates.

Results: A total of 281 patients (OS: 114, MIS: 167) met the study criteria; 28 covariates were imbalanced before matching. Total post-match sample sizes were: PSM=198 (13% loss vs. maximum 1:1 matched sample N=228) and CM=226 (1% loss; match1); PSM=192 (16% loss) and CM=220 (3% loss; match2); and PSM=162 (29% loss) and CM=218 (4% loss; match3). In the 1st, 2nd and 3rd match, there were 4, 5 and 11 imbalanced matching covariates, respectively, for PSM; CM resulted in 0 imbalanced covariates.

Conclusions: In this applied comparison of CM vs. PSM in a small sample of patients undergoing total pancreatectomy, CM outperformed PSM in terms of post-match sample size and covariate balance. Optimization techniques may be superior to regression-based propensity score techniques when matching in rare populations.

4975 | plasmode simulation to address confounding bias due to missing data in a large electronic health records dataset

Svetlana Puzhko, Gillian Bartlett and Tibor Schuster
McGill University, Montreal, QC, Canada

Background: Missing data on salient variables in large databases is an important issue as naïve complete case (CC) analysis may invalidate effect estimates due to confounding induced by non-random case selection. There are different statistical approaches to deal with this issue but no general rule on how to evaluate their applicability and validity. 'Plasmode' simulation studies are a promising tool to systematically assess the potential effect of missing data on a specific real-world dataset.

Objectives: Using plasmode simulation, to compare accuracy and precision of estimated exposure effects using CC and multiple imputation by chained equations (MICE) in the presence of missing data in a large dataset.

Methods: Source. The Canadian Primary Care Practice-based Electronic Medical Record Database (CPCSSN), for 2011-2016. **Measures.** Exposure: obesity; outcome: antidepressants prescribing; covariates: age, sex, comorbidities. **Analysis.** We generated 200 plasmode datasets. Exposure and outcome data, and a missingness pattern were simulated using structure of the original dataset; original data covariates were included. Proportion of missing data was similar to the original dataset and was stochastically dependent on measured covariates. MICE with predictive mean matching was used. CC and MICE were analyzed by binary logistic regression and compared for accuracy and precision.

Results: In the original dataset, 47% data on weight was missing. Each generated plasmode dataset contained 62145 observations; CC datasets lacked data on exposure for 29445 observations. The mean true exposure coefficient (log odds ratio ß) was 0.154, standard error (SE)=0.019; the mean estimates for ß were 0.155 for CC and 0.153 for MICE, respectively; SE=0.026 for both CC and MICE. Relative bias for both CC and MICE was <0.001. The empirical mean root mean square error was 0.6218 for MICE and 0.6041 for CC. Simulation settings inducing stronger associations between the covariates and missing data prevalence did not substantially change the results.

Conclusions: Our results show robustness of the CC analysis regarding confounding bias due to missing data in our specific data setting. Our observations are likely explained by the structure of our data: there was low variation of propensity score levels across individuals, suggesting limited potential confounding impact of the covariates considered. This may suggest that CC analysis of the original data is appropriate, imputing data with MICE would not be of benefit. Plasmode simulation studies are helpful to choose how best to handle missing data in large real-world datasets.

5013 | Discriminative ability of new injury severity score to predict outcomes after fracture repair surgery

Zhenna Huang[1], Deepak Krishnan[2], Chantal Holy[1], Mollie Vanderkarr[1] and Sparks Charisse[1]
[1]*Johnson and Johnson, New Brunswick, NJ;* [2]*Mu-sigma, Bangalore, India*

Background: New injury severity score (NISS) is the simple sum squares of the three most severe injuries (highest abbreviated injury scales) regardless of body region. It is shown to be predictive of survival after injury. The Elixhauser comorbidity index (ECI) has been used as a risk-adjustment tool in quality and safety data.

Objectives: This study aims to investigate whether NISS should be included in addition to ECI for postoperative outcomes prediction following fracture repair surgery.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: Through a partnership with Mercy Technology Services, a retrospective database analysis of Mercy electronic health records was conducted. Patients 18 years and older who underwent fracture repair surgery between 2011-2018 were identified. Postoperative outcomes assessed were: (1) 3-month infection after surgery, (2) all-cause 3-month readmissions, (3) 1-year all-cause mortality, (4) extended LOS (≥ 3days) and (5) skilled nursing/rehabilitation discharge. For each outcome, four multivariable logistic regression models were constructed: 1) Age + gender + BMI, 2) Age + gender + BMI + ECI, 3) Age + gender + BMI + NISS and 4) Age + gender + BMI + ECI + NISS. The predictive performance was assessed using area under the curve analysis (AUC) derived from these models.

Results: A total of 14,044 fracture repair patients were included in the analysis (age median: 65, IQR, 47-81, 59% female). NISS outperforms ECI in the prediction of extended LOS and skilled nursing/rehabilitation discharge. The model AUC (95% Confidence Interval (CI)) of baseline, ECI, NISS, ECI+NISS for extended LOS were 0.72 (0.72-0.73), 0.76 (0.75-0.76), 0.84 (0.83-0.84), and 0.85 (0.85-0.86) respectively. The model AUC (95% CI) of baseline, ECI, NISS, ECI +NISS for skilled nursing/rehabilitation discharge were 0.85 (0.85-0.86), 0.867 (0.86-0.87), 0.89 (0.885-0.896), and 0.898 (0.893-0.903) respectively. NISS did not add significant additional discrimination ability to ECI models for infection, mortality and readmission.

Conclusions: In addition to traditional ECI comorbidity predictor, NISS adds significant additional discrimination ability for length of stay and discharge status prediction following fracture repair surgery. The use of NISS may help to set up appropriate patient expectation after surgery.

5082 | A systematic review of the use of propensity scores in published observational research

Tiansheng Wang[1], Michael Webster-Clark[1], Robert James Glynn[2] and Til Stürmer[1]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: Propensity score (PS) methods have been widely used in observational studies in the last 20 years, but PS methods are implemented in a variety of ways. As observational studies increasingly use these methods, our systematic review sought to identify time trends in study designs, balance evaluation, effect estimation and reporting in studies utilizing PS methods.

Objectives: To conduct a systematic review of trends in the use and reporting of PS methods in observational studies.

Methods: To assess overall trends in use, we searched PubMed, Embase, Web of Science, and Scopus for articles published between 2004-2019 with the text "propensity score". To assess trends of implementation and reporting, we randomly abstracted 50 applied articles that used PS methods from each of four years: 2004, 2009, 2014, and 2019. Reviewers abstracted a variety of elements of the manuscripts, including subject area, active vs non-user comparator, PS implementation, and covariate balance assessment.

Results: A total of 28,494 articles were identified in all years from 2004-2019. Uptake has been steady and in 2019, we estimate that over 6,000 papers applied propensity scores across a wide variety of academic disciplines, including medicine, economics, and political science. Among the 200 randomly abstracted articles from 2004 to 2019, proportions of articles using active comparators increased from 38% in 2004 to 54% in 2019. The proportion of studies implementing PSs using regression methods and stratification dropped from 2004 to 2019 (in 2004, 26% of papers used regression and 20% used stratification; in 2019, 6% of papers used regression and we saw no cases of stratification). The use of PS matching increased over time from 50% in 2004 to 88% in 2019 and PS weighting increased slightly from 4% in 2004 to 6% in 2019. While the proportion of studies that did not assess balance after adjustment has shrunk over time (from 64% in 2004 to 32% in 2019), only some of this was due to increased use of standardized mean differences (from 0% in 2004 to 24% in 2019). Instead, much of the trend was due to the misapplication of P-values to assess balance (from 18% in 2004 to 50% in 2019).

Conclusions: We saw a large increase in the number of published manuscripts using PS methods from 2004 to 2019. Over time, more of these studies employed active comparators and PS matching, while use of stratification and regression dwindled. Also, an increasing percentage of studies assessed balance, though there was an increasing trend to inappropriately use P-values for this purpose.

5088 | Evolving channeling among initiators of SGLT2 inhibitors as first-line treatment for type 2 diabetes

HoJin Shin[1,2], Sebastian Schneeweiss[2], Robert Glynn[2] and Elisabetta Patorno[2]

[1]Harvard T.H. Chan School of Public Health, Boston, MA; [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: SGLT2 inhibitors (SGLT2i), a newer antidiabetic drug class that showed cardiovascular benefits in clinical trials, may be increasingly considered as first-line treatment for type 2 diabetes (T2D) patients, particularly among those with cardiovascular disease (CVD), with implications for confounding control in comparative effectiveness research targeting this population.

Objectives: To assess evolving differences in the baseline characteristics of initiators of SGLT2i as first-line T2D treatment and the likelihood of receiving SGLT2i compared to metformin initiators, the recommended first-line T2D treatment, during the time after launch.

Methods: Using claims from two US commercial insurance databases and Medicare fee-for-service, we identified T2D patients aged ≥ 18 years (>65 in Medicare), who initiated SGLT2i or metformin from 4/2013 (the date of SGLT2i launch) through 12/2017. We restricted to patients with no evidence of any diabetes treatment in the prior 365 days (or more, depending on data availability). We evaluated yearly differences for 45 baseline characteristics, using standardized

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

difference (SD) with meaningful imbalances set at >0.1, pooling across datasets. The likelihood of SGLT2i vs metformin was estimated in a series of propensity score models for 3 consecutive time-blocks (4/2013-12/2014; 1/2015-6/2016; 7/2016-12/2017), and the discrimination (c-statistic) was evaluated.

Results: We identified 7,153 first-line initiators of SGLT2i and 682,871 first-line initiators of metformin. Patients who initiated SGLT2i in 2013 were younger (SD -0.64), had a lower prevalence of CVD (SD -0.19), and had more visits with endocrinologists (SD 0.22), compared to metformin initiators. Such stark differences lessened in 2017 for age (SD -0.17) and endocrinologist encounter (SD 0.07), and reversed for CVD (SD 0.10). The overall differences in patient characteristics between SGLT2i and metformin initiators, as measured by the proportion of the 45 variables with SD >0.1, decreased over time (from 67% in 2013 to 20% in 2017). Changes in baseline characteristics were mirrored by decreasing c-statistics from the first to the last time-block: from 0.79 to 0.72 in Clinformatics, from 0.69 to 0.68 MarketScan, and from 0.72 to 0.69 in Medicare.

Conclusions: Baseline characteristics of first-line initiators of SGLT2i changed rapidly over the years following their launch, and these changes affected the likelihood of receiving SGLT2i vs metformin. Rapidly evolving channeling should be expected and accounted for in comparative effectiveness research on first-line diabetes treatment.

5111 | Development of the claims-based comorbidity index for cardiovascular disease patients

Heejin Kim[1], Sangshin Park[2], Mi-Sook Kim[3], Young-Jin Ko[3] and Nam-Kyong Choi[1]

[1]Ewha Womans University, Seoul, Republic of Korea; [2]Graduate School of Urban Public Health, University of Seoul, Seoul, Republic of Korea; [3]Seoul National University College of Medicine, Seoul, Republic of Korea

Background: Various Comorbidity indices have been developed for predicting mortality of patients. However, more disease-specific comorbidity indices are needed to better control confounding factors.

Objectives: We aimed to develop a cardiovascular patient-specific comorbidity index for predicting mortality in Korean adults.

Methods: In the NHIS-NSC(National health institute system-national sample cohort), we used 70% of myocardial infarction or stroke patients admitted firstly between January 1, 2004 and December 31, 2012 and ≥25 aged to develop CVD-CI (cardiovascular disease comorbidity index) for predicting 3-year mortality. We selected comorbidities among the CCI and ECI of conditions significant related with our subjects and scoring by using Cox hazard regression model adjusted for factors known to affect the prognosis of cardiovascular patients. In the 30% of cohort, we validated our index by comparing the performance with CCI and ECI using the Roc curve.

Results: Of the 18,554 patients, 12,988 and 5,566 were assigned in development cohort and validation cohort, respectively. A total of 18 new comorbidities were selected and the weight ranged from -1 to 9. The most strongly associated comorbidities on mortality were metastatic cancer, severe liver disease, kidney disease, drug abuse, and pulmonary circular disease. C-statistics of CVD-CI was 0.775 [95% confidence interval (CI): 0.761-0.790], CCI was 0.766 (95% CI: 0.751-0.781), and ECI was 0.767(95% CI: 0.752-0.782) after adjusted for age, sex, degree of disability, surgical status, hospitalization history, and type of healthcare system.

Conclusions: CVD-CI performed better than traditional indices like CCI and ECI for predicting mortality of patients with stroke or myocardial infarction and could be a useful method for adjusting comorbidities.

5128 | Use of negative controls in a prescription sequence symmetry analysis used to mitigate time-varying bias

Scott M. Vouri[1,2], Xinyi Jiang[1], Babette Brumback[3,2] and Almut G. Winterstein[1,4]

[1]University of Florida College of Pharmacy, Gainesville, FL; [2]University of Florida, Gainesville, FL; [3]University of Florida College of Public Health & Health Professions College of Medicine, Gainesville, FL; [4]University of Florida, University of Florida, FL

Background: A prescription sequence symmetry analysis (PSSA) is a case-only pharmacovigilance approach that can be used to evaluate prescribing cascades - treatment of drug-induced adverse events with another medications. PSSA adjusts for secular trends in drug use in the overall population (e.g., because of market uptake) but ignores patient-level factors that can result in similar trends. Negative controls are useful to evaluate within-patient, time-varying bias (e.g., disease progression) by assessing medication use trends within a similar population but not at risk for the prescribing cascade. However in published studies, negative controls are only visually assessed and not formally incorporated in the PSSA.

Objectives: To advance PSSA by adjusting for patient-level drug utilization trends obtained from negative controls using the example of the calcium channel blocker (CCB) - loop diuretic prescribing cascade.

Methods: Using our previously published prescribing cascade data, we explored four negative control cohorts that initiated levothyroxine, tiotropium inhalers, non-benzodiazepine (non-BZD) hypnotics, or angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARB]). We used a difference-in-difference (DiD) measure to estimate the relative sequence ratio (SR) of loop diuretic after/loop diuretic before use in the CCB cohort compared to the same SR for each negative control as a reference.

Results: New SRs were generated for the CCB cohort after removing patients who utilized both DH-CCB and the negative control medications (SR range - 1.94 to 1.99). The PSSA which incorporated the negative control for levothyroxine (SR 1.11) resulted in a relative SR of 1.72 (95% CI 1.67-1.78). Corresponding PSSAs for adjustments obtained from the tiotropium (SR 1.10) or non-BZD hypnotics cohorts (SR 1.05) resulted in a relative SR of 1.74 (95% CI 1.66-1.73) and 1.81 (95% CI 1.75-1.86), respectively. Finally, the PSSA which incorporated the negative control for ACE inhibitor/ARB (SR 1.31) resulted in the largest attenuated relative SR of 1.43 (95% CI 1.39-1.47).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: The use of levothyroxine, tiotropium, and non-BZD hypnotics as negative controls resulted in similar interpretations of the prescribing cascade; however, the use of ACE inhibitors/ARBs as a negative control further attenuated the SR as it likely captured natural disease progression resulting in loop diuretic use for hypertension (i.e., a time-varying bias).

Methods in Pharmacoepidemiology -> Measurement
Methods - Validation methods to confirm data (including Patient Reported Outcomes development and validation); methods to deal with missing data

63 | Treatment duration estimation based on claims vs primary care prescriptions data: An analysis of opioid use in the SIDIAP database

Junqing Xie, Gary Collins, Victoria Y. Strauss and D. Prieto-Alhambra
University of Oxford, Oxfordshire, United Kingdom

Background: Treatment duration assigned to each prescription is typically estimated either from claims/dispensations or electronic medical records (EMR) data, with no opportunities for comparison between the former and the latter. The System for the Development of Research in Primary Care (SIDIAP) database is one of the few data sources where both prescriptions and dispensations can be linked and can therefore be used to compare both and hence inform future drug utilisation methods.
Objectives: To compare the treatment duration estimated using the fixed-time period method based on dispensation data to those recorded on EMR in primary care.
Methods: Data were obtained from the SIDIAP database (Catalonia, Spain), which comprises both EMR and pharmacy dispensation information, covering about 6 million people (>80% of the Catalan population). All users of opioids (fentanyl, morphine, tramadol, codeine) during 2007-2017, aged 18 years or older, and with linked prescription and dispensation data were included. Treatment duration for each dispensation was estimated using the fixed-time period method (number of packages * fixed pre-specified and clinically informed window) and compared to those recorded on EMR. Three fixed windows were tested based on clinical assumptions, namely 7, 15, and 30 days. The consistency/agreement between both was quantified based on the metric of the median difference.
Results: The fixed window of 15-days showed a median difference of -4 and 0 days, with 23 and 14 days underestimation for the 7-day window, and 22 and 20 days overestimation for the 30-day window for fentanyl and morphine respectively. Similarly, the assumption of 15-day window for tramadol performed better than others, with a 5-day median difference. Codeine showed different results, and the assumption of 7-day window led to the lowest median difference of 1 day.
Conclusions: The treatment duration estimated by dispensation data using fixed-time period method is comparable to that directly recorded on EMR in aggregate level. Clinical insights should be carefully considered to pre-set a reliable time window for different drugs when using claims data.

76 | Incidence rates of acute exacerbations of COPD in US claims data using ICD-9 and ICD-10

Ashley Cole[1], Yunhao Liu[1] and Kieran J. Rothnie[2]
[1]GlaxoSmithKline, Collegeville, PA; [2]GlaxoSmithKline, London, United Kingdom

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are important endpoints in research leveraging administrative claims data. Prior work developed and validated a US claims-based AECOPD algorithm using ICD-9 diagnosis codes, but it is unclear whether this algorithm will perform consistently following transition to ICD-10.
Objectives: To describe incidence rates (IR) by calendar year for moderate and severe AECOPD using a US claims-based algorithm applied before, during, and after transition to ICD-10 coding.
Methods: Using Optum's de-identified Clinformatics® Data Mart Database, we identified person time at risk for AECOPD during 2013-2018 from the earliest observed COPD diagnosis or study start (2012) until the earliest of death, disenrollment, or end of data. Incident events included all AECOPD (moderate and severe calculated separately) observed during the at risk period. We used a previously validated algorithm to define AECOPD related diagnostic codes. Severe AECOPD was defined as hospitalizations with a primary diagnostic code for AECOPD; moderate AECOPD was defined as outpatient/emergency visits with a primary diagnostic code for AECOPD and a fill for systemic steroids, antibiotics, or methylxanthines ≤14 days later. We used ICD-9 codes from the validated definition and performed a crosswalk exercise to translate these to equivalent ICD-10 codes. ICD-9 codes were applied to all time prior to 1 Oct 2015 and ICD-10 codes were applied afterwards. We calculated IR for each calendar year before (2013-2014), during (2015-2016), and after (2017-2018) ICD-10 transition.
Results: We identified 1,979,470 moderate and 280,804 severe AECOPD in 2,134,298 subjects. For both moderate and severe AECOPD, the lowest IR were observed in 2015 and the highest IR in 2016, with similar rates in periods before and after ICD-10 transition (IR/person year [95% CI], Severe AECOPD: 2013, 0.077 [0.076-0.077]; 2014, 0.063 [0.063-0.064]; 2015, 0.052 [0.051-0.052]; 2016, 0.093 [0.093-0.094]; 2017, 0.086 [0.085-0.086]; 2018, 0.061 [0.061-0.062]; Moderate AECOPD: 2013, 0.492 [0.490-0.493]; 2014, 0.434 [0.432-0.435]; 2015, 0.433 [0.431-0.434]; 2016, 0.635 [0.633-0.637]; 2017, 0.540 [0.539-0.542]; 2018, 0.485 [0.484-0.487]).
Conclusions: The ICD-9 to ICD-10 transition period was associated with higher variability in IR and researchers may want to use caution when ascertaining AECOPD during this time. Similar rates of AECOPD ascertained before and after the ICD-9 and ICD-10 period suggests that our ICD-10 algorithm performs in a similar way to the validated ICD-9 algorithm. Funding: GSK (213478).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

122 | The impact of refill gaps on the estimation of persistence with opioids use

Junqing Xie, Gary Collins, Victoria Y. Strauss and D. Prieto-Alhambra
University of Oxford, Oxfordshire, United Kingdom

Background: Long-term opioid use for the treatment of common pain syndromes is increasing worldwide, with little evidence on their long-term effectiveness and safety. Refill gaps are used in drug utilisation research to define treatment discontinuation, but the choice of length of these gaps is usually subjective. There is little understanding of how different refill gaps might influence the estimation of persistence in studies of long-term opioid therapy.
Objectives: To explore the impact of different refill gaps on estimates of 1-year persistence with continued opioid use. Secondly, we compared the results obtained based on dispensation vs prescription data.
Methods: Data were obtained from the SIDIAP (The System for the Development of Research in Primary Care) database, which comprises both electronic medical records and pharmacy dispensation information, covering about 6 million people (>80% of the Catalan population). All incident users of opioids (fentanyl, morphine, tramadol, codeine) based on ATC codes during 2007-2017, aged 18 years or older, and with linked prescription and dispensation data were included. For each of the prescription and dispensation data, persistence was calculated as the time from initiation to discontinuation of therapy. Refill gaps of 1, 2, and 3 months were used to identify discontinuation. 1-year persistence was defined as the proportion of individuals who had one-year or more continuous opioid use.
Results: 1-year persistence with different opioids estimated using electronic prescription data increased slightly with refill gap length from 1 to 3 months, ranging from 0.6% to 0.7% (codeine), 5.6% to 7.2% (tramadol), 4.4% to 5.7% (morphine) and 14.7% to 17.8% (fentanyl). Estimates were similar when based on dispensation data, eg 0.1% to 0.3%, 2.4% to 5.4%, 3.9% to 6.3% and 14.9% to 19.1% accordingly.
Conclusions: Although the longer refill gap can result in a higher estimate of 1-year persistence with different opioids, the variation seems to be acceptable when refill gaps ranging from 1 to 3 months. Also, the results are similar when dispensation vs prescription data are used to estimate persistence. Sensitivity analyses using variable refill gaps are needed for drug utilisation and safety/effectiveness studies.

2411 | The positive predictive value of hip fracture diagnoses and surgical procedure codes in the danish multidisciplinary hip fracture registry and the danish national patient registry

Thomas J. Hjelholt[1], Nina M. Edwards[1], Jeppe D. Vesterager[1], Pia K. Kristensen[1,2] and Alma B. Pedersen[1]
[1]*Aarhus University, Aarhus, Denmark;* [2]*Horsens Regional Hospital, Horsens, Denmark*

Background: The Danish Multidisciplinary Hip Fracture Registry (DMHFR) may be a valuable source for epidemiological research, if the data are valid. Previous hip fracture studies based on DMHFR have relied on few validation studies of hip fracture diagnosis registered in Norway, Finland, USA and Canada, with coding practices and healthcare systems different from Denmark.
Objectives: To examine the validity of hip fracture diagnoses and surgical procedure codes in the DMHFR and the Danish National Patient Registry (DNPR) by calculating the positive predictive value (PPV).
Methods: We identified a random sample of 750 hip fracture patients registered in the DMHFR between 2014 and 2017, treated at five specific hospitals in the Central or Northern region of Denmark. The hospitals were representative for the entire region, which is comparable to the national population in terms of sociodemographic and health-related characteristics. Diagnoses were coded by the 10th revision of the International Classification of Diseases, while procedures were coded by the Nordic Medico-Statistical Committee classification in the DNPR and directly transferred to the DMHFR. Using the surgical procedure description from the medical record as gold standard, we estimated the PPV of the hip fracture diagnoses and surgical procedure codes in the DMHFR and the DNPR with 95% confidence interval (CI).
Results: The PPV was 90% (95% CI: 86%-93%) for fracture of the neck of femur, 92% (95% CI: 87%-95%) for trochanteric fracture, and 83% (95% CI: 78%-88%) for subtrochanteric fracture. Joining trochanteric and subtrochanteric fracture resulted in a PPV of 97% (95% CI: 95%-98%). Procedure codes had a PPV of 100% for primary prosthetic replacement and internal fixation with intramedullary nail, 96% (95% CI: 85%-99%) for internal fixation using screws alone, 91% (95% CI: 84%-96%) for internal fixation using plates and screws, and 89% (95% CI: 83%-94%) for internal fixation with other or combined methods. Stratifying by age group, gender, hospital type and calendar year of surgery were comparable to the overall PPV estimates.
Conclusions: Our findings indicate a high quality of the hip fracture diagnoses and corresponding procedure codes in the DMHFR and the DNPR, with a majority of PPVs above 90%. Thus, the DMHFR and the DNPR are a valuable data source on hip fracture for epidemiological research.

2464 | Identifying valid algorithms for number of chemotherapy treatment lines in the danish national patient registry

Signe Sørup[1], Bianka Darvalics[1], Jakob S Knudsen[1], Anne S Rasmussen[1], Cathrine F Hjorth[1], Søren V Vestergaard[1], Leo Russo[2], Dina Oksen[3], Emmanuelle Boutmy[3], Patrice Verpillat[3], Henrik T Sørensen[1], Mikael Rørth[4] and Deirdre Cronin-Fenton[1]
[1]*Aarhus University Hospital, Aarhus, Denmark;* [2]*Pfizer, Collegeville, PA;* [3]*Merck Healthcare KGaA, Darmstadt, Germany;* [4]*Rigshospitalet and University of Copenhagen, Copenhagen, Denmark*

Background: Information on treatment with chemotherapy in all Danish hospitals is registered in the Danish National Patient Registry (DNPR). Yet, the number of lines of chemotherapy, which is important when evaluating cancer treatment, is not directly captured.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To identify which algorithms for number of lines of chemotherapy per patient based on treatment codes and dates in the DNPR have the highest percentage agreement with a reference standard of documentation in medical records.

Methods: We included patients diagnosed between January 1, 2012, and December 31, 2016, with American Joint Committee on Cancer stage III or IV epithelial ovarian cancer, stage III or IV gastric adenocarcinoma, stage III or IV renal cell carcinoma, stage III or IV non-small cell lung cancer, or stage II, III, or IV urothelial cell carcinoma, who received chemotherapy at the Department of Oncology, Aarhus University Hospital, Denmark. We developed 2 algorithms for number of chemotherapy lines based on dates and treatment codes (eg, "treatment with cisplatin" or "cytostatic treatment") in the DNPR. Algorithm I used the number of days between consecutive chemotherapy administrations (any chemotherapy treatment code). Algorithm II also used information on chemotherapy drugs if available or the number of days between consecutive chemotherapy administrations if chemotherapy drugs were unspecified. We evaluated the algorithms, setting the number of allowed days between administrations from 28 to 50. We calculated the percentage agreement between the number of chemotherapy lines identified from the algorithms and the reference standard—information on chemotherapy drugs abstracted from medical records and subsequently coded according to lines of chemotherapy.

Results: In total, 179 patients were included (approximately 36 patients with each cancer type). For algorithm I, the highest percentage agreement with the reference standard was found when using <45 days between consecutive dates of chemotherapy (67.6% [95% CI: 60.1%-73.8%]). However, the percentage agreement was higher for algorithm II using <45 days between consecutive dates of chemotherapy administration for registrations with unspecified chemotherapy drugs (90.5% [95% CI: 85.0%-93.7%]).

Conclusions: The highest percentage agreement between the data from medical records on number of lines of chemotherapy (reference standard) was found for an algorithm based on routinely recorded data from DNPR that incorporated both registration of specific chemotherapy drugs and <45 days between consecutive administrations if the drug name was unspecified.

2473 | Missing data analysis in multi-center studies when access to person-level data is restricted

Qoua Her[1], Yury Vilk[1], Xiaojuan Li[1], Di Shu[1], Rui Wang[1,2], Jenna Wong[1], Mia Gallagher[1] and Sengwee Toh[1,3]

[1]*Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA;* [2]*Harvard TH Chan School of Public Health, Boston, MA;*[3]*OptumLabs, Cambridge, MA*

Background: Distributed regression analysis (DRA) is a privacy-protecting analytical method that performs multivariable-adjusted regression analysis in multi-database settings using only summary-level information. However, data quality issues such as missing data continue to challenge the utility of DRA. Few method recommendations are available to guide analyses with missing data in multi-center studies where access to person-level data is restricted.

Objectives: To evaluate the performance of DRA after handling missing data with multiple imputation by chain equations (MICE) at each data-contributing site.

Methods: We created simulated cohort studies (n=10,000) of bariatric surgery patients based on data from the OptumLabs® Data Warehouse, which includes de-identified administrative claims and electronic health record data, to evaluate the comparative safety and effectiveness of two common bariatric procedures. Three types of outcomes were evaluated: percent weight change by the first post-surgery year (continuous), rehospitalization within the first 30 post-surgery days (binary), and time to first rehospitalization during the first post-surgery year (time-to-event). We induced missing data to the pre-surgery BMI variable under different missing mechanisms (missing completely at random, missing at random, and missing not at random) and levels of missingness (10%, 50%, and 80%). We partitioned the data into 3 datasets of approximately equal size to simulate a 3-site multi-center study with missing data, where access to person-level data is restricted. We performed site-specific MICE to create 5 imputed datasets and then conducted DRA (linear, logistic, and Cox proportional hazards) to estimate the global regression parameters and standard errors using summary-level information. We compared the results obtained from this approach to the results obtained from the benchmark analysis of the pooled person-level data where MICE was conducted by site. A difference of $<10^{-6}$ between estimates from the two approaches was deemed to demonstrate the validity of DRA.

Results: The use of MICE and DRA produced regression parameter estimates and standard errors that were precise to those computed from the benchmark analyses under all missing data scenarios considered. The difference in the regression results from the DRA compared to those the from benchmark ranged from 10^{-15} to 10^{-17}.

Conclusions: MICE plus DRA can be used to handle missing data without sharing any person-level data in multi-center studies.

2618 | Assessment of a claims-based osteonecrosis of the Jaw algorithm in the United States

Lauren Stevens[1], Leslie Spangler[2], Laura Yochum[1], Yan Ding[1] and Florence Wang[1]

[1]*Optum Epidemiology, Boston, MA;* [2]*Amgen, Inc., Thousand Oaks, CA*

Background: Osteonecrosis of the jaw (ONJ) is a rare condition associated with certain drug therapies. Pharmacoepidemiologic studies often rely on electronic healthcare data to evaluate potential occurrence of adverse events following drug exposure. To date, few studies have been conducted to develop and validate claims-based ONJ identification algorithms.

Objectives: To assess performance of a claims-based ONJ algorithm by chart review of potential cases among postmenopausal (PM) women and women with PM osteoporosis (PMO).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: PM women and women with PMO were identified in a large US commercial health insurance database affiliated with Optum. Potential ONJ cases were identified by ICD-9 (526.4, 522.7, 526.5, 733.45) and ICD-10 (M27.2, K04.6, M27.3, M87.180, M87.08, M87.28, M87.38, M87.88, M87.9) diagnosis codes; 200 potential ONJ cases were selected for chart retrieval, with the goal of obtaining 100 charts in each coding era (ICD-9, ICD-10). Procured charts were redacted with respect to identifiable information and osteoporosis treatment received, then reviewed by a practicing oral surgeon who applied a case definition to determine final ONJ case status. Positive predictive values and 95% confidence intervals were calculated overall, and by cohorts and coding eras. Baseline characteristics of all potential cases were assessed. Two potential algorithm refinements were explored: using a restricted set of ICD diagnosis codes that included only a subset of codes that identified true cases of ONJ; requiring antibiotic use after ONJ diagnosis.

Results: 1,273 potential cases were identified by ONJ diagnosis codes. Of the 200 potential cases selected, 104 (52%) charts were procured, and six cases were confirmed across the two cohorts (PPV 5.8%, 95% CI 2.2, 12.1). Baseline characteristics among potential cases were largely similar across all strata, and among those with procured and non-procured records. Applying potential algorithm refinements resulted in marginal PPV improvement.

Conclusions: This study identified only a small number of confirmed cases, and the resulting PPVs were generally low, but consistent with previously reported studies. Potential refinements to the algorithm resulted in minimal improvements. To our knowledge, our study is the first to report on the identification of ONJ using ICD-10 codes in the US.

2629 | Validation of a US health insurance claims-based algorithm to identify acute exacerbations of chronic obstructive pulmonary disease

Douglas W. Mapel[1], Susan R. Sama[2], Douglas W. Roblin[3], Melissa H. Roberts[1], Priyanka J. Bobbili[4], Wendy Y. Cheng[4], Julia M. Certa[3], Devi Sundaresan[2], Thomas S. Whiting[3], Catherine Nguyen[4], Philippe Thompson-Leduc[4], Jennifer L Brown[3], Melissa K. Van Dyke[5], Kieran J. Rothnie[6] and Mei Sheng Duh[4]

[1]University of New Mexico, Albuquerque, NM; [2]Reliant Medical Group, Inc., Worcester, MA; [3]Kaiser-Permanente Mid-Atlantic States, Rockville, MD; [4]Analysis Group, Inc., Boston, MA; [5]GlaxoSmithKline, Upper Providence, PA; [6]GlaxoSmithKline, Brentford, United Kingdom

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are important events which may lead to adverse outcomes and are a common endpoint in observational research. However, the algorithms to identify AECOPD in US administrative claims data have not been validated.

Objectives: To develop claims based algorithms identifying moderate and severe AECOPD, separately, in two US healthcare systems and to evaluate their positive predictive value (PPV) and negative predictive value (NPV).

Methods: Computerized healthcare databases (inclusive of insurance claims and electronic health records [EHR] of medical services) from Kaiser-Permanente Mid-Atlantic States and Reliant Medical Group were used (Q1 2010-Q3 2015). Eligible patients were identified using ICD-9 diagnosis codes for COPD. The first prescription fill for a COPD maintenance medication was defined as the index date after which AECOPD were identified for each patient. The algorithm to identify potential moderate AECOPD consisted of outpatient or emergency department visits associated with AECOPD related diagnosis codes and antibiotic or systemic steroid dispensings. A second algorithm to identify potential severe AECOPD consisted of inpatient visits associated with AECOPD related diagnosis codes. Objective criteria for exacerbations were developed from Global Initiative for Chronic Obstructive Lung Disease guidelines. To estimate PPV, a random sample of 300 potential moderate AECOPD and 250 potential severe AECOPD identified by the claims algorithms were abstracted from the EHR and adjudicated by physician review. To estimate NPV, a random sample of 200 patients without any AECOPD identified by the claims algorithms (100 without moderate and 100 without severe AECOPD) during the two years following the index date were abstracted from the EHR and adjudicated by physician review to identify any AECOPD in the EHR missed by the algorithm.

Results: The PPV was 98.3% (95% CI: 96.1-99.5) for the moderate algorithm and 96.0% (95% CI: 92.5-98.2) for the severe algorithm. The NPV for the moderate algorithm was 75.0% (95% CI: 65.3-83.1) and was 95.0% (95% CI: 88.7-98.4) for the severe algorithm. Results were consistent across both sites.

Conclusions: The PPV for both algorithms and NPV for severe algorithm was very high, which validates the combinations of diagnoses and procedures used in the algorithms. The NPV for the moderate algorithm was modest. Further replication and validation of the algorithm to the post ICD-10 era would bolster the validity and relevance of the findings. Funding: GSK (210043).

2637 | Intentional self-harm classification in medicare: An interrupted time series analysis comparing ICD-9 definitions to corresponding ICD-10 definitions

Richard S. Swain[1], Dinci Pennap[1], Sandia Akhtar[2], Jiemin Liao[2], Yuqin Wei[2], Yuhui Feng[2], Michael Wernecke[2], Thomas MaCurdy[3,2], Jeffrey Kelman[4], Andrew Mosholder[1] and David Graham[1]

[1]Food and Drug Administration, Silver Spring, MD; [2]Acumen LLC, Burlingame, CA; [3]Stanford University, Stanford, CA; [4]Centers for Medicare & Medicaid Services, Washington, DC

Background: Epidemiologic studies often rely on International Classification of Diseases, Clinical Modification (ICD-CM) codes to classify outcomes. The consistency of ICD definitions from ICD-9 to ICD-10 has not been fully described. Previous studies have estimated validity of ICD-9 codes to classify intentional self-harm (ISH) recorded in medical claims data. With several years since the transition to ICD-10 (Oct 1, 2015), there remains a need to adapt ICD-9 definitions of ISH and estimate their performance in ICD-10.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To explore temporal patterns in ISH claims, and to perform an Interrupted Time Series (ITS) analysis to examine estimated ISH rates across the ICD-9 to ICD-10 transition.

Methods: We identified two ICD-9 ISH definitions with high positive predictive value and adapted them to ICD-10: ISH diagnosis codes (ISH-DC) and an algorithm validated by Patrick and colleagues (PA) requiring injury and mental disorder diagnoses on an inpatient claim. We estimated monthly rates of beneficiaries with ISH events using ISH-DC and PA based on monthly Medicare fee-for-service (FFS) enrollment from 2012 to 2018. We conducted an ITS analysis, adjusting for seasonality using a Fourier transform and autocorrelation using an autoregressive moving average model with order chosen to minimize Akaike information criterion.

Results: We identified 2,456 beneficiaries with inpatient ISH events captured by ISH-DC, 4,333 captured by PA, and 4,989 captured by ISH-DC or PA, out of 32,194,551 FFS Medicare enrollees in January 2012, yielding rates per million enrollees (M) of 76.3, 134.6, and 155.0, respectively. By January 2018, rates decreased to 63.0, 106.0, and 126.0, respectively. Each ISH definition displayed seasonal variability, with rates approximately 20% higher during late summer (Jul-Aug) compared to winter. The ITS analysis showed a slight increase in level for event rates per M for ISH-DC [3.4; (95% C.I. 1.7, 5.1)] and PA [11.5 (8.4, 14.6)] across the ICD-9/10 transition. For the ITS analysis classifying ISH as events identified by ISH-DC or PA, the ICD-9 to ICD-10 transition produced a similar estimated effect on level [11.2 (8.5, 13.8)].

Conclusions: The adapted ISH definitions resulted in consistent estimates across the ICD transition, with small differences in level indicating a slight increase in the number of ISH events classified in ICD-10. These findings suggest the validity of the adapted ISH definitions may be consistent with the original ICD-9 versions. Further validation efforts are needed to assess the performance of a combined ISH definition.

3743 | Electronic medical records vs insurance claims: Comparing the magnitude of opioid use prior, during, and following surgery

Jessica C. Young[1], Nabarun Dasgupta[1], Virginia Pate[1], Til Sturmer[1], Brooke A. Chidgey[2] and Michele Jonsson Funk[1]

[1]University of North Carolina, Chapel Hill, NC;[2]University of North Carolina School of Medicine, Chapel Hill, NC

Background: Pharmacoepidemiology studies often use insurance claims and electronic medical record (EMR) data. However, the implications of data source choice on key study design elements are not well understood.

Objectives: Use linked claims-EMR data (separately and together) to characterize opioid use as it relates to study eligibility criteria, and exposure and outcome assessment.

Methods: EMR data from a large healthcare system were linked to Medicare insurance claims for patients undergoing invasive surgery in an ongoing study on opioid use. Drug utilization based on order and fill dates came from 3 sources: EMR inpatient orders, EMR outpatient orders, and Medicare Part D claims. We evaluated 3 study design elements: a) Study selection - opioid use 182 days before surgery to identify opioid naïve patients; b) Exposure ascertainment- perioperative opioid use; c) Outcome assessment - prolonged opioid use 90 days post-op.

Results: We identified 12,023 surgery patients in the linked claims-EMR data. **Eligibility:** For baseline opioid exposure, 30% (outpatient EMR) vs 28% (claims) had an opioid order (EMR) or fill (claims). Using both claims and outpatient EMR, 44% of patients had evidence of exposure in at least one data source. **Perioperative Exposure:** For use during surgical admission, combined inpatient and outpatient EMR orders documented much higher use of opioids (81%) compared to claims-only (32%). Combining the 3 data sources, 87% had evidence of opioids ordered or filled during the surgical admission. On the date of surgical discharge 56% (outpatient EMR), 31% (claims), and 65% (claims or outpatient EMR) had evidence of opioids ordered or filled. In the 7 days immediately after surgery, outpatient EMR found 3.0% with orders, claims found 9.2% with opioid fills, and combining the 2 data sources suggested 11% could have received opioids. **Prolonged Use Outcome:** Outpatient EMR found 4.7% with 90-day postsurgical opioid orders, claims found 6.0%, and combining claims and outpatient EMR found 9.4%.

Conclusions: When characterizing opioid exposure, we found substantial non-overlap between EMR and claims depending on time window relative to surgery and care setting, driven by inpatient opioids only captured in EMR and primary nonadherence. In studies that straddle hospital and outpatient settings, the potential for misclassification of drug utilization must be evaluated carefully, and choice of data source may have large impacts on key study design elements. Both EMR and claims data are needed to provide a more complete picture of opioid exposure prior to, during and after surgery.

3788 | Validity of claims-based definitions for ulcerative colitis in Japan: Can intractable disease registry be used as gold standard?

Haoqian Chen[1], Haruei Ogino[2], Taku Kobayashi[3], Keita Fukaura[4], Hiromu Morikubo[3], Tasuku Okui[2], Naoki Nakashima[2], Sean Gardiner[5], Naonobu Sugiyama[5], Tsutomu Kawaguchi[5], Noritoshi Yoshii[5], Edward Nonnenmacher[1] and Soko Setoguchi[1,6]

[1]Rutgers, the State University of New Jersey, New Brunswick, NJ; [2]Kyushu University Hospital, Fukuoka, Japan; [3]Kitasato University Kitasato Institute Hospital, Tokyo, Japan; [4]Saiseikai Futsukaichi Hospital, Fukuoka, Japan; [5]Pfizer Japan Inc., Tokyo, Japan; [6]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

Background: Regulatory agencies in Asia encourage the use of real world data (RWD) for postmarketing surveillance. However, in Japan, algorithms to define many medical conditions in common RWD are not yet validated. Ulcerative colitis (UC), a chronic inflammatory disease, has been included in the intractable disease registry (IDR) by the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Japanese government to financially support these patients. This poses a unique opportunity for validation studies, if IDR can be used as a gold standard (GS).

Objectives: To assess the validity of claims-based algorithm for UC using medical record-based GSs (physician diagnosis and expert adjudication) vs. IDR.

Methods: We analyzed claims data and medical records from two large tertiary care teaching centers. A committee comprised of clinical/epidemiology experts developed a claims-based definition for UC. We randomly sampled medical records of the claims-based cases (200 per site) and abstracted GS information, which were independently adjudicated by specialists. We summarized case characteristics using descriptive statistics. We calculated positive predictive value (PPV) of the algorithm with 95% confidence interval (95% CI) for three GSs; 1) physician diagnosis of UC in medical records, 2) adjudication by experts considering the Japanese UC guidelines, and 3) IDR enrollment status.

Results: We identified 709 claims-defined UC cases (mean age 44 and 43% female) at Site 1 and 448 cases (mean age 45 and 51% female) at Site 2. Among 400 randomly sampled cases, all received ≥1 drug treatment: immunosuppressives, biologics, steroids, or antidiarrheals. Clinical symptoms were recorded for most cases (4-21% missing) showing 63% bloody stool, ~50% abdominal pain, and 24% frequent stools. Colonoscopy was done in 92% of cases, and 88% showed specific findings. Laboratory results for hemoglobin, white blood cell (WBC), and C-reactive protein (CRP) were available for most cases (2-4% missing) showing 58% anemia, 55% high WBC, and 62% high CRP. When physician diagnosis was used as a GS, PPV was 91% (95% CI: 88-93). PPV with expert adjudication was also 91% (95% CI: 88-93). However, PPVs with IDR were significantly lower at 41% (95% CI: 37-46).

Conclusions: The PPV of the claims-based UC definition using medical record-based GSs fell within reported PPVs from US and Canada. Low PPV for IDR suggests that case registration was not complete, and IDR cannot be used as a GS. Considering up to 60% of UC patients are seen by specialists at tertiary care centers, our claims-based algorithm is likely to identify UC cases with high PPV for postmarketing studies using claims database.

3811 | Validation of acute outcomes among patients with type 2 diabetes mellitus in medicare: A pilot study

Heather E. Danysh[1], J. Bradley Layton[2], Daniel C. Beachler[3], Alejandro Arana[4], Manel Pladevall-Vila[4], Rita Schmid[5], Brian Calingaert[2], Ryan Ziemiecki[2], Phillip R. Hunt[6], Alicia Gilsenan[2] and Catherine Johannes[1]

[1]RTI Health Solutions, Waltham, MA; [2]RTI Health Solutions, Research Triangle Park, NC; [3]HealthCore, Wilmington, DE; [4]RTI Health Solutions, Barcelona, Spain; [5]South Bend Clinic, Granger, IN; [6]AstraZeneca, Gaithersburg, MD

Background: In an ongoing postauthorization drug safety study, a pilot assessment was conducted in the United States (US) Medicare claims database to evaluate the validity of algorithms to identify acute outcomes among individuals with type 2 diabetes mellitus (T2DM) who initiated an antidiabetic (AD) drug.

Objectives: To estimate the positive predictive values (PPV) of claims-based algorithms for hospitalization for acute kidney injury (AKI), acute liver injury (ALI), and severe complications of urinary tract infection (UTI).

Methods: Patients were fee-for-service US Medicare enrollees aged ≥ 65 years initiating an AD drug (2014-2015). Algorithms were: AKI-hospital diagnosis of acute renal failure or dialysis, ALI-hospital diagnosis of ALI or liver transplant, UTI-inpatient or emergency department diagnosis of (1) pyelonephritis or (2) sepsis within 7 days of a UTI diagnosis. Patients with chronic renal or liver disease were excluded from AKI and ALI analyses, respectively. Medical records were requested for algorithm-identified cases (AKI n = 150, UTI n = 150, ALI n = 59). Up to 75 received patient records were included in each outcome-specific validation sample for clinical review. Using abstracted medical record information and prespecified case definitions, adjudicators classified each algorithm-identified case as a confirmed case, confirmed noncase, or postreview provisional case (insufficient information to assign case status). PPVs and 95% confidence intervals (CI) were estimated as the proportion of confirmed cases: (1) among all cases in the validation sample (postreview provisional cases treated as false positives); (2) removing postreview provisional cases from the denominator.

Results: We obtained 62.7% (AKI n = 94), 76.3% (ALI n = 45), and 53.3% (UTI n = 80) of requested patient records. Algorithm-identified cases included in the validation samples: AKI n = 75, UTI n = 75, ALI n = 38. The PPV (95% CI) for the algorithms (1) including all cases and (2) excluding postreview provisional cases were: AKI (1) 46.7% (35.1%-58.6%), (2) 58.3% (44.9%-70.9%); ALI (1) 52.6% (35.8%-69.0%), (2) 55.6% (38.1%-72.1%); UTI (1) 68.0% (56.2%-78.3%), (2) 78.5% (66.5%-87.7%).

Conclusions: Claims-based algorithms resulted in moderate validity for identifying hospitalizations for AKI, ALI, or severe complications of UTI among older patients with T2DM in Medicare, with considerable variability in PPV estimates. Our AKI and ALI results are consistent with other comparable algorithms in the literature, and, to our knowledge, there are no published algorithms for our UTI case definition of pyelonephritis or urosepsis.

3815 | Validation of breast cancer and bladder cancer among patients with type 2 diabetes mellitus in medicare: A pilot study

Heather E. Danysh[1], Alicia Gilsenan[2], Daniel C. Beachler[3], James A. Kaye[1], Xabier Garcia-Albeniz[4], Rita Schmid[5], Shannon Hunter[2], Phillip R. Hunt[6], Jaume Aguado[4], Brian Calingaert[2], J. Bradley Layton[2] and Lia Gutierrez[4]

[1]RTI Health Solutions, Waltham, MA; [2]RTI Health Solutions, Research Triangle Park, NC; [3]HealthCore, Wilmington, DE; [4]RTI Health Solutions, Barcelona, Spain; [5]South Bend Clinic, Granger, IN; [6]AstraZeneca, Gaithersburg, MD

Background: In an ongoing postauthorization drug safety study, the validity of algorithms to identify cancer outcomes among individuals with type 2 diabetes mellitus (T2DM) and taking an antidiabetic drug

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(AD) was evaluated as a pilot validation assessment in the United States (US) Medicare administrative claims database.

Objectives: To estimate the positive predictive values (PPV) of claims-based algorithms for female invasive breast cancer and in situ or invasive bladder cancer among individuals with T2DM in US Medicare.

Methods: Patients were fee-for-service US Medicare enrollees aged ≥ 65 years initiating an AD drug (2014-2015). Algorithms included two recorded diagnoses of female invasive breast cancer (ICD-9-CM 174.* or ICD-10-CM C50.*; males excluded) or in situ or invasive bladder cancer (ICD-9-CM 233.7 or 188.* or ICD-10-CM D09.0 or C67.*) in any setting on separate days and within 60 days of each other. Patients with the following in the 180 days prior to study entry were excluded: breast biopsy (breast cancer cohort) or hematuria, cystoscopy/bladder biopsy, or urine cytology (bladder cancer cohort). Medical records were requested for 109 breast cancer and 87 bladder cancer algorithm-identified cases. Up to 50 received patient records were included in each outcome-specific validation sample for clinical review. Using abstracted medical record information and prespecified case definitions, adjudicators classified each algorithm-identified case as a confirmed case, a confirmed noncase, or a postreview provisional case (insufficient information to assign case status). PPVs and 95% confidence intervals (CI) were estimated as the proportion of confirmed cases: (1) among all cases in the validation sample (postreview provisional cases treated as false positives); (2) removing postreview provisional cases from the denominator.

Results: We obtained 38.5% (breast cancer, n = 42) and 59.8% (bladder cancer, n = 52) of requested patient records. Validation samples included 42 breast cancer and 48 bladder cancer algorithm-identified cases, with 28 and 43 classified as confirmed cases, respectively. The PPV (95% CI) for the algorithms (1) including all cases and (2) excluding postreview provisional cases were: breast cancer (1) 66.7% (50.5%-80.4%), (2) 77.8% (60.8%-89.9%); bladder cancer (1) 89.6% (77.3%-96.5%), (2) 95.6% (84.9%-99.5%).

Conclusions: The algorithms applied in this pilot validation study have moderate validity for identifying female invasive breast cancer and high validity for identifying bladder cancer among older patients with T2DM and taking an AD drug in US Medicare.

3821 | multimorbidity case definition and lookback window: Impact on prevalence and associated health outcomes in population health administrative databases

Marc Simard[1], Elham Rahme[2], Marjolaine Dubé[1] and Caroline Sirois[3]
[1]*Public Health National Institute, Quebec City, QC, Canada;* [2]*McGill University Health Center, Montréal, QC, Canada;* [3]*Laval University, Quebec City, QC, Canada*

Background: Health administrative databases are a precious source of information to measure multimorbidity at the population level, but no consensual measure exist.

Objectives: To evaluate the simultaneous impact of multimorbidity case definitions and lookback windows (LW) used to identify medical conditions on multimorbidity prevalence estimate and health outcome predictions in health administrative databases.

Methods: This population-based study used linked hospitalization and physician claims records from 1995 to 2016 of a random sample of 2% (n=100,000) of the adult population in the province of Quebec, Canada. A hospital claim provides up to 25 diagnosis codes (International classification of diseases, ICD-10th edition) while a physician claim provides one ICD-9 code diagnosis. Medical conditions were identified from a pre-defined list of 31 medical conditions. One hospitalization for a condition or two physician claims at least 30 days apart were used to ascertain the presence of a condition. We evaluated the impact of two definitions of multimorbidity (2+ and 3+ conditions), five different LW (1, 2, 5, 10 and 20 years of retrospective search of ICD codes) and one different length of maximal time allowed between two claims (one year instead of the entire LW) on 1) the prevalence of multimorbidity and 2) the prediction of 1-year mortality and frequent health services utilization by age group (<65, ≥65 years). Health services included general practitioner visits (≥7), specialist visits (≥10), emergency department admissions (≥3). C-statistics from logistic regression models were used to compare prediction performance.

Results: According to age and LW, multimorbidity 2+ prevalence ranged from 2%[LW=1y] to 23%[LW=20y] in those <65y and from 12% [LW=1y] to 65%[LW=20y] in those ≥65y. Prevalence increased considerably for LW between 1 and 5 years and slower afterwards. Length of maximal time allowed between two claims had virtually no impact on prevalence. Prediction of health outcomes with 2+ definition was optimal with LW=5y (c-statistic: 0.90 for mortality, 0.72 for specialist, 0.65 for general practitioner and emergency). Multimorbidity 2+ is better than 3+ to predict health outcome in the younger (c-statistic 0.05 higher) but not in the older group.

Conclusions: Five years of prior data (LW) is required to have a stable prevalence estimate of multimorbidity. Multimorbidity 3+ should be preferred to 2+ in those ≥65 years of age. These findings will inform the elaboration of a consensual multimorbidity measure using health administrative databases.

3874 | Validation of an algorithm identifying relapses in multiple sclerosis using the French nationwide claims database

Pauline Bosco-Levy[1,2], Patrick Blin[1], Séverine Lignot-Maleyran[1], Régis Lassalle[1], Abdelilah Abouelfath[1], Pauline Diez-Andreu[1], Marc Debouverie[3], Bruno Brochet[4], Céline Louapre[5,6], Olivier Heinzlef[7], Elisabeth Maillart[6] and Nicholas Moore[1,8]
[1]*Bordeaux PharmacoEpi, Univ. Bordeaux-INSERM CIC1401, Bordeaux, France;* [2]*Bordeaux Population Health Research Centre, INSERM UMR 1219, Bordeaux, France;* [3]*Department of Neurology, Nancy University-Hospital, EA 4360 APEMAC, Vandoeuvre-Lès Nancy, France;* [4]*CRC SEP, Service de Neurologie, CHU de Bordeaux, Bordeaux, France;* [5]*Sorbonne Université, Institut du Cerveau et de la Moelle épinière, ICM, Hôpital de la Pitié Salpêtrière, Inserm UMR S 1127, CNRS UMR 7225, Paris, France;* [6]*Neurology Department, Pitie Salpetriere Hospital, APHP, Paris, France;* [7]*Department of Neurology, Hôpital CHI de Poissy/Saint-Germain-en-Laye, Paris, France;* [8]*CHU de Bordeaux, Bordeaux, France*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Relapse (MS) can be identified through algorithm in claims database to assess disease modifying therapies effectiveness in multiple sclerosis (MS) in real word setting.

Objectives: The objective of this study was to assess the validity of an algorithm identifying relapses in MS patients in SNDS.

Methods: A random sample of 200 patients (100 with at least one relapse and 100 without relapse screened by the algorithm) were randomly selected from a cohort of 37,986 MS patients previously identified in the SNDS. For each case, all data available in the SNDS, including those related to the dispensing of corticosteroids, hospitalizations for potential MS relapse or for administration of high dose of steroids were examined by 2 neurologists to assess the presence or absence of relapses, blind to the result of the algorithm. In the event of an inter-expert discrepancy, the summary sheets were reviewed in a collegiate manner, in order to reach a consensus. Algorithm performance was estimated using the positive and negative predictive values (PPV, NPV).

Results: Among the 37,986 MS patients identified in the SNDS between 01/07/2015 and 31/12/2017, 9.6% had at least one relapses according to the algorithm. Among the 200 patients randomly selected, neurologists confirmed 95 patients with relapses and 96 without relapse, with a PPV of 95% and a NPV of 96%. After adjusting the algorithm based on neurologists' conclusions, the PPV and the NPV were respectively 95.2% and 100%.

Conclusions: The wealth of data available in the SNDS allows a holistic view of the patient in the health system, and makes it possible to define algorithms for detecting complex events such as relapses in MS. This claim-based algorithm appeared to well detect MS relapse and could thus be applied to future observational MS studies in SNDS.

3886 | Assessing outcomes of uterine perforation and IUD expulsion before and after ICD-9-CM to ICD-10-CM transition in women with IUD insertions

Catherine Saltus[1], Alex Asiimwe[2], Jeffrey Peipert[3], Susan Reed[4], Darios Getahun[5], Amy Alabaster[6], Mary E Ritchey[7], Laura Ichikawa[8], Jennifer Gatz[9], Vicki Chiu[5], Maqdooda Merchant[6], Michael Fassett[5], Ann-Kathrin Frenz[2], Mary Anne Armstrong[6], Jinyi Wang[7], Shannon Hunter[7], Giulia Chillemi[6] and Mary Anthony[7]

[1]RTI Health Solutions, Waltham, MA; [2]Bayer AG, Berlin, Germany; [3]Indiana University School of Medicine, Indianapolis, IN; [4]Kaiser Permanente Washington, University of Washington, Seattle, Seattle, WA; [5]Kaiser Permanente Southern California, Pasadena, CA; [6]Kaiser Permanente Northern California, Oakland, CA; [7]RTI Health Solutions, Research Triangle Park, NC; [8]Kaiser Permanente Washington, Seattle, WA; [9]Regenstrief Institute, Indianapolis, IN

Background: Healthcare databases are increasingly used for medication and device postmarket safety studies. Electronic health records (EHRs) provide a rich source of structured and unstructured data, but changes in the data over time and the potential impact on study results must be considered. On October 1, 2015, the US transitioned from the use of ICD-9-CM to ICD-10-CM coding. We conducted a study that developed algorithms including ICD-9-CM codes to identify intrauterine device (IUD)-related uterine perforation and expulsion.

Objectives: The purpose of this analysis was to assess the reliability of algorithms developed that were validated with ICD-9-CM codes, and then transitioned to ICD-10-CM codes, under the assumption of no temporal trends that would affect the incidence of the outcomes of interest.

Methods: Four sites in the US participated: three Kaiser Permanente sites—Northern California, Southern California, Washington—and Regenstrief Institute in Indiana. The proportion of patients with an IUD who had a uterine perforation or IUD expulsion in the 12 months before and 12 months after implementation of ICD-10-CM coding was assessed. For this evaluation, the previously validated, site-specific algorithms for uterine perforation and IUD expulsion—developed using structured data (e.g., ICD-9-CM, Current Procedural Terminology codes, National Drug Codes) and unstructured data (Natural Language Processing terms)—were utilized, replacing ICD-9-CM with the mapped ICD-10-CM codes.

Results: The number of IUD insertions per year at each site ranged from 3,074 to 49,866. The number of uterine perforation events per year ranged 0.06%-0.33%, and IUD expulsions ranged 0.50%-0.91%. In the data pooled across sites, the proportion of women with an IUD and a uterine perforation was 0.11% in the 12 months before ICD-10-CM code implementation and 0.12% in the 12 months after. The proportion of women with an IUD expulsion in the 12 months before and 12 months after ICD-10-CM code implementation was 0.72% and 0.77%, respectively. At each research site, the proportions before and after ICD-10-CM code implementation were relatively consistent, except at the smallest site, where estimates were more variable but based on a small number of events. At this site, all potential cases were manually reviewed to verify case status.

Conclusions: Algorithms developed and validated for uterine perforation and IUD expulsion showed no evidence of change due to transition from ICD-9-CM to ICD-10-CM codes, resulting in a consistent proportion of women classified as experiencing these outcomes.

3903 | IUD type and indicators of difficult insertion among women with intrauterine devices

Catherine Saltus[1], Susan Reed[2], Jeffrey Peipert[3], Michael Fassett[4], Maqdooda Merchant[5], Alex Asiimwe[6], Mary E Ritchey[7], Fagen Xie[4], Mary Anne Armstrong[5], Jennifer Gatz[8], Laura Ichikawa[9], Darios Getahun[4], Richard Lynen[10], Jinyi Wang[7], Shannon Hunter[7], Giulia Chillemi[5] and Mary Anthony[7]

[1]RTI Health Solutions, Waltham, MA; [2]Kaiser Permanente Washington, University of Washington, Seattle, Seattle, WA; [3]Indiana University School of Medicine, Indianapolis, IN;[4] Kaiser Permanente Southern California, Pasadena, CA; [5]Kaiser Permanente Northern California, Oakland, CA; [6]Bayer AG, Berlin, Germany; [7]RTI Health Solutions, Research Triangle Park, NC; [8]Regenstrief Institute, Indianapolis, IN;[9] Kaiser Permanente Washington, Seattle, WA;[10]Bayer HealthCare, Whippany, NJ

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Approximately 16% of women who use contraception in the United States use long-acting reversible contraceptives such as an intrauterine device (IUD). There are two types of IUDs: copper and levonorgestrel-releasing (LNG). Both types are indicated for prevention of pregnancy. Difficulty with device insertions that might be associated with negative outcomes for the user may differ by IUD type.

Objectives: To describe the proportion of women who have indicators of potentially difficult insertion during IUD placement for LNG and copper IUDs.

Methods: Women receiving IUDs were identified at each of four sites (three Kaiser Permanente sites—Northern California, Southern California, and Washington—and Regenstrief Institute, Indiana). Structured (National Drug Codes, International Classification of Diseases 9 and 10-Clinical Modification (ICD 9/10), Current Procedural Terminology) and unstructured (clinical notes) data were used to identify IUD type, and five indicators of potentially difficult IUD insertion (cervical dilation, ultrasound guidance, paracervical block, provider note for "difficult insertion," and misoprostol use). ICD 9/10 was also used to identify recent menorrhagia. The proportion of women with difficult insertion was assessed overall as well as by IUD type and by recent menorrhagia diagnosis.

Results: Among 326,658 women with IUD insertions, 63,664 (19.5%) received copper, and 259,234 (79.4%) received LNG-IUDs. Overall, 9.1% of women (site range, 3.5%-16.3%) experienced some indication of difficult insertion; a lower proportion of women with copper IUDs had any of these five indicators of difficult insertion (7.3%) versus women with LNG IUDs (9.5%). As expected, women with menorrhagia and concomitant procedures were more likely to receive LNG IUDs than copper IUDs (12.% vs. 1.3% and 8.9% vs. 4.2%, respectively), and the proportion of women with an indicator of difficult insertion was higher among women with recent menorrhagia (11.5%) than among those without this diagnosis (8.8%). The most common indicator was paracervical block (4.5% of insertions); however, misoprostol use and cervical dilation were more common at some sites.

Conclusions: The proportion of women with an indicator of potentially difficult insertion was higher among those receiving LNG IUDs compared with those receiving copper IUDs. However, as LNG are also secondarily indicated for heavy menstrual bleeding and more likely to be inserted with concomitant procedures, these factors might play a mediating role in this difference.

3905 | Data element agreement in CPRD aurum: Concordance between labs, diagnoses, and treatments

Katrina Wilcox Hagberg[1], Rebecca Persson[1], Catherine Vasilakis-Scaramozza[1], Tim Williams[2], Puja Myles[2] and Susan S Jick[1,3]

[1]*Boston Collaborative Drug Surveillance Program (BCDSP), Lexington, MA;* [2]*Clinical Practice Research Datalink (CPRD), Medicines and Healthcare Products Regulatory Agency, London, United Kingdom;* [3]*Boston University School of Public Health, Boston, MA*

Background: CPRD is now providing data from a new medical record database, CPRD Aurum collected with EMIS® software. Evaluating and understanding the presence or absence of common data elements is critical for making decisions about a database's suitability for use in medical research. A useful research database should have high concordance between data elements (e.g. lab results indicative of a chronic disease and codes for corresponding diagnoses and treatments).

Objectives: To evaluate data element agreement between lab values, diagnoses and treatments of GP-treated conditions in CPRD Aurum.

Methods: This was a descriptive study in a random sample of 37,502 patients (aged 20+) who had a lab test result between 2005-2018. Among patients with abnormal HbA1c, cholesterol, or hemoglobin lab values we described frequency with corresponding coded diabetes, hyperlipidemia and anemia diagnoses and treatments.

Results: There were 15,063 patients with ≥1 HbA1c lab record, of which 5,352 had ≥1 result above the upper limit of normal (ULN). Of these, 66% had a diagnosis for diabetes (60% were type 2) and 57% received a hypoglycemic prescription. Among those with HbA1c levels >120% above ULN, the proportion of patients with a diabetes diagnosis increased to 98% (88% were type 2) while the proportion with a treatment increased to 93%. There were 22,981 patients with cholesterol lab record, of which 13,764 had ≥1 result above the ULN. Only 28% of these had a hyperlipidemia diagnosis and 53% received a statin. Among those with levels >120% above ULN, the proportion of patients with a hyperlipidemia diagnosis remained low (45%) while the proportion with a statin prescription increased to 71%. There were 36,152 patients with ≥1 hemoglobin lab result, of which 11,855 had a result below the lower limit of normal (LLN). Of these, 37% of females had an anemia diagnosis and 62% received iron supplement prescriptions, whereas for males 33% were diagnosed an<80% LLN) the proportion of patients diagnosed (59%) and treated (75%) for anemia increased but remained higher for females.

Conclusions: Concordance between presence of abnormal lab values and coded disease diagnoses was highest among patients with diabetes (for which there are extensive National Health Service Quality and Outcome Framework (QOF) reporting requirements). Concordance was lower for hyperlipidemia and anemia (where there is no QOF). In CPRD Aurum, if only diagnoses are used to identify disease it is likely that some chronic conditions will be underestimated, particularly for diseases not incentivized under QOF.

3908 | Quality and completeness of cancer diagnoses recorded in the new CPRD aurum database

Katrina Wilcox Hagberg[1], Rebecca Persson[1], Catherine Vasilakis-Scaramozza[1], Tim Williams[2], Tarita Murray-Thomas[2], Puja Myles[2] and Susan S. Jick[1,3]

[1]*Boston Collaborative Drug Surveillance Program (BCDSP), Lexington, MA;* [2]*Clinical Practice Research Datalink (CPRD), Medicines and Healthcare Products Regulatory Agency, London, United Kingdom;* [3]*Boston University School of Public Health, Boston, MA*

Background: The Clinical Practice Research Datalink (CPRD) now provides a new medical record database, CPRD Aurum collected using EMIS® software. Understanding the validity and completeness of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

diagnoses recorded in any new data source is critical for making decisions about the data's suitability and use in medical research.

Objectives: This study examined data source agreement to describe cancer diagnoses recorded in CPRD Aurum compared with those present in linked Hospital Episode Statistics APC data (HES). This comparison provides information on CPRD Aurum data 'correctness' (e.g. accuracy, validity) and 'completeness' (e.g. presence, missingness).

Methods: Patients with a cancer diagnosis at a specified site were selected from a random sample of 50,000 patients in CPRD Aurum (1997-2018) with HES linkage. We calculated the proportion of cancer cases recorded in CPRD Aurum who also had a cancer diagnosis at the same site recorded in HES, overall and by cancer site (correctness). We also evaluated completeness, overall and by cancer site, by identifying all cancer diagnoses in HES and calculating the proportion also present at the same cancer site in CPRD Aurum.

Results: There were 6772 patients with a cancer record: 4376 had a diagnosis in CPRD Aurum, 6124 had a diagnosis in HES, and 3728 had a cancer diagnosis in both data sources. The proportion of patients with a cancer diagnosis in CPRD Aurum with a corresponding diagnosis in HES (correctness) was 85%, which varied depending on cancer site (thyroid/endocrine [67%] - digestive organs [90%]). The proportion confirmed remained high (>79%) regardless of diagnosis year and was slightly higher for males (87%) than females (83%). The completeness of cancer diagnoses in HES compared to CPRD Aurum was 61%. This varied by cancer site, with the highest completeness for breast cancer (83%) and male genital cancers (81%) and lowest for common metastatic sites (bone [7%] - brain [36%]). Completeness estimates did not differ by sex but were lower (51%) early in the study period (1997-2002) and have since stabilized to about 63% (2003-2017). Explanations for the recording of cancer diagnoses in only one of the two data sources are currently being explored to help researchers use the data.

Conclusions: Findings suggest that site specific cancer diagnoses recorded in CPRD Aurum are of relatively high 'correctness' for use in medical research. However, completeness estimates were low and varied by cancer site and calendar year. This may underestimate cancer diagnoses when using CPRD Aurum data only. Use of additional codes or linked data may achieve more complete cancer case ascertainment.

3924 | Validating claims-based algorithms identifying pregnancy outcomes

Keran Moll[1], Hui Lee Wong[2], Kathryn Fingar[1], Shayan Hobbi[3], Minya Sheng[1], Timothy Burrell[1], Bethany Baer[2], Steven Immel[3], Nasim Lari[3], Linda Eckert[4], Flor Munoz[5], William Rosenfeld[3], Joyce Obidi[2], Kristin Sepulveda[2], Azadeh Shoaibi[2] and Steven Anderson[2]

[1]IBM Watson Health, Cambridge, MA; [2]US Food and Drug Administration, Center for Biologics Evaluation and Research, Silver Spring, MD; [3]IBM Global Business Services, Bethesda, MD; [4]University of Washington School of Medicine, Seattle, WA; [5]Baylor College of Medicine, Houston, TX

Background: Identification of pregnancy outcomes and estimation of gestational age (GA) are critical in maternal vaccine safety studies. Validated pregnancy outcome algorithms based on the International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS) have yet to be published.

Objectives: To develop ICD-10-CM/PCS-based pregnancy outcome algorithms in claims databases using linked electronic medical records (EMRs) adjudicated by physicians as the reference method.

Methods: Pregnancy outcomes (live birth, spontaneous abortion [SA], and stillbirth [SB]) were identified using ICD-10-CM/PCS and service codes on claims for women aged 12-55 years in the 2016-2018 IBM® MarketScan® Explorys® Claims-EMR Data Set (CED). Multiple outcomes for the same woman were distinguished based on a hierarchy and spacing requirements. If multiple estimates of GA were present, a pregnancy start date was determined using estimates with the highest clinical accuracy (i.e., fertility procedures, GA on diagnosis, and prenatal scans). Among pregnancies with available structured obstetric EMR data, 100 full-term and preterm live births (FLBs/PLBs), 100 SAs, and 24 SBs were drawn as validation samples for which EMR charts were populated. Guided by Global Alignment of Immunization safety Assessment in pregnancy (GAIA) case definitions, physicians adjudicated cases and assigned a GAIA level of certainty to each one. Percentage positive agreement (PPA) was calculated, comparing results from the algorithms and adjudication.

Results: The claims-based algorithms identified 34,204 pregnancy episodes and their outcomes in CED (26,825 FLBs, 3,776 PLBs, 3,452 SAs, 151 SBs) and estimated GA at outcome date. Obstetric EMRs were available for 10% (3,390: 2,736 FLBs, 363 PLBs, 267 SAs, 24 SBs) of the episodes, which resembled the overall CED pregnancy population on demographic and clinical characteristics (most standardized mean differences <0.2). Of sampled episodes, physicians adjudicated the outcome and GA at outcome with GAIA levels of certainty of 1-3 for 93 PLBs, 92 FLBs, 75 SAs, and 24 SBs. Among these episodes, the PPA on the outcome was 98% for FLBs, 62% for PLBs, 100% for SAs, and 71% for SBs. The PPA on GA within 7 and 14 days, respectively, was 86% and 99% for FLBs, 82% and 93% for PLBs, 61% and 81% for SAs, and 67% and 79% for SBs.

Conclusions: ICD-10-CM/PCS-based pregnancy outcome algorithms were developed and validated with a high level of agreement with physician-adjudicated results from EMR review. This study demonstrates the application of GAIA case definitions to retrospectively collected EMR data.

4078 | Bias considerations due to outcome misclassification in observational studies evaluating association between treatments and mortality using administrative claims

Rishi J. Desai, Raisa Levin, Kueiyu Joshua Lin and Elisabetta Patorno

Harvard Medical School/Brigham & Women's Hospital, Boston, MA

Background: The bias implications of outcome misclassification arising from imperfect capture of mortality in claims-based studies are not well-understood.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To report performance characteristics of various approaches for ascertaining mortality in claims using national death index (NDI)-recorded mortality as the gold standard, and to investigate the impact of outcome misclassification on treatment effect estimates.

Methods: We designed an observational cohort study using Medicare claims (2012-2016) to identify patients with diagnosis of type 2 diabetes mellitus (T2D) (n=8.6 million) or heart failure (HF) (n=3.1 million). Within the two cohorts, mortality was identified from claims using the following approaches- 1) all-place all-cause mortality (from Master Beneficiary Summary File or hospitalization claims with discharge status of death), 2) in-hospital all-cause mortality only, 3) all-place cardiovascular (CV) mortality (based on diagnosis codes for a major CV event within 30 days of death date) or 4) in-hospital CV mortality (based on diagnosis codes for a major CV event within 30 days of death date in hospital). Empirically identified sensitivity and specificity based on observed values in the two cohorts were used to conduct Monte Carlo simulations for treatment effect estimation under differential and non-differential misclassification scenarios.

Results: From NDI, 1,544,805 deaths (549,996 [35.6%] CV deaths) in the T2D cohort and 1,175,202 deaths (523,430 [44.5%] CV deaths) in the HF cohort were included. Sensitivity was 99.997% and 99.207% for the all-place all-cause mortality approach, while 27.71% and 33.71% for in-hospital all-cause mortality approach in the DM and HF cohorts, respectively with perfect positive predicted values (PPVs). For all-place cardiovascular mortality, sensitivity was 52.01% in the DM cohort and 53.83% in the HF cohort with PPVs of 49.98% and 53.83%, respectively. When using only hospitalization claims for identifying cardiovascular mortality, sensitivities and PPVs were further compromised. Simulations suggested possibility for substantial bias in treatment effects, especially with differential misclassification, for approaches based on in-hospital mortality only and relying on ICD coding prior to mortality to ascertain cardiovascular death.

Conclusions: Approaches to identify mortality from claims had variable performance compared to NDI. Investigators should appreciate the potential for bias from outcome misclassification when using claims to capture mortality.

4139 | Value of adding secondary read diagnosis codes to identify breast cancer and bladder cancer in the clinical practice research datalink: A pilot validation study

Lia Gutierrez[1], Heather E. Danysh[2], Jaume Aguado[1], Phillip R. Hunt[3], James A. Kaye[2], Xabier Garcia-Albeniz[1] and Alicia Gilsenan[4]
[1]RTI Health Solutions, Barcelona, Spain; [2]RTI Health Solutions, Waltham, MA; [3]AstraZeneca, Gaithersburg, MD; [4]RTI Health Solutions, Research Triangle Park, NC

Background: Previous studies validating cancer outcomes in the United Kingdom's Clinical Practice Research Datalink (CPRD) evaluated algorithms using primary Read (pR) and ICD-10 diagnosis codes. In an ongoing postauthorization drug safety study, we performed a pilot validation of algorithms that also included secondary Read morphology (sR [M]) codes to identify breast and bladder cancer outcomes among individuals with type 2 diabetes mellitus (T2DM) in CPRD.

Objectives: To estimate positive predictive values (PPV) for algorithms when combining codes and when using individual codes to identify female invasive breast cancer and in situ or invasive bladder cancer among individuals aged ≥40 years with T2DM and taking an antidiabetic drug in CPRD.

Methods: The outcome-specific algorithms applied to CPRD (2012-2017) included at least one diagnosis code from (1) primary B… 00 [Neoplasms] or (2) secondary BB* [M] chapters of the Read medical code listing in CPRD GOLD or (3) ICD-10 diagnosis code in patients linkable to the Hospital Episodes Statistics. For each outcome, a sample of provisional cases were reviewed for clinical case validation using information from clinical patient profiles, general practitioner questionnaires, and prespecified case definitions. The PPV was estimated as the proportion of confirmed cases among all provisional cases in the validation sample. PPVs were calculated for all codes combined with and without sR [M] codes and separately for each code type.

Results: For female breast cancer, 110 provisional cases were reviewed; 98 were confirmed. The PPVs (95% confidence interval [CI]) were: all codes combined, 89.1% (81.7%-94.2%); ICD-10 code C50.9, 69.2% (38.6%-90.9%). The PPVs (95% CI) for the pR codes ranged from 93.6% (85.7%-97.9%) for B34..00 to 100.0% (54.1%-100.0%) for B34z.00. No cases were identified through sR [M] codes. For bladder cancer, 74 provisional cases were reviewed; 56 were confirmed. The PPVs (95% CI) were: all codes combined, 75.7% (64.3%-84.9%); ICD-10 code C67.9, 90.5% (69.6%-98.8%); pR code B49..00, 85.7% (67.3%-96.0%); sR [M] codes, 18.2% (2.3%-51.8%); ICD-10 and pR codes combined and excluding sR [M] codes, 85.7% (74.6%-93.3%).

Conclusions: Overall, the validity of the algorithms was high (breast, 89.1%) or moderately high (bladder, 75.7%). However, sR [M] codes contributed no additional cases for the breast cancer algorithm and had a low PPV and were detrimental to the overall validity of the bladder cancer algorithm. We recommend to not include sR [M] codes to identify breast or bladder cancers in CPRD.

4170 | Comparing the centers for medicare and medicaid services (CMS) enrollment database death dates to the national death index (NDI)

Dinci Pennap[1], Scott Swain[1], Sandia Akhtar[2], Jiemin Liao[2], Yuqin Wei[2], Jiaqi Li[2], Michael Wernecke[2], Thomas MaCurdy[2], Jeffrey Kelman[3], Andrew Mosholder[1] and David Graham[1]
[1]FDA, Silver Spring, MD; [2]Acumen LLC, Burlingame, CA; [3]CMS, Washington, DC

Background: Epidemiologic studies with mortality outcomes often rely on Medicare data for outcome ascertainment. Medicare data

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

released to external investigators may have incomplete death records due to the Social Security Act, which limits the disclosure of state death information. Internally, CMS has access to all deaths reported to it by Social Security Administration, which are incorporated into its Medicare enrollment database (EDB). Agreement between the EDB death information and death records from the NDI has not been comprehensively evaluated.

Objectives: To evaluate the agreement of death dates between CMS EDB and NDI.

Methods: Using Medicare fee-for-service (FFS) and NDI data from 1999 through 2016, we identified Medicare beneficiaries who were reported dead in the CMS EDB, linked these beneficiaries to the NDI using CMS Health Insurance Claim number and Social Security Number, and compared death dates between the two data sources. To assess agreement between our data sources, we identified individuals who were reported dead in both databases or otherwise presumed to be alive within Medicare and calculated kappa scores; where a kappa of 1 indicates perfect agreement and a kappa of 0 indicates agreement equivalent to chance. Death date comparisons were classified by presence in both databases and by differences in dates reported. CMS assigns the death date to the last day of the death month if they are unable to ascertain the exact death date. Thus, cases where CMS death date was the last day of the same month as NDI death date were also considered as potential matches. We also examined CMS to NDI linkage and death date matching for stability over time.

Results: Of the 36,785,640 Medicare beneficiaries reported dead in CMS death files from 1999 to 2016, 97.5% were linked to the NDI. A kappa score of 0.98 showed a near perfect agreement between NDI and CMS reported deaths. 97.2% of the linked beneficiaries had matching death dates in the CMS and NDI files, an additional 0.9% were matched within ±1 day, and another 1.2% were matched on the last day of their CMS death month. Over time, while the percentage of beneficiaries linked from CMS to NDI remained stable, the percentage of linked cases exactly matching on death dates increased from 94.8% in 1999 to 99.35% in 2016.

Conclusions: Our findings suggest strong concordance between death dates as recorded by CMS and the NDI in the entire Medicare FFS population. These findings may not generalize to Medicare data with incomplete death data.

4219 | Analytical approaches to reduce selection bias in as-treated analyses with missing in-hospital drug information

Yeon-Hee Baek[1], Yunha Noh[1], In-Sun Oh[1], Han Eol Jeong[1], Kristian B. Filion[2,3,4], Hyesung Lee[1] and Ju-Young Shin[1]

[1]Sungkyunkwan University (SKKU), Suwon, Republic of Korea; [2]McGill University, Montreal, QC, Canada; [3]McGill University, Montreal, QC, Canada; [4]Lady Davis Research Institute - Jewish General Hospital, Montreal, QC, Canada

Background: While much attention has focused on immeasurable time bias as a source of information bias in the absence of data on in-hospital drug use, it may also result in selection bias due to informative censoring in studies that use an as-treated exposure definition. However, little is known about analytical approaches to reduce informative censoring in this setting.

Objectives: To assess the performance of analytical approaches to minimize informative censoring due to missing in-hospital drug data using a case study of β-blocker use and all-cause mortality among patients with heart failure (HF).

Methods: We conducted a cohort study using South Korea's healthcare database from 2003 to 2015, which covers both in- and outpatient drug data. Exposure to β-blocker was assessed in the 30 days after HF diagnosis and defined using an as-treated exposure definition in which patients were followed until death or censoring due to β-blocker discontinuation (in the exposed group), β-blocker initiation (in the unexposed group) or end of the study period. We defined gold standard analysis by using both in- and outpatient drug data and used a Cox proportional hazard model to estimate the hazard ratio (HR) and 95% confidence interval (CI) of mortality. We repeated analyses using outpatient drug data only to mimic settings with missing in-hospital drug data and compared approaches to reduce informative censoring: 1) weighting by inverse probability weight (IPW) estimated for treatment crossovers, 2) censoring patients on hospitalization with weighting by IPW for hospitalization, 3) stratifying by deciles of cumulative hospitalization duration, and 4) restricting the cohort to those hospitalized <50% of their total follow-up duration.

Results: The study cohort included 19,480 patients. We found a HR of 0.87 (95% CI 0.72-1.05) for β-blocker use compared to non-use in the gold standard analysis. However, when restricting exposure assessment to outpatient data only, β-blockers were associated with a substantial mortality benefit (0.54, 0.43-0.66). Weighing by IPW for treatment crossovers (0.59, 0.48-0.72), censoring on hospitalization with IPW weighting (0.64, 0.46-0.89), stratifying by the duration of hospitalization (0.62, 0.50-0.77), and restricting the cohort (0.68, 0.52-0.90) marginally reduced the bias.

Conclusions: Selection bias due to informative censoring induced by the absence of in-hospital drug data was substantial in our case study. Censoring on hospitalization with IPW weighting, stratifying, and restricting the cohort by the duration of hospitalization only marginally reduced the bias.

4244 | Translation, cross-cultural adaptation, and psychometric properties of the danish version of the revised patients' attitudes towards deprescribing questionnaire

Carina Lundby[1], Trine Simonsen[1], Jesper Ryg[1], Jens Søndergaard[2], Anton Pottegård[1] and Henrik Hein Lauridsen[3]

[1]Odense University Hospital, Odense C, Denmark; [2]University of Southern Denmark, Odense C, Denmark; [3]University of Southern Denmark, Odense M, Denmark

Background: To effectively carry out deprescribing, information about patients' goals and treatment preferences is needed. The revised

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients' Attitudes Towards Deprescribing (rPATD) questionnaire is a 22-item self-report instrument capturing older patients' beliefs and attitudes towards deprescribing.

Objectives: To translate, cross-culturally adapt, and validate the rPATD questionnaire into Danish in a cohort of nursing home residents.

Methods: The rPATD questionnaire was translated and cross-culturally adapted during five stages of forward and backward translation. The pre-final questionnaire was pilot tested among 11 nursing home residents and ultimately adjusted into a final version. The validation of the Danish rPATD questionnaire included 162 nursing home residents (median age of 84 years; 67% women). Validity and reliability were assessed through exploratory factor analysis (structural validity), hypothesis testing (construct validity), and internal consistency. Floor and ceiling effects were also examined.

Results: The rPATD questionnaire was successfully translated and cross-culturally adapted into Danish. The exploratory factor analysis revealed a 4-factor structure similar to the original rPATD questionnaire, with items loading into four factors related to level of involvement in medication, perceived burden of taking medication, belief in appropriateness of using medication, and concerns about stopping medication. The questionnaire was adjusted to the Danish nursing home population and the Danish health care system by omission of two items, concerning medication expenses and inconvenience of taking medication, which resulted in a model generally showing acceptable structural validity, with factor loadings ranging from 0.292-0.837 and only minor cross-loading. Construct validity correctly predicted 67% of the hypothesized correlations (6/9 hypotheses correctly predicted). Internal consistency of all factors was generally acceptable with Cronbach's α ranging from 0.667-0.776. Participants obtaining the lowest or highest possible score in any factor ranged from 0-5.6%, i.e., no floor or ceiling effects were identified.

Conclusions: Our results suggest that the Danish modified model of the rPATD questionnaire has acceptable validity and reliability. Although the proposed model omits two items, it may still be relevant to include either all or only some items in clinical practice in terms of initiating describing conversations and aiding clinical decision making in the nursing home population.

4347 | Validity of self-reported antidepressants use—The norwegian women and cancer study

Marit Waaseth[1], Guro Forsdahl[1], Martina Havelkova[1], Eiliv Lund[2] and Tomas Log[3,4]

[1]UiT The Arctic University of Norway, Tromsø, Norway; [2]UiT The Arctic University of Norway, Tromsø, Norway; [3]Nord University, Bodø, Norway; [4]Helgeland Hospital Trust, Mo i Rana, Norway

Background: Medication use may be measured in different ways, e.g. self-report, prescription registries or plasma concentrations. If questionnaires provide valid data on medication use, it is preferable due to the comprehensive information obtainable at low costs, including data on confounding factors.

Objectives: We aimed to validate self-reported use of selective serotonin receptor inhibitors (SSRI) in the Norwegian Women and Cancer Cohort (NOWAC).

Methods: The study population included 105,855 women (born 1943-57) from NOWAC, a nationwide, questionnaire based cohort. A subgroup (n=3966) from the NOWAC Biobank provided plasma concentration measures for 93 pairs of SSRI-users (citalopram/escitalopram, sertraline and paroxetine) and non-users defined from a small questionnaire following the blood samples. The data was collected from 2002-2006. We compared, in a cross-sectional design, SSRI-information from the questionnaire following the blood samples and the plasma SSRI concentrations, and calculated validity measures (sensitivity and specificity). An upcoming record linkage with the Norwegian Prescription Database will provide prescription information on SSRI use for further analyses on the complete study population.

Results: Comparing questionnaire information on current SSRI-use with plasma concentration measures as gold standard (n=186), we found a sensitivity of 100.0% and a specificity of 98.9%, i.e. one participant reported using paroxetine but this was not detected in plasma. Results from the record linkage will be presented at the conference.

Conclusions: The questionnaire following blood samples collected in the NOWAC Biobank gives a highly valid measure of SSRI use according to plasma concentrations. Further findings awaits the record linkage with the Norwegian Prescription Database.

4355 | Use of the waiting time distribution method to determine the duration and number of episodes of antipsychotic treatment in older people

Juan Carlos Bazo-Alvarez[1,2], Mary Elizabeth Jones[3], Cini Bhanu[3], Tra My Pham[3], Claudia Cooper[3], Tim P Morris[3], Joseph Hayes[3], Kate Walters[3] and Irene Petersen[3,4]

[1]University College London, London, United Kingdom; [2]Universidad Católica Los Ángeles de Chimbote, Chimbote, Peru; [3]University College London, London, United Kingdom[4]Aarhus University, Aarhus, Denmark

Background: In longitudinal studies with routinely collected data, it can be crucial to define the most accurate measurement of treatment exposure over time at patient level. In these data, the number and time between prescriptions, within and between patients and drug types, may vary enormously. Thus, defining episodes of drug treatment and their duration is not always straightforward.

Objectives: To examine antipsychotic treatment episodes and durations from people ≥60 years, overall and stratified by drug type, sex and age.

Methods: Using electronic health records from UK, we evaluated first (haloperidol, chlorpromazine, trifluoperazine) and second (olanzapine, quetiapine, risperidone) generation antipsychotics treatment for patients observed between 2007-2017. We applied Waiting Time Distribution (WTD) approach to determine the usual period (percentile 95) for a patient to receive a new prescription. With that period estimated, we could define episodes, gaps between episodes and their duration for each patient. We modelled recurrent episodes with robust Cox models

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

to estimate median duration of episode (adjusted for calendar year). We fitted robust Poisson models to estimate proportion of observed time (person-years) covered by antipsychotic treatment.

Results: From WTD, we estimated that 95% of patients received a new prescription of antipsychotics within 35 days. Median number and duration of treatment episodes varied by antipsychotics. For haloperidol it was 1 (interquartile range IQR 1), while for olanzapine it was 3, IQR 6 and for trifluoperazine 4, IQR 10. First generation was prescribed for shorter periods (median duration 30 days) compared to second generation (median duration 100 days). Overall, patients were treated for 1/3 the time they were observed (31.5% [CI95%:31.2-31.8]). However, this varied by drug type (haloperidol 12.2% [11.9-12.6] and olanzapine 48.1% [47.2-49.0]). There was no difference in number of treatment episodes between genders (median 2, IQR 3). However, median duration was 60 days for men and 85 days for women. Males were treated 28% [27.6-28.6] the time they were observed, whereas females were treated 34% [33.4-34.2]. Median number of treatment episodes were 2, IQR 5 for individuals aged 60-69 years, while median was 1, IQR 2 for people aged 90-99 years. Median duration was 75 days for all ages but 25% those aged 80-99 years had treatment episodes >250 days.

Conclusions: Using WTD approach we were able to obtain detailed information and demonstrate substantial differences in duration of antipsychotic treatment by age, gender and drug types.

4387 | The validity of diagnostic algorithms to identify asthma patients in healthcare administrative databases: A systematic review

Alia Yousif[1,2], Roxanne Dault[3,4], Mireille Courteau[5], Lucie Blais[1,6], Anne-Marie Cloutier[7], Anaïs Lacasse[8] and Alain Vanasse[3,4]

[1]Université de Montréal, Montréal, QC, Canada; [2]Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'île-de-Montréal, Montreal, QC, Canada; [3]Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada; [4]Université de Sherbrooke, Sherbrooke, QC, Canada; [5]Centre Hospitalier Universitaire de Sherbrooke, Montréal, QC, Canada; [6]Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'île-de-Montréal, Montreal, QC, Canada; [7]Université de Sherbrooke, Montréal, QC, Canada; [8]Université du Québec en Abitibi-Témiscamingue, Montréal, QC, Canada

Background: Healthcare administrative databases have been widely used in epidemiology and drug safety/effectiveness research in asthma. However, since these data are primarily used for billing purposes and are by-products of complex healthcare systems, there is a concern that misclassification of clinical information may introduce bias. Thus, it is crucial to assess the validity of these data sources to identify asthma patients.

Objectives: To review the available evidence supporting the validity of algorithms to identify asthma patients in healthcare administrative databases.

Methods: A systematic search was conducted on multiple databases (Medline, Embase, CINAHL, AgeLine, PsycINFO, and all EMB Reviews) from inception to November 2018 to identify studies that reported the validity of at least one case-finding asthma algorithm applied to healthcare administrative data. After initial screening of abstracts, two investigators independently assessed the full text of studies which met the eligibility criteria. Study population and algorithm characteristics were extracted. A revised version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to evaluate the risk of bias and generalisability of studies.

Results: A total of 17 studies were included. Among these, seven were conducted in pediatric populations, seven in adults, and three included both adult and pediatric populations. Reference standards used to distinguish asthma cases from non-cases were mainly obtained from medical chart reviews or self-reported data. Algorithms incorporating at least one diagnostic code for asthma over a one-year period appeared to be valid in both adult and pediatric populations; (sensitivity ≥85%; specificity≥89%; PPV ≥70%). The validity was enhanced when: 1) the time frame to capture asthma cases was increased to two years; 2) at least two asthma diagnoses were considered; and 3) when diagnoses were recorded by pulmonologists. Algorithms which integrated pharmacy claims data appeared to correctly identify asthma patients, although the extent to which asthma medications can improve validity is unclear. The methodological quality of many studies was high, although disease progression bias and biases related to self-reported data was observed in some studies.

Conclusions: Healthcare administrative databases are an adequate source to identify asthma patients. More restrictive definitions based on both asthma diagnoses and asthma medications may enhance validity, although further research is required to confirm this hypothesis.

4404 | Validation of venous thromboembolism diagnoses in patients receiving rivaroxaban or warfarin in the health improvement network database of primary care electronic health records in the United Kingdom

Ana Ruigomez[1], Gunnar Brobert[2], Pareen Vora[3] and Luis García Rodríguez[1]

[1]Centro Español de Investigación Farmacoepidemiológica (CEIFE), Madrid, Spain; [2]Bayer AB, Stockholm, Sweden [3]Bayer AG, Berlin, Germany

Background: Data on the effectiveness of rivaroxaban for venous thromboembolism (VTE) indications among patients receiving the drug in routine clinical practice have thus far come from patient registries, claims database studies, or observational field studies. Rivaroxaban effectiveness studies could also be conducted efficiently using databases of electronic health records; however, it is recommended that outcome identification using such databases involves supportive evidence to validate the recorded diagnosis and avoid misclassification.

Objectives: To describe the effect of validation of VTE coded entries in The Health Improvement Network (THIN) primary care database in the United Kingdom on incidence rates of VTE among a cohort of rivaroxaban or warfarin users.

Methods: Among 36,701 individuals in THIN with a first prescription for rivaroxaban or warfarin between 2012 and 2015, we performed a

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

two-step VTE case identification process followed by a two-step case validation process involving manual review of patient records. A valid case required a coded entry for VTE with evidence of referral/hospitalization either as a coded entry or in the free text comments. Positive predictive values (PPVs) with 95% confidence intervals (CIs) were calculated using validated cases as the gold standard. Incidence rates were calculated per 1000 person-years with 95% CIs.

Results: We identified 2166 patients with a coded entry of VTE, corresponding to an incidence rate of 45.31 per 1000 person-years (95% CI: 43.49-47.22). After manual review of patient records including the free text comments, there were 712 incident cases of VTE - an incidence rate of 14.90 per 1000 person-years (95% CI: 13.85-16.02). The PPV for coded entries of VTE alone was 32.9%, and the PPV for coded entries of VTE with a coded entry of referral/hospitalization was 39.8%; this increased to 69.6% after manual review of coded clinical entries in patient records.

Conclusions: Among anticoagulant users in THIN, valid VTE case identification requires manual review of patient records including the free text comments to prevent outcome misclassification and substantial overestimation of VTE incidence rates. Our findings highlight the need to encourage owners of databases such as THIN to make anonymized free text comments available for research purposes.

4440 | Validity of healthcare database codes and vital statistic records for identifying neural tube defects (NTD) in infants

T Craig Cheetham[1], Sascha Dublin[2], Gaia Pocobelli[2], Jennifer Bobb[2], Susan Andrade[3], Rulin Hechter[4], Cecilia Portugal[4], Mercedes Munis[4], Ladia Albertson-Junkans[2], Gladys Salgado[2], Lawrence Wong[5], Timothy Maarup[6], Kecia Carroll[7], Marie Griffin[8], Marsha Raebel[9], David Smith[10], De-Kun Li[11], Pamala Pawloski[12], Sengwee Toh[13], Lockwood Taylor[14], Wei Hua[15], Miriam Dinatale[16], Carrie Ceresa[16], James Trinidad[15] and Denise Boudreau[2]

[1]Chapman University - School of Pharmacy, Irvine, CA; [2]Kaiser Permanente Washington Health Research Institute, Seattle, WA; [3]Meyers Primary Care Institute & University of Massachusetts Medical School, Worcester, MA; [4]Kaiser Permanente Department of Research & Evaluation, Pasadena, CA; [5]The Permanente Medical Group, Oakland, CA; [6]Southern California Permenente Medical Group, Downey, CA; [7]Vanderbilt University Medical School, Nashville, TN; [8]Vanderbilt University Medical School, Nashville, TN; [9]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO; [10]Center for Health Research, Kaiser Permanente Northwest, Portland, OR; [11]Kaiser Permanente Northern California, Division of Research, Oakland, CA; [12]Health Partners Research Foundation, Bloomington, MN; [13]Harvard Medical School and Harvard Pilgrim Health Care Research Institute, Boston, MA; [14]IQVIA Biotech, Austin, TX; [15]CDER, Food and Drug Administration, Silver Spring, MD; [16]CDER, Food and Drug Administration, Silver Spring, MD

Background: The ability to accurately identify NTD cases using healthcare database codes (from claims or electronic medical records) or vital statistics records (birth certificates) can avoid the time and costs required to conduct chart reviews for adjudication of outcomes.

Objectives: To evaluate the validity of various algorithms for identifying NTDs in infants using healthcare database codes and vital statistics records.

Methods: This analysis used data from a study whose primary aim was to evaluate the association between maternal prescription opioid use in early pregnancy and the risk of NTDs. The study was conducted within the Medication Exposure in Pregnancy Risk Evaluation Program, a multisite collaboration between 9 health plans and FDA. Potential NTDs were identified using specific inpatient and outpatient diagnosis and/or procedure codes in maternal and infant records as well as birth-defect flags in birth certificates. Potential NTD cases were abstracted, then reviewed and the outcomes confirmed by clinical experts. Positive predictive values (PPVs) and 95% confidence intervals (95% CI) were generated for various algorithms using the healthcare database codes and vital statistics records.

Results: The cohort included 113,168 singleton, live-born infants (55,960 with opioid exposure and 57,208 unexposed to opioids during pregnancy). Of the 84 potential NTD cases identified, 73 had charts available for review and adjudication. With an algorithm that included any indicator for a NTD, from healthcare database codes and vital statistics records, the PPV was 41% (95% CI; 35%-47%). Restricting the algorithm to inpatient database codes in the infants' record increased the PPV to 72% (95% CI; 64%-80%) whereas restricting to outpatient database codes in the infants' record had a PPV of 19% (95% CI; 10%-28%). Requiring both a NTD diagnosis code and a NTD procedure code from the infants' healthcare database yielded a PPV of 92% (95% CI; 85%-100%) but identified only 12 of 30 (40%) confirmed NTDs. Finally, restricting the algorithm to vital statistics birth certificate flags resulted in a PPV of 80% (95% CI; 67%-93%) but this approach only identified 8 of 30 (27%) confirmed NTDs.

Conclusions: Algorithms using healthcare database codes and vital statistics records did not accurately identify NTDs with a high PPV. The exception was the algorithm using a combination of diagnosis and procedure codes, but this approach missed 60% of confirmed NTDs. These results indicate that chart review with confirmation of outcomes is important when conducting observational studies of NTDs using these types of data.

4554 | Lookback period definition in electronic medical record data

Mackenzie M. Herzog[1], Stephen W. Marshall[2], Nancy A. Dreyer[1] and Christina D. Mack[1]

[1]IQVIA, Durham, NC; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Electronic medical records (EMR) provide a rich source of health data; however, limitations in ability to determine patient enrollment periods (when a lack of observation indicates no care vs. missing data for care obtained outside of the EMR system) may

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

lead to measurement error. The National Basketball Association (NBA) and its teams use a league-wide EMR for all players that is linked with participation data on each player's "enrollment" in the league (similar to continuous insurance enrollment).

Objectives: Compare lookback period definitions using EMR data alone compared to EMR plus participation data to assess the association between history of ankle sprain and incident game ankle sprain among NBA players.

Methods: All players who played in at least one NBA game from 2013-14 through 2016-17 were included. Index game ankle sprains and history of ankle sprain defined using the player's history were obtained from the audited NBA EMR. The primary approach included sprains in the past year with a lookback period that required ≥1 year of participation. This approach was compared to four alternative methods using EMR data alone: 1) all available lookback regardless of participation or observation in the EMR; 2) fixed 1-year lookback for all players regardless of participation or observation in the EMR; 3) ≥1 EMR observation for any encounter during the 1-year lookback period; 4) ≥1 EMR observation for any encounter prior to the start of the lookback period. Incidence rates were calculated per 10,000 player-minutes of participation and compared between players with and without a history of ankle sprain.

Results: Across the 4-season study period, 554 game ankle sprains were reported among 946 players and 122,010 player-games. Using the primary lookback approach, players with a history of ankle sprain in the past year were 1.41 (95% CI 1.13, 1.74) times as likely to sustain an incident ankle sprain as players with no history of ankle sprain. Alternative definition #1 led to biased, null results (IRR=1.01, 95% CI 0.80, 1.27), and alternate definitions #2 (IRR=1.37, 95% CI 1.12, 1.68) and #3 (IRR=1.35, 95% CI 1.10, 1.65) led to a small bias toward the null. Method #4 led to nearly identical results as the primary approach (IRR=1.40, 95% CI 1.12, 1.74).

Conclusions: In this population of professional athletes, not accounting for enrollment time when defining the lookback period resulted in measurement error for history of ankle sprain and therefore biased results. Requiring observation of the player in the EMR prior to the start of the lookback period may help mitigate this bias in the absence of enrollment data.

4579 | Validation study of medication adherence based on claims data in Japan

Yoshiyuki Saito[1], Hiroshi Yoshihara[1], Ataru Igarashi, Dr[1], Chieko Ooe[2] and Takeo Nakayama, Dr[3]

[1]University of Tokyo, Tokyo, Japan; [2]Fukuoka Branch of Japan Health Insurance Association, Fukuoka, Japan; [3]Kyoto University, Kyoto, Japan

Background: It is very important to understand medication adherence of patients for appropriate medication behavior promotion. Recently, many studies based on real world data try to evaluate drug safety, efficacy and detect medication adherence. Proportion of Days Covered (PDC) and Medication Possession Ratio Modified (MPRm) are one of the methods to measure medication adherence using claims data. However, it is not clearly reported how much different objective adherence scale such as PDC and MPRm and subjective adherence score.

Objectives: To understand usefulness of objective adherence scale such as "PDC" or "MPRm" on claims data in Japan.

Methods: We randomly sampled 1,500 from 31,461 patients in claims data of Fukuoka branch of Japan Health Insurance Association, Japan, between May to July in 2017 and distributed questionnaire to them on March on 2018. The selection criteria were aged 40 to 74 patients taking seven or more oral medications prescribed only for 14 days or more, except for short-term prescriptions. Medication adherence score on questionnaire was measured by Ueno methods (U-MAS-12) which is comprehensive score of medication adherence and including not only medication compliance but also other factors such as Collaboration with healthcare providers, Willingness to access and use information about medication, Acceptance to take medication and how taking medication fits patient's lifestyle. We calculated PDC by claims data in between April 2017 to March 2018. Finally, We combined subjective adherence with objective adherence and calculated Correlation, Sensitivity, Specificity, PPV, NPV, AUC and ROC curve according to subjective adherence as "Gold Standard" Analysis were conducted by Python3.6.3, Scikit-learn Version 0.19.1.

Results: We collected 472 answers and 294 were included in analysis data set. The mean of medication adherence (score is between 0-60) was 47.5(SD 6.0), medication compliance (0-15) was 14.3 (SD 1.4), collaboration (0-15) was 10.9 (SD 2.7), Literacy was(0-15) was 10.0 (SD 2.7), Life style(0-15) was 12.2 (SD 1.6) respectively. The mean of PDC (0-100%) was 87.7% (SD 11.2%), MPRm was 89.3% (SD 11.4%) respectively. There were no statistically correlation in any combinations. Sensitivity, Specificity, PPV, NPV, AUC and ROC curve according to subjective adherence as "Gold Standard" were 0.61, 0.66, 0.43, 0.80, 0.63 in MPRm>=90 and 0.63, 0.58, 0.39, 0.79, 0.61 in PDC>=90 respectively.

Conclusions: Objective adherence scale has low power to predict subjective adherence score. Subjective adherence score might not be "*Gold Standard*", there were totally different.

4605 | Registration of pharmacological treatment registered in the danish hip and knee arthroplasty registries: A validation study within the capital region of Denmark

Astrid Blicher Schelde[1], Janne Petersen[2,3], Thomas Bo Jensen[1], Kirill Gromov[4], Søren Overgaard[5,6], Jonas Bjerring Olesen[7] and Espen Jimenez-Solem[1,8]

[1]Department of Clinical Pharmacology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark; [2]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [3]Center for Clinical Research and Prevention, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark; [4]Department of Orthopaedic Surgery, Copenhagen University Hospital, Hvidovre, Copenhagen, Denmark; [5]Department of Orthopaedic Surgery and Traumatology, Odense

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

University Hospital, Odense, Denmark; [6]Department of Clinical Research, University of Southern Denmark, Odense, Denmark; [7]Department of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Copenhagen, Denmark; [8]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Background: Information on pharmacological treatment registered in the Danish Hip and Knee Arthroplasty Registries (DHR and DKR) has not previously been validated. High validity is important when extracting information from the clinical registries for use in quality analysis and register-based research.

Objectives: To validate pharmacological treatment registration in the DHR and DKR in relation to total hip and knee arthroplasties (THAs and TKAs).

Methods: We conducted a population-based validation study in the Capital Region of Denmark, January 2012 to April 2016. Using structured electronic health records as the reference standard, positive and negative predictive values (PPVs and NPVs) were calculated with 95% confidence intervals (CIs) for pharmacological treatment (antithrombotic, hemorrhage, and antibiotic) registered in the DHR and DKR. The PPVs and NPVs were presented both overall and on specific drugs.

Results: We identified a total of 13,442 THAs from the DHR and 9,813 TKAs from the DKR during the study period. The preliminary analysis showed that for DHR registrations, overall PPVs and NPVs were 77.9% (95% CI: 77.2 to 78.6) and 51.1% (95% CI: 40.4 to 61.7) for antithrombotic treatment, 70.9% (95% CI: 70.1 to 71.7) and 84.5% (95% CI: 82.6 to 86.4) for hemorrhage treatment, and 82.9% (95% CI: 82.2 to 83.5) and 34.0% (95% CI: 24.8 to 44.2) for antibiotic treatment, respectively. For DKR registrations, the preliminary analysis showed that overall PPVs and NPVs were 80.6% (95% CI: 79.8 to 81.4) and 41.4% (95% CI: 28.6 to 55.1) for antithrombotic treatment, and 82.8% (95% CI: 82.1 to 83.6) and 0.0% (95% CI: 0.0 to 70.8) for antibiotic treatment, respectively. The PPVs were ≥ 80% for dicloxacillin and vancomycin in the DHR, and for rivaroxaban in the DKR. The NPVs were ≥ 80% for all specific drugs in the DHR, and for dalteparin, enoxaparin, dabigatran, tinzaparin, penicillin, cefuroxime, dicloxacillin, and vancomycin in the DKR.

Conclusions: The study provides valuable knowledge regarding these high-quality registries. The validity of overall pharmacological treatment registered in the DHR and DKR was generally high. Furthermore, misclassifications in the DHR and DKR are important to take into consideration when extracting pharmacological information from the registries.

4621 | Identification and validation of major bleeding in a primary care database in Spain

Airam de Burgos Gonzalez, Luz María Leon Muñoz, Verónica Bryant Cerezo, Miguel Ángel Macia Martínez, María Dolores Montero Corominas and Consuelo Huerta Álvarez

Spanish Agency of Medicines and Medical Devices (AEMPS), Madrid, Spain

Background: Diverse major bleeding (MB) definitions have been proposed in different studies, mostly based on laboratory parameters. Electronic health records (EHRs) from primary care (PC) report on MB, although some information is usually missing or incomplete, so case confirmation requires complex algorithms that need to be validated for each study.

Objectives: In this study, we propose a strategy for identification and validation of MB cases from a cohort of new users of DOACs (Direct Oral Anticoagulants) in a database with incomplete laboratory data. The impact of validation is also addressed.

Methods: A cohort of patients aged >18 years with a first prescription of DOACs between 1st January 2008 and 31st December 2018 was identified from BIFAP, a Spanish PC database managed by AEMPS. Registered bleedings were firstly identified using ICPC-2 and ICD-9 codes, then classified as intracranial (ICB), gastrointestinal (GIB) and extracranial (ECB) bleedings and considered potential cases.

Based on the MB definition from the International Society on Thrombosis and Hemostasis, hospitalization and location of the bleeding in a critical organ or area were used as proxies for MB confirmation. A validation algorithm was developed with 1) information from an external source for hospital discharges (only available for some years and regions), 2) a free-text based algorithm created to identify hospitalization in EHRs and 3) manual revision of the patients' EHRs. Validation steps were sequential and exclusive to prevent manual revision.

Hospitalization algorithm's validity and precision were assessed in random samples with manually reviewed cases as gold standard.

Results: Estimated parameters of the hospitalization algorithm were PPV = 0.91, SP =0.97, NPV =0.90 and SE =0.71, with small variations between bleeding groups.

Out of 6,143 potential cases (4,606 GIB, 519 ICB and 1,018 ECB) preliminary results show 1,380 (772 GIB, 442 ICB, 177 ECB) confirmed MB cases. Their distribution by step of validation is 332 (5.4%) from step 1, 811 (13.2%) from step 2 and 244 (4%) from step 3. Only 18.8% of MB cases were confirmed by EHR manual revision.

Conclusions: Combined information from hospitalization and critical localization in MB confirmation is a valid approach in PC EHRs with incomplete information on laboratory values or other clinical data.

A specific algorithm was developed and validated to detect hospitalization with a high PPV, allowing confirmation of all hospitalized patients as MB cases along with patients confirmed by discharge information. Despite algorithm's high NPV, non-hospitalized patients require further evaluation by manual review.

4684 | Impact of exposure misclassification due to information from different prescribers on the risk of bleeding associated with DOACs

Mirjam Hempenius[1], Rolf HH Groenwold[2], Patrick C Souverein[1], Antonius Boer, de[1], Olaf H Klungel[1,3] and Helga Gardarsdottir[1,4,5]

[1]Utrecht University, Utrecht, Netherlands; [2]Leiden University Medical Center, Leiden, Netherlands; [3]University Medical Center Utrecht, Utrecht,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Netherlands; [4]*University Medical Center Utrecht, Utrecht, Netherlands;* [5]*University of Iceland, Reykjavik, Iceland*

Background: Drug exposure measurement based on routinely collected data might be misclassified due to different sources of prescriber information.

Objectives: To quantify the impact of misclassification of exposure due to different prescriber information on the risk of major bleeding associated with direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKAs).

Methods: Incident anticoagulant users (>6 months drug-free period) in the Dutch PHARMO Database Network between 2008 and 2017 were included. Drug exposure assessment was based on pharmacy dispensing information and classified according to general practitioner (GP) prescriptions, specialist prescriptions, or both. Cox regression analysis was used to estimate the adjusted risks of hospital admission for major bleeding for DOAC vs. VKA use. Hazard ratios were estimated also for gastrointestinal bleeding, intracranial bleeding, and stroke/TIA.

Results: We included 114,130 VKA-initiators and 25,586 DOAC-initiators. GP prescriptions accounted for 80% of VKA exposure time, and 60% of DOAC exposure time. Current DOAC use showed lower risk of major bleeding than VKA use; HR 0.67 (95%CI 0.55-0.81), 0.78 (0.67-0.89), and 0.81 (0.72-0.91), when exposure was based on specialist prescriptions only, GP prescriptions only or both, respectively. Similar results were found for the other bleeding outcomes. For stroke/TIA the HRs were 0.76 (0.62-0.94), 0.99 (0.84-1.16), and 0.97 (0.86-1.11), respectively.

Conclusions: Compared to using all dispensing information, including only anticoagulant dispensings prescribed by GPs does not materially impact the effect estimates of the risk of major bleeding and stroke/TIA. Using specialist prescribed dispensing information only yielded lower effect estimates, which may indicate differential exposure misclassification.

4762 | Are diabetes and glucose-lowering drugs equivalently reco(r)ded in CPRD GOLD and aurum?

Estel Plana[1], Ryan Ziemiecki[2], David Martinez[1], Jaume Aguado[1] and Cristina Rebordosa[1]

[1]*RTI-HS, Barcelona, Spain;* [2]*RTI-HS, RTP, NC*

Background: In England, many primary care practices migrated from VISION to EMIS software. In 2017, Clinical Practice Research Datalink launched Aurum, incorporating some of these migrating practices from GOLD and new practices using EMIS.

Objectives: To evaluate data migration and new recording in Clinical Practice Research Datalink Aurum by comparing the prevalence of diabetes and glucose-lowering drugs (GLDs) in GOLD and Aurum before and after first collection date (fcd) from EMIS.

Methods: Among practices migrating from GOLD to Aurum, 7 were randomly selected, and adult patients registered in the practice at least 1 year before the last collection date for GOLD (migration) were included. Diabetes diagnoses and GLDs were evaluated for both GOLD and Aurum within 1 year before migration and, for Aurum, also within 1 year after EMIS fcd. The availability of information on duration of prescriptions was assessed.

Results: A total of 40,196 adults in GOLD and 40,699 in Aurum were included in this study. Among those, 9.2% in GOLD and 9.6% in Aurum had a recorded diagnosis of diabetes any time before the migration. In GOLD, 7.0% of patients had diabetes within 1 year before migration. Among those, 80.9% were treated: 24.0% with insulin, 82.6% with metformin, 34.0% with sulphonylureas, 15.6% with DPP4i, 6.8% with thiazolidinediones, 5.8% with SGLT2i, 3.9% with GLP-1 receptor agonists, 0.2% with meglitinides, and 0.1% with alpha glucosidase inhibitors. In Aurum, 7.5% of patients had diabetes within 1 year before migration. Among those, 80.2% were treated: 24.4% with insulin, 82.5% with metformin, 34.2% with sulphonylureas, 18.5% with DPP4i, 5.7% with thiazolidinediones, 8.4% with SGLT2i, 3.8% with GLP-1 receptor agonists, 0.2% with meglitinides, and 0.1% with alpha glucosidase inhibitors. In Aurum, within 1 year after EMIS fcd, 8.9% of patients had diabetes, and 67.4% were treated. The duration of non-Insulin GLDs prescriptions was available for 79.7% of prescriptions in GOLD and 87.7% in Aurum within 1 year before migration, and for 96.3% of prescriptions in Aurum within 1 year after EMIS fcd. For Insulin prescriptions, duration was available for 3.6% of prescriptions in GOLD and 23.8% of prescriptions in Aurum within 1 year before migration, and for 61.1% of prescriptions in Aurum within 1 year after EMIS fcd.

Conclusions: Migration of recording of diabetes diagnoses and GLDs resulted in similar prevalence of diabetes diagnoses and medication use. New recording of diabetes diagnoses was in line with prior data. Availability of data on duration of GLDs were more complete in Aurum than in GOLD.

4788 | Reco(r)ding of lifestyle variables in CPRD aurum compared with GOLD

Jaume Aguado[1], David Martinez[1], Estel Plana[1], Ryan Ziemiecki[2] and Cristina Rebordosa[1]

[1]*RTI-HS, Barcelona, Spain;* [2]*RTI-HS, North Carolina, NC*

Background: In England, many primary care practices migrated from VISION to EMIS software. In 2017, Clinical Practice Research Datalink launched Aurum, incorporating some of these migrating practices from GOLD and new practices using EMIS. No publications to date exist evaluating data migration in Clinical Practice Research Datalink Aurum.

Objectives: To compare the recording of lifestyle variables in GOLD and Aurum before and after migration and check the validity of the new algorithm in Aurum.

Methods: Among practices migrating from GOLD to Aurum, 7 were randomly selected, and adult patients registered in the practice at least 1 year before the last collection date for GOLD (migration) were

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

included. Smoking status and alcohol consumption were defined in GOLD through entity types and codes, and the algorithm was adapted to Aurum using data up to 10 years before migration. Smoking status was defined as current, former, never, or missing. Alcohol consumption was defined as never, former, low to moderate (≤ 6 units/day), heavy (≥ 7 units/day) drinker, drinker unknown amount, or missing. Body mass index is under study.

Results: A total of 40,196 adults in GOLD and 40,706 in Aurum were included in this study. Median age was 49 years, and approximately 50% were females in both data sources. Smoking status was recorded for 95.4% of patients in GOLD versus 95.6% in Aurum. The distribution of smoking status in GOLD versus Aurum was 19.3% versus 20.4% for current, 28.7% versus 28.1% for former, and 52.0% versus 51.5% for never-smokers. Alcohol consumption was recorded for 67.9% in GOLD versus 68.4% in Aurum. The distribution of alcohol consumption in GOLD versus Aurum was 19.8% versus 21.4% for never-drinkers, 3.2% versus 3.3% for former drinkers, 68.9% versus 66.9% low-to-moderate drinkers, 3.5% versus 3.6% heavy drinkers, and 4.6% versus 4.7% drinkers (unknown amount).

Conclusions: Using the GOLD and Aurum adapted algorithms, distribution of lifestyle variables in GOLD and Aurum were very similar and in line with population distribution in the United Kingdom.

4809 | Is chronic obstructive pulmonary disease reco(r)ded similarly in CPRD GOLD and aurum?

David Martinez[1], Ryan Ziemiecki[2], Jaume Aguado[1], Estel Plana[1] and Cristina Rebordosa[1]

[1]RTI-HS, Barcelona, Spain; [2]RTI-HS, RTP, NC

Background: In England, many primary care practices migrated from VISION to EMIS software. In 2017, Clinical Practice Research Datalink launched Aurum, incorporating some of these migrating practices from GOLD and new practices using EMIS.

Objectives: To evaluate data migration and new recording in Clinical Practice Research Datalink Aurum by comparing the prevalence of chronic obstructive pulmonary disease (COPD) diagnosis and medications in GOLD and Aurum before and after first collection date (fcd) from EMIS.

Methods: Among practices migrating from GOLD to Aurum, 7 were randomly selected, and patients aged 40 years or older and registered in the practice at least 1 year before the last collection date for GOLD (migration) were included. COPD diagnoses and use of COPD controller medications were evaluated for both GOLD and Aurum within 1 year before migration and, for Aurum, also within 1 year after EMIS fcd. The availability of information on duration of prescriptions was assessed.

Results: A total of 26,666 patients in GOLD and 26,994 in Aurum were included in this study. Among those, 4.6% in GOLD and 4.4% in Aurum had a recorded diagnosis of COPD any time before the migration. In GOLD, 3.2% of patients had COPD within 1 year before migration. Among those, 81.4% were treated: 61.7% with long-acting muscarinic antagonists (LAMA), 59.3% with long-acting β2-agonists/inhaled corticosteroids (LABA/ICS), 10.6% with LABA, and 0.7% with LAMA/LABA. In Aurum, 3.3% of patients had COPD within 1 before migration. Among those, 81.4% were treated: 62.7% with LAMA, 59.7% with LABA/ICS, 8.8% with LABA, and 3.3% with LAMA/LABA. In Aurum, within 1 year after EMIS fcd, 3.4% of patients had COPD. Among those, 81.7% were treated: 56.3% with LAMA, 49.6% with LABA/ICS, 6.2% with LABA, and 14.1% with LAMA/LABA. The duration of COPD prescriptions was available for 76.7% of the prescriptions in GOLD and 94.1% in Aurum within 1 year before migration and in 97.6% in Aurum within 1 year after EMIS fcd.

Conclusions: Migration of recording of COPD diagnoses and medications resulted in similar prevalence of patients with COPD and medication use. New recording of COPD diagnoses was in line with prior data. In Aurum, use of COPD medications after EMIS fcd increased for LAMA/LABA and decreased for LABA and LABA/ICS. Availability of data on duration of COPD medications was more complete in Aurum than in GOLD.

4810 | An application of natural language processing to validation of melanoma and non melanoma skin cancers in a Spanish electronic healthcare database

Luz M León-Munoz[1], Jesus Santamaria[2], Ana LLorente[1], Airam de Burgos[1], Arturo Alvarez[1], Dolores Montero[1] and Consuelo Huerta[1]

[1]Spanish Agency for Medicines and Medical Devices-AEMPS, Madrid, Spain; [2]Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

Background: Traditional methods of validation in Electronic Health Records (EHR) include manually reviewing patient's clinical history and *ad hoc* algorithm which usually increases cost and complicate reproducibility.

Objectives: To develop a natural language processing (NLP) approach to validate skin cancer cases from primary care EHR and compare results with those obtained from traditional methods.

Methods: The Spanish Database for Pharmacoepidemiological Research in Primary Care-BIFAP, containing about 12 million patients was used. From patients >18 years old, with a registered code of any of melanoma (MM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) from 2007-2017, a random sample by type of cancer was selected, manually reviewed by experts and classified as "confirmed" or "not-confirmed". They represented the training sets for both validation approaches. The main idea is to classify remaining cases not included in the samples based on the information from those cases already classified. This was done A) by the researchers in the traditional approach; B) by automatic tools in NLP. F-score (harmonic mean of precision and recall, ranging from worse=0-best=1) was calculated. It also helped in choosing the best model from all those generated in NLP. Comparisons were explored according to F-score, percentage of confirmation and agreement between approaches when models were applied to remaining cases.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Out of 7,463 potential cases of MM; 46,664 of BCC and 10,270 of SCC identified, a sample of around 200 by type of cancer was selected. F-score was greater than 0,90 in MM and SCC for both approaches, and around 0,90 and 0.85 in BCC for traditional method and NLP respectively. After applying to the remaining potential cases, around 70%, 50% and 55% of potential cases of MM, BCC and SCC respectively were confirmed by both methods, agreement confirmation between them was around 60%, 36% and 45% of cases in MM, BCC and SCC respectively.

Conclusions: Validation results are consistent using both approaches, yielding good results in terms of precision and recall, being quite similar in proportion of confirmed cases. However, NLP is considerable less time consuming and different models can be tested determining the ability of each one to correctly classify cases, avoiding ambiguity of the language and subjectivity of the researchers. NLP contributes to increase repeatability and reproducibility of the validation process. As NLP does not always take into account clinical criteria, clear explanations of the tools and methods are needed.

4826 | How to deal with missing data in interrupted time series analysis with electronic health records

Juan Carlos Bazo-Alvarez[1,2], Tim P Morris[1], Tra My Pham[1], James R Carpenter[1,3] and Irene Petersen[1,4]

[1]*University College London, London, United Kingdom;* [2]*Universidad Católica Los Ángeles de Chimbote, Chimbote, Peru;* [3]*London School of Hygiene and Tropical Medicine, London, United Kingdom;* [4]*Aarhus University, Aarhus, Denmark*

Background: Interrupted time series (ITS) is a widely used quasi-experimental approach that evaluates the potential impact of an intervention over time, using longitudinal data. ITS is becoming more widespread in health research, and performing ITS with routinely collected patient-level data is more frequent in last years. In ITS studies performed with these individual-level data, it is common to average the outcome of interest at each time point and then perform a segmented regression (SR) analysis.

Objectives: In this study, we illustrate that such 'aggregate-level' analysis produces biased estimates when data are missing at random (MAR) and provide alternative analysis methods for solving this problem.

Methods: Using electronic health records, we evaluated weight change over time induced by the initiation of antipsychotic treatment (olanzapine). We contrasted estimates from 'aggregate-level' SR analysis against estimates from mixed models with and without multilevel multiple imputation of missing covariates, using individual-level data. Then, we conducted a simulation study to compare the methods in a 'controlled' environment.

Results: 'Aggregate-level' SR analysis suggested a substantial weight gain after initiation of treatment compared with mixed models (average short-term weight change from SR: 0.799kg/week compared to mixed models: 0.412kg/week). Simulation studies confirmed the 'aggregate-level' SR analysis was biased when data were MAR. In simulations, mixed models gave less biased estimates than SR analysis and, in combination with multilevel multiple imputation, provided unbiased estimates. We demonstrate that same combined methods can be successfully used with other types of ITS outcomes (e.g. proportions or counts); and that other methods or models applied in ITS, such as ARIMA or GEE, do not help to correct the bias problem due to data MAR.

Conclusions: 'Aggregate-level' SR analysis can severely bias the ITS estimates when data are MAR, affecting the final interpretation of the studied effect. Omitting the averaging-step and using mixed models help to avoid this issue. Moreover, when covariates are also missing -which is very common in observational data - mixed models can be used in combination with multilevel multiple imputation to obtain unbiased estimates.

4865 | Identification of cases of NSCLC in the pathology registry of the University Hospital of Siena: A validation study

Andrea Spini[1], Pietro Rosellini[1], Cristiana Bellan[2], Folco Furiesi[2], Silvano Giorgi[2], Sandra Donnini[3], Rosa Gini[4], Marina Ziche[3], Francesco Salvo[1] and Giuseppe Roberto[4]

[1]*University of Bordeaux, Bordeaux, France;* [2]*Azienda Ospedaliera Universitaria Senese, Siena, Italy;* [3]*Università di Siena, Siena, Italy;* [4]*Agenzia Regionale di Sanità della Toscana, Firenze, Italy*

Background: In order to efficiently query large electronic databases and generate reliable evidence on the real-world utilization, effectiveness and safety of anti-cancer medications in non-small cell lung cancer (NSCLC) patients, data-source tailored case-finding algorithms have to be designed and validated.

Objectives: To design and validate a NSCLC-finding algorithm to retrieve NSCLC cases from the pathology registry (PR) of the University Hospital of Siena (UHS) in Italy.

Methods: Anonymized data from the PR of UHS were obtained (2009-2017). Based on local database and clinical experts' consultation, a NSCLC-finding algorithm (CFA) was built based on free-text keywords and on SNOMED morphology and topography codes. Patients that received a drug with NSCLC as indication of use were retrieved from the hospital pharmacy (HP) database of UHS, and the share identified by CFA was computed: based on the assumption that sensitivity of CFA is non-differential per treatment status, this ratio was used to estimate sensitivity (SE). Cases retrieved from PR were manually validated by two authors blinded to each other, based on PR free text. Per each case, the following four items were assessed and classified as "Yes", "No", "Maybe" : 1) *tumor*; 2) *lung*; 3) *NSCLC morphology*, 4) *primary origin*. Cases classified with four "Yes" or with three "yes" and "maybe" in the *primary origin* field were considered valid and were used to estimate the positive predictive value (PPV) of the algorithm.

Results: The CFA was composed by the intersection of cases identified by 10 morphology codes (M81403, M80703, M82463, M85603,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

M83233, M85503, M84303, M82503, M80033, M80123) or 4 morphology keywords (*non microcit*, *adenocarcin*, *squamocell*, *grandi cell*) AND 1 topography code (T-2*) or 2 topography keywords (POLM*, BRONCH*). CFA retrieved 2,003 cases, that in particular comprised 373 cases out of 469 patients retrieved from the HP database (SE=79.5%; 95%CI:75.6-82.9). Manual review confirmed 1,496 cases (PPV=74.7%; 95%CI:72.8%-76.6%). False positives were mostly trachea and neuroendocrine cancers.

Conclusions: Results from the validation of the tested CFA were promising. New algorithms will be designed based on the lessons learned from the manual review, using the validated dataset as a training set.

4867 | Developing a structured process to identify fit for purpose data framework

Ulka B. Campbell[1,2], Robert F. Reynolds[3], Emily Rubinstein[4] and Nicolle M. Gatto[5,6]

[1]Pfizer, New York, NY; [2]Columbia Mailman School of Public Health, New York, NY; [3]GlaxoSmithKline, New York, NY; [4]Aetion, New York, NY; [5]Aetion, New York, NY; [6]Columbia Mailman School of Public Health, New York, NY

Background: To complement standard guidelines, the 2019 SPACE framework (A Structured Preapproval and Postapproval Comparative study design framework to generate valid and transparent real-world Evidence) elucidated a process for designing valid and transparent real-world studies. SPACE prioritized the evaluation of secondary data sources against minimal size and measurement criteria.

Objectives: To develop a structured process for conducting feasibility assessments to identify regulatory grade, fit for purpose data applied in the SPACE framework.

Methods: The process was designed and developed by researchers with expertise in pharmacoepidemiology and real-world data from industry, academia, and data analytics. The process was informed by literature reviews, discussions, and consensus among the stakeholders. Regulatory-grade and fit for purpose data were defined based on the FDA's framework for a real-world evidence program.

Results: A structured framework for feasibility assessments with step-by-step guidance was developed. Step one requires prioritization of a small number of criteria to narrow the field of data sources. Checklist items are based on database size, structure, data availability and completeness, such as: (1) Are the data sufficiently large to achieve the needed number of patients? (2) Do the patients have sufficient length of follow-up? (3) Are therapeutic area specific variables captured (e.g. cancer stage)? (4) Are treatments administered in specialized settings captured (e.g. infusion vs. oral)? (5) Are results from procedures and biospecimen analysis captured? (6) Is data linkage possible with unstructured data (e.g. verbatim medical information)? (7) Are the data capable of automated abstraction (e.g. natural language processing)? Subsequently, in step two, the investigator uses a template to tabulate the responses from the initial feasibility questions. Step three further narrows the potential data sources by adding criteria as additional information emerges. For example, the investigator may need to identify a minimum number of patients with a given indication and prior medication use based on sample size calculations and varying assumptions. Lastly, operational considerations, such as time and budget, are factored into the decision.

Conclusions: A structured process for conducting feasibility assessments contextualizes the steps of identifying secondary data sources fit for regulatory decision making.

4886 | Validation of diagnosis code-based algorithms to identify metastatic renal cell carcinoma patients in medicare claims data

Danielle Chun[1], Blánaid Hicks[2], Sharon Peacock-Hinton[1], Hung-Jui Tan[3], Alex Keil[1], Til Stürmer[1] and Jennifer Lund[1]

[1]Gillings School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Queen's University Belfast, Belfast, Ireland; [3]School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Medicare claims data are a potentially powerful resource to understand treatment patterns and outcomes in patients diagnosed with metastatic renal cell carcinoma (mRCC). Previous validation studies have evaluated the accuracy of claims-based algorithms to identify incident cancers, but they did not specifically consider mRCC.

Objectives: Examine the accuracy of diagnostic coding-based algorithms to identify incident mRCC in Medicare claims data.

Methods: Adults aged ≥ 66 were identified in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (2007-2015). Non-cases were identified in the accompanying 5% non-cancer sample. Gold standard mRCC cases were patients diagnosed with stage IV RCC with 6 months of Medicare Parts A, B, and D before and 3 months after the month of diagnosis. This 9-month window was determined to be adequate to identify diagnostic work-up and initial treatment for mRCC cases. For cases and non-cases, 9-month continuous enrollment windows were created for each patient, advancing in 1-month increments from the start of their eligible Medicare enrollment start date. We computed sensitivity (SE), specificity (SP), and positive predictive values (PPV) with 95% confidence intervals (CI) at the person-level using the following definitions (def) of incident mRCC: (1) having a diagnosis code for RCC and metastasis in the primary and 1st secondary diagnosis positions, (2) having a diagnosis code for RCC and metastasis in the primary and any secondary diagnosis position, and (3) having a diagnosis code for RCC and metastasis in any diagnosis position.

Results: We identified 2,027 mRCC cases and 458,219 non-cases with at least one 9-month window of continuous enrollment. The incidence rate of mRCC in this population was 46 per 1,000 person-years. All definitions showed high SP (≥99%). Def 3 had the highest SE (76%, CI: 74%-78%) followed by def 2 (73%, CI: 71%-75%), and def 1 had the lowest SE (63%, CI: 61%-65%). In contrast, def 1 had the highest PPV (59%, CI: 57%-61%), followed by def 2 (57%, CI: 55%-58%), and def 3 had the lowest PPV (55%, CI: 53%-56%).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: We assessed the validity of claims-identified cancer cases compared to a gold standard in a cancer registry. Our findings showed that claims data can be used to identify incident mRCC with very high specificity. However, given a relatively low PPV, researchers should consider the appropriateness of using diagnosis code-based algorithms for mRCC cohort identification. These results were consistent with the findings of other diagnosis code-based algorithms for incident solid tumors.

4910 | Harmonizing fit for purpose assessment of datasources, the next step towards creation of credible real-world evidence

Miriam C. Sturkenboom[1], Jeff Brown[2], Robert Ball[3], Caitlin Dodd[1], Peter Arlett[4], Rosa Gini[5]

[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]Harvard Pilgrim Health Care, Boston, MA; [3]FDA, Rockville, MD; [4]European Medicines Agency, Amsterdam, Netherlands; [5]Agenzia Regionale di Toscana, Florence, Italy

Background: The big hurdle towards full implementation of real world evidence is the perceived lack of quality of data. In the past years, through network initiatives many assessments have been set up, but they have not been harmonised. The key challenge is to assess whether a datasource is fit-for-purpose for the specific study question. These are not generic features, impact of misclassification due to missingness heavily depends on the design of a study, the exposure and the study question. Currently generic dashboards for quality and accreditation processes based on informatics principles are being put in place. As a society using epidemiology and health data science we have an opportunity to ste the standards as the ultimate consideration for the assessment is whether there will be misclassification in key study variables.

Objectives: 1. To learn how fit-for-purpose assessment of datasources in networks is being done, which checks are conducted and how are rules created

2. Understand what regulators desire as quality assessment of datasources.

3. To establish and discuss whether we are ready to put thresholds and transparent criteria

Description: The workshop will have the following topics

1. Introduction to the topic and challenges: Miriam Sturkenboom

2. Example of fit-for-purpose assessment in Sentinel, does study and study design matter? Generic and study specific assessment: Jeff Brown

3. Example of fit-for purpose assessment of datasources in the ConcePTION system: Caitlin Dodd

4. Regulatory standards for 'quality of real world evidence' from FDA: Robert Ball

5. Regulatory standards for 'quality of real world evidence' from EMA: Peter Arlett

6. Modelling of misclassification: methods: Rosa Gini

7. Discussion

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4979 | Comparison of international classification of diseases, tenth revision coding patterns between the United States and Japan

Patricia Prince, Kammy Kuang and Emily Rubinstein
Aetion, Inc, New York, NY

Background: The United States (US) has adopted the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), a modification of the World Health Organization (WHO)'s ICD-10 diagnostic system. In Japan, diagnoses are reported in standard disease codes, which are mapped to the WHO ICD-10 codes within administrative claims. The differences in coding practices between the US and Japan and the variation in subclassification of disease codes between the ICD-10 coding systems can have important implications in clinical and epidemiological research.

Objectives: To determine whether differences in diagnostic coding systems between the US and Japan drive different distributions of ICD-10 codes employed when characterizing patients with prevalent cardiovascular conditions.

Methods: This study used the IBM MarketScan Commercial Claims and Encounters Database and the Japanese Medical Data Center (JMDC) Database. Patients included in this study were aged 18-64, enrolled between Oct 1, 2015 - Sept 30, 2018 and had a diagnosis for one of the diseases of interest. Acute myocardial infarction (AMI) and angina pectoris were chosen as the diseases of interest because angina pectoris (ICD-10: I20*) includes the same subcodes in both coding systems while AMI (ICD-10: I21*) has additional subcodes provided for further classification in the US ICD-10 coding system. All analyses were conducted via the Aetion Evidence Platform™ v3.19.

Results: A total of 119,404 and 310,764 patients were identified in JMDC and MarketScan, respectively. For both disease areas, a smaller percentage of diagnoses were classified with specified disease codes in JMDC. Specified codes represented only 23% of AMI diagnoses in JMDC compared to 98% in MarketScan. There are eight additional subcodes for AMI in the US ICD-10 coding system compared to the WHO ICD-10 version, which account for 31% of AMI diagnoses in MarketScan. Angina pectoris has the same diagnosis codes available in both coding systems, however, angina pectoris diagnoses were still less frequently coded in specified codes in JMDC than MarketScan (30% vs 50%).

Conclusions: This study highlights an example of the differences in ICD-10 coding specificity between Japan and the US. With higher percentages of specified diagnoses, MarketScan offers more granular information than JMDC for ICD-10 diagnoses. Researchers should be aware of implications in real-world evidence generation when selecting fit for purpose data sources.

5017 | Classifying exposure: An Application of the waiting time distribution to estimate treatment status and duration

Morten Madsen[1], Henrik Støvring[2], Astrid Lunde[3], Grethe S Tell[3], Helle Kieler[4], Gerhard Sulo[5] and Vera Ehrenstein[1]
[1]*Aarhus University Hospital, Aarhus, Denmark;* [2]*Aarhus University, Aarhus, Denmark;* [3]*University of Bergen, Bergen, Norway;* [4]*Karolinska Institutet, Stockholm, Sweden;* [5]*Norwegian Institute of Public Health, Bergen, Norway*

Background: In patients with non-valvular atrial fibrillation (NVAF), prescribed daily dose of warfarin varies by the international normalized ratio (INR). Data on INR or prescribed daily dose are typically not available from routinely collected data.

On the other hand, the reverse Waiting Time Distribution (WTD) based on time since last dispensing for all cohort members, can be used to estimate duration of individual prescriptions, based on percentiles of WTD. Little is known on how the choice of percentile affects the classification of observation time into full treatment episodes of multiple prescriptions.

Objectives: To examine the effect of using the 80th and 95th percentiles of WTD on classification of treatment episodes of warfarin therapy.

Methods: Using national registries in Denmark, Norway, and Sweden, we assembled a population-based cohort of 79,171 warfarin initiators with NVAF in 2013-2016, with follow-up through 2016. We used a WTD with a log-normal backward recurrence distribution with random index dates in 2015 to obtain estimates of the 80th and 95th percentile of the WTD, which we used as discontinuation criteria. We included number of pills, age, gender and country as covariates in the modelling of the WTD.

Based on the estimated percentiles, we classified observation-time as being for new users, stoppers, re-starters or switchers.

We calculated the cumulative incidence function (with 95% confidence intervals (CI)) for transitions from new users to stoppers and from stoppers to restarters, as well as the mortality among individuals staying in the new user state.

Results: Among the cohort of warfarin new users, probability of stopping within the first 12 months for the 80th and 95th WTD percentiles were 50% (CI 50% - 51%) and 25% (CI 25% - 25%).

Among stoppers, probability of restarting warfarin within 3 month after being classified as a stopper for the 80th and 95th percentiles were 68% (CI 67% - 68%) and 50% (CI 50% - 51%).

The one-year mortality within the first treatment-episode for the 80th and 95th percentiles was 5.9% (CI 5.7% - 6.1%) and 7.0% (CI 6.8% - 7.2%).

Conclusions: Many patients were classified as stoppers and fast subsequent restarters, especially when using the estimated 80th WTD percentile, which appears to be due to misclassification of observation time. This misclassification was less but still relevant using the 95th percentile.

In classifying treatment episodes, choice of WTD percentile as stop criterion not only affects the amount of observation time, but also the mortality within this observation time.

5060 | Machine learning methods to predict unmeasured confounders in claims data: A real-world application

Yasser Albogami[1,2], Michael J Daniels[3], Yu-Jung Wei[1], Kenneth Cusi[4] and Almut G Winterstein[1]
[1]*Department of Pharmaceutical Outcomes & Policy, University of Florida, Gainesville, FL;* [2]*Clinical Pharmacy Department, King Saud University,*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Riyadh, Saudi Arabia; [3]Department of Statistics, University of Florida, Gainesville, FL; [4]College of Medicine, University of Florida, Gainesville, FL

Background: Obesity and tobacco use are two examples of confounders considered unmeasured in claim data. Machine learning approaches may enhance previous attempts to impute obesity and tobacco use.

Objectives: To evaluate predictive performance and confounding bias reduction of machine learning algorithms versus simple logistic regression models and claims-based ICD9-CM measures of obesity and tobacco use.

Methods: About 2 million participants in the IBM MarketScan Health Risk Assessment database, which includes survey responses of obesity and tobacco use, were linked to MarketScan Commercial Claims data. One-year of clinical conditions, drug use, healthcare service utilization and demographics information were collected from the claims database before the survey completion date. The linked data were then divided into 70% for training and cross-validation and the remaining 30% for testing. Gradient Boosting Machine (GBM) and Bayesian Additive Regression Trees (BART) were used to predict obesity and tobacco use. The best-performing algorithm based on the c-statistic was selected. We then designed a pharmacoepidemiological study to replicate the effect of glucagon-like peptide-1 receptor agonists (GLP-1RA) on acute pancreatitis from previous observational studies. The prediction algorithm was deployed to classify patients for obesity and tobacco use based on Youden's index. Multivariate proportional hazards regression was then fit to obtain hazard ratios.

Results: GBM exhibited the highest-performing algorithm to predict obesity (C-statistic 0.73) and tobacco use (C-statistic 0.76) followed by BART (0.72 and 0.75) and logistic regression (0.70 and 0.71). We identified a cohort of 780,145 enrollees who initiated GLP-1RA or non-GLP-1RA antidiabetic drugs. The incidence rate of acute pancreatitis among GLP-1RA users was 1.25 per 1000 person-years (95% CI: 1.06-1.46) compared to 1.50 per 1000 person-years among non-users (95% CI: 1.40-1.60). The unadjusted hazard ratio was (HR: 0.84 [95% CI: 0.62-1.15]). After using ICD-9 measures of obesity and tobacco use, in addition to other pre-specified confounders, the HR was 0.82 [95% CI: 0.59-1.16.]. When we replaced ICD-9 measures with the GBM- or logistic regression-predicted obesity and tobacco use, the HR was 0.79 [95% CI: 0.56-1.13] and 0.81[95% CI: 0.58-1.15], respectively.

Conclusions: Machine learning predictive probabilities with optimized sensitivity and specificity only marginally improved ICD9-based or regression-based measures of obesity of tobacco use.

5076 | Plasmode simulation of multiple imputation performance using internal validation data to adjust for unmeasured confounders

Yasser Albogami[1,2] and Almut G Winterstein[1]

[1]Department of Pharmaceutical Outcomes & Policy, University of Florida, Gainesville, FL; [2]Clinical Pharmacy Department, King Saud University, Riyadh, Saudi Arabia

Background: Using internal validation data from linked subsamples to perform multiple imputation has shown to reduce bias due to unmeasured confounders. We present an applied example how the stability of multiple imputation and respective bias reduction with varying levels of missingness, i.e., the % missing data in the parent cohort, can be tested within the target research question.

Objectives: To evaluate the performance of multiple imputation using internal validation data with varying levels of missingness.

Methods: We used IBM Marketscan Commercial Claims linked to Health Risk Assessment data which provides patients' body mass index. We then identified diabetes patients initiated on glucagon-like peptide-1 receptor agonists (GLP-1RA) or sulfonylureas. From the first day of receiving the study drug, we followed patients for one-year or until diagnosed with depression (study outcome) or discontinuation of study drug. Using pre-specified information from this cohort including obesity, comorbidities, drug use and healthcare services utilization, we then applied plasmode simulation. We simulated data in which the association between study drugs and depression is null (HR=1.00) conditional on the pre-specified information. The simulation was iterated 50 times to create 50 datasets each of which included 5000 patients. We then randomly amputated the obesity information to have 20%, 50% and 90% obesity missingness. In each scenario, we obtained crude and multiple imputation estimates of the study drug effect on depression.

Results: We identified about 20,000 patients who newly used GLP-1RA or sulfonylurea. Similar to the empirical data, simulated data included 44% of GLP-1RA users, 75% obese and about 65% hypertensive patients. Average follow-up in the empirical data and simulated data was about 290 days. The crude HR of depression for GLP1-RA users was 1.63 (95%CI 1.57-1.69). Adjusting for pre-specified information including obesity yielded 1.04 (95%CI 1.00-1.08). After simulated data were amputated, multiple imputation analysis respectively showed HRs of 1.03 (95%CI 0.99-1.08), 1.01 (95%CI 0.95-1.08) and 0.97 (95%CI 0.82-1.15) for 20%, 50% and 90% obesity missingness.

Conclusions: Even with large missingness of a single confounder obtained from internal validation data, multiple imputation consistently showed an estimate approximating the true effect.

5099 | Impact of extending the lookback period on the estimated prevalence of inflammatory bowel disease in administrative claims data

Ghadeer K. Dawwas[1], Kevin Haynes[2], Lauren Parlett[3], Colleen M. Brensinger[1], Xiaoxue Chen[2], Qufei Wu[1], Michael D. Kappelman[4] and James D. Lewis[5]

[1]University of Pennsylvania, Philadelphia, PA; [2]HealthCore, Inc., Wilmington, DE; [3]HealthCore, Inc., Alexandria, VA; [4]University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]University of Pennsylvania, Philadelphia, PA

Background: Health administrative claims data are commonly used for chronic disease surveillance; yet the data on the optimal lookback

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

period for the ascertainment of prevalent cases of chronic diseases remains limited.

Objectives: To assess the impact of using 1 year and 4 years lookback periods on the estimated prevalence of inflammatory bowel disease (IBD) in administrative claims data.

Methods: We used data from Optum Clinformatics and HealthCore from 2010 to 2013 as primary, and conceptual replication datasets, respectively. We defined IBD based on the presence of ≥2 diagnoses of IBD by a physician, at least one by a gastroenterologist or surgeon; ≥1 diagnosis of IBD by a gastroenterologist and treatment with any of the following: mesalamine, balsalazide olsalazine, or vedolizumab; or ≥1 diagnosis of IBD by a gastroenterologist and treatment with sulfasalazine, anti-TNF therapy, ustekinumab, azathioprine, 6 mercaptopurine, or methotrexate. We conducted two separate analyses restricting the cohort to individuals who have (1) a minimum of one year of continuous enrollment from Jan 1, 2013 to Dec 31, 2013 and are alive on Dec 31, 2013, and (2) those who have a minimum of four years of continuous enrollment from Jan 1, 2010 to Dec 31, 2013 and are alive on Dec 31, 2013, respectively. We reported the age- and sex-standardized prevalence estimates per 100 population, using the 2010 US Census data as the reference population, overall and stratified by Crohn's disease (CD) and ulcerative colitis (UC).

Results: A total of 8,251,449 and 3,742,500 individuals were identified in Optum using the 1 year and the 4 years lookback periods, respectively. Among patients with a minimum of 4 years of continuous enrollment after a first physician diagnosis of IBD in Optum, the maximum interval between physician encounters with a coded IBD diagnosis was >1.15 years for 50%, >2.10 years for 25% and >4.51 years for 5%. Compared to the minimum 1 year lookback period, we ascertained a higher prevalence of IBD using a minimum 4 year lookback period (0.51 vs. 0.61), CD (0.21 vs. 0.25), and UC (0.27 vs. 0.33). We observed nearly identical results in the HealthCore dataset for IBD (0.48 vs. 0.66), CD (0.21 vs. 0.28), and UC (0.25 vs. 0.35).

Conclusions: In this population-based analysis, increasing the length of the minimum lookback period from 1 to 4 years increased the estimated prevalence of IBD by approximately 25% in two commercial databases. The use of the common 12 months lookback period may be insufficient to accurately ascertain IBD diagnosis in administrative claims database.

5117 | Utility of electronic health records to support post-marketing drug safety surveillance

Nancy D Lin[1], Jenna Calderbank[1], David Anderson[2] and John Seeger[1]
[1]*Optum Epidemiology, Boston, MA;* [2]*UnitedHealthGroup, Eden Prairie, MN*

Background: Claims data sources that serve as a backbone for the FDA Sentinel program may not include variables that detail patient care or represent clinical status or severity, because they do not represent a billable service. The increased availability of EHR data represents an opportunity to address this limitation by providing greater clinical granularity that can enhance research.

Objectives: To assess potential applications of EHR data to support drug safety evaluation, specifically: (1) validation of health outcomes of interest (HOIs) and (2) use within a case-control study paradigm. Acute pancreatitis is examined as one example.

Methods: We identified adults in a US health insurer population linked to EHR data who had an emergency department or inpatient claim with an acute pancreatitis diagnosis (potential case) or acute appendicitis diagnosis (potential control) between 4/2016-12/2018, a corresponding diagnosis in the EHR, and at least 6 months prior continuous health plan enrollment and observation time in the EHR. We assessed the capture of relevant laboratory results in the EHR over 30 days following index diagnosis, and baseline prevalence of selected diagnoses and medications based on EHR vs claims. Odds ratios (OR) were estimated as measures of association.

Results: Of 8,473 acute pancreatitis cases and 7,274 acute appendicitis controls identified in the claims, 520 cases and 649 controls met all eligibility criteria. Over 90% of acute pancreatitis cases had a lipase test result (most proximal result to index: median=624 u/l; interquartile range: 192-2218). Compared to controls, cases were older (mean: 49.7 vs 41.4 years) and more likely to be male (53% vs 48%). Cases were also more likely to have a claim for Type 2 diabetes (T2DM) (21% vs 8.5%, OR=2.9) and cholelithiasis (21% vs 3%, OR: 8.8). Compared to claims, EHR-derived prevalence of these conditions was lower in both cases and controls, while the relative odds among cases vs controls was similar for T2DM (OR=3.0) and higher for cholelithiasis (OR=13.0).

Conclusions: These study findings illustrate the feasibility of using EHR data to characterize certain HOIs, and indicate potential utility of linked claims-EHR data to support validation of claims-based algorithms. Considerations for designing a case-control study within an EHR database are more complex. Our findings suggest comparability of information capture among cases and controls varies depending on the exposure or covariates evaluated, and the specific providers contributing EHR data. Future work will expand the analysis to include assessment across more exposures and potential confounders.

5142 | Analysis of risk associated with delayed renal function recovery among medication-related acute kidney injury survivors

You-Lin Tain[1] and Chien-Ning Hsu[2]
[1]*Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan;*
[2]*Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*

Background: Medication-related acute kidney injury (AKI) is increasing recognized as a significant contributor of subsequent incident and progressive chronic kidney disease in hospitalized patients. Timing and degree of renal function recovery may affect long-term outcomes of AKI, but a time-series approach is limited among medication-related AKI survivors.

Objectives: 1. To assess patterns of renal function trajectory over one-year follow-up, and 2. to determine association between renal function trajectory patterns and initiation of chronic dialysis therapy.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: Electronic health records of 234,867 hospitalized adult patients from a large medical organization in Taiwan were used to identify initial hospitalization for medication-related AKI between January 1, 2010, and December 31, 2017. To identify medication-related AKI cases, 16-class nephrotoxic medications were screened in a 3-month or 7-day interval among patients with community- or hospitalized-acquired AKI. Serum creatinine (SCr) and estimated glomerular filtration rate measurements at baseline, during and discharge from hospital, and every 3 months after discharge from hospitalization for AKI were assessed to categorize renal function recovery (SCr return <1.5× baseline) patterns. Association between renal function trajectories and renal outcome was assessed by Cox proportional hazard model controlling for potential confounders, and subdistribution hazard ratio (SHR) with [95% CI] was analyzed for competing risk of kidney transplantation and early death. Sensitivity analysis with linear mixed model, commonly used for dealing missing data in longitudinal electronic health records was conducted.

Results: Among 3 months AKI survivors (n=24,132), 14.28% (n=3430) without renal function recovery. Three distinct renal function recovery patterns were further identified at 6 months, persistent non-recovery (SCr no return at 3 and 6 months: 10.18%), non-recovery (14.33%) and recovery (75.5%). Patients with persistent non-recovery renal function had the highest risk of chronic dialysis initiation (3.7/ 1000 person-months). Comparing to survivors without medication-related AKI, renal function trajectories were significantly associated with increased risk of renal replace therapy initiation within 5 years follow-up (SHR 10.2 [6.29-16.57] for persistent non-recovery, SHR 9.5 [5.89-15.33] for non-recovery, SHR 5.47 [3.56-8.42] for recovery).

Conclusions: Renal function trajectory patterns can be used to identify patients with AKI who should receive intensive post-discharge management.

Methods in Pharmacoepidemiology -> Study Design - Studies assessing study design (e.g., choice of comparator, self-controlled methods, avoiding immortal time bias)

79 | Prevalence of time-related biases in pharmacoepidemiology studies of anti-emetics, antifungal, and antibiotic medications during pregnancy: A systematic review

Ugochinyere Vivian Ukah, Wusiman Aibibula, Robert W. Platt and Kristian B. Filion
McGill University, Montreal, QC, Canada

Background: The occurrence of time related biases, such as immortal time and time-window bias, have been demonstrated in observational studies including drug effectiveness studies. These biases often result in an observation of false protective associations between a treatment or exposure and the outcomes of interest. However, the prevalence of these biases in perinatal pharmaco-epidemiology has not been described.

Objectives: To systematically review and estimate the prevalence of time-related biases (immortal time bias and time-window bias) in observational studies of classes of medications commonly used during pregnancy (antibiotic, antifungal and antiemetic drugs) via systematic review.

Methods: We systematically searched Medline and EMBASE databases between January 2013 and December 2019 for observational studies reporting the association between the antibiotic, antifungal, and antiemetic drugs and adverse pregnancy outcomes related to gestational age. Pregnancy outcomes of interest were those defined by gestational age such as pre-eclampsia, gestational hypertension, gestational diabetes, spontaneous abortion, stillbirth, preterm delivery and small for gestational age. Articles were reviewed independently for eligibility and for time-related biases by 2 reviewers.

Results: Of the 1,450 articles identified during our search, 17 studies were included in our systematic review (13 cohort, 3 nested case-control studies and 1 case-control study). Among these, 11 studies reported on antibiotics, 4 on anti-emetic, and 2 on anti-fungal medications. Spontaneous abortion (N=10 studies), and stillbirth and preterm birth (N=7 studies each) were the most reported outcomes. Eight studies (50%) had the potential to have time-related bias, specifically immortal time bias due to the misclassification of person-time between cohort entry and initiation of drug exposure. None of the included studies had time-window bias. Medications in studies with time-related biases appeared to be more protective for similar outcomes and comparators, compared with studies without time-related biases.

Conclusions: The potential for immortal time bias occurs frequently in epidemiological studies of medications during pregnancy. There is need for more appropriate analyses in these studies, such as time-dependent analyses, to avoid time-related biases.

128 | Impact of the choice of clinical code set on the outcomes of a real-world database study

Audrey Artignan[1] and Amy Buchanan-Hughes[2]
[1]*Costello Medical, Cambridge, United Kingdom;* [2]*Costello Medical, Boston, MA*

Background: Analysis of real-world data commonly requires the development of clinical code sets to define particular conditions used in determining patient eligibility, outcomes and covariates of interest. However, little guidance exists on developing code sets and these can show wide discrepancies across studies of the same condition.

Objectives: Using the example of chronic obstructive pulmonary disease (COPD), we evaluated the impact of the choice of code set on study outcomes including demographics, costs and resource use.

Methods: Thirteen unique code sets for COPD using the International Classification of Diseases, 10th Revision (ICD-10) were drawn from a previous literature review. These were mapped to ICD-10 Clinical Modification (ICD-10-CM) and used to select patients based on 2016 weighted national estimates from the US National Inpatient Sample (NIS). Demographics, costs and resource use were compared between the populations identified by each code set, both in full and after excluding codes common to all sets (J44*, "Other COPD").

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Although code sets comprised 3-56 codes (identifying n=626,019-918,314 patients), the three J44* codes accounted for ≥98% of principal diagnoses in the majority (n=10/13) of analyses (68-74% in the other 3 analyses); therefore, age, sex, length-of-stay (LOS) and costs were similar across all code sets. Compared to patients with a principal diagnosis of J44* (n=626,019), patients with other principal diagnoses were typically younger (lowest proportion of patients ≥65 years was 17.9% vs 59.8% for J44*), had higher costs (highest mean $29,593 vs $8,445 for J44*) and longer LOS (highest mean 14.1 vs 4.2 days for J44*).
Conclusions: The dominance of J44* as a principal diagnosis led to large overlaps between the 13 cohorts, so overall results were broadly similar among code sets. However, the additional patients identified by broader code sets typically had different characteristics to the "core" cohort. These results highlight the importance of validation studies to identify appropriate code sets, including careful consideration of the context in which specific codes are used in clinical practice and claims billing.

2362 | The application of mixed methods research in pharmacoepedemiology: A synthesis review

Hongling Chu[1], Bin Zhu[1], Fengwei Li[2], Lin Zeng[1], Nan Li[1], Liyuan Tao[1], Lin Zhuo[1], Yanyan Shi[1], Hua Zhang[1], Xiaoxiao Wang[1], Siyan Zhan[1] and Yiming Zhao[1]

[1]Peking University Third Hospital, Beijing, China; [2]Beijing Aerospace General Hospital, Beijing, China

Background: Mixed methods research (MMR) combined with research on the basis of quantitative and qualitative data, can answer research questions comprehensively and deeply by integrating qualitative and quantitative study. Specifically, qualitative research can be used to generate research hypotheses before analyzing data, answer the question like “what, how, why”, further explain the research results; or used to test the completeness of the data.
Objectives: In this synthesis review we aimed to answer 4 key questions: What kinds of questions in the field of pharmacoepidemiology can be solved by using MMR; how the MMR solve the problems of pharmacoepidemiologic studies; What are the observed benefits of using MMR; What are the limitations and barriers of using MMR.
Methods: We searched MEDLINE, EMBASE, Cochrane, SAGE, Web of Science, Google Scholar, CNKI, WANGFANG TADA. Included studies were published in English or Chinese, of any using MMR in the field of pharmacoepidemiologic. Data were analyzed using framework analysis and meta-synthesis approach.
Results: We included 56 studies using MMR in the field of pharmacoepidemiologic. In general, MMR by integrating qualitative and quantitative data can be used to: comprehensively and deeply analyze the factors affecting the description of a medication; evaluate the feasibility of translating the finds from study to real world practice; deeply explain the quantitative result from the big data; establish or select the meaningful outcomes; and solve problem related to medication management. The mainly limitation is mainly about shortage of an optimal design before implementing the MMR.
Conclusions: Mixed methods research can be used in the field of pharmacoepidemiology to overcome some disadvantages generated by only using quantitative study, to further improve the quality of research.

2406 | Drug-drug interaction surveillance study: Comparing self-controlled designs in five empirical examples in real-world data

Katsiaryna Bykov[1], Hu Li[2], Sangmi Kim[2], Vincent Lo Re III[3] and Joshua J. Gagne[1]

[1]Brigham and Women's Hospital, Boston, MA; [2]Eli Lilly and Company, Indianapolis, IN; [3]University of Pennsylvania, Philadelphia, PA

Background: Two self-controlled designs, the case-crossover (CCO) and the self-controlled case series (SSCS), have been utilized for studying drug-drug interactions (DDI) in real-world data (RWD). While sharing the strength of controlling for time-invariant confounding, these designs rely on different assumptions and may vary in their susceptibility to bias in RWD analyses.
Objectives: To compare the CCO and the SCCS for identifying DDIs in electronic healthcare data.
Methods: Using a large US commercial healthcare insurance database, we implemented the CCO and the SCCS designs to evaluate the following 5 DDI-outcome scenarios: (1) simvastatin-clarithromycin and muscle-related toxicity (expected, harmful DDI); (2) atorvastatin-valsartan and muscle-related toxicity; and (3-5) dabigatran-P-glycoprotein inhibitor (clarithromycin, amiodarone, verapamil) and bleeding. For both designs and all scenarios, analyses were conducted within person-time exposed to the object drug (statins and dabigatran). In the CCO, the odds of exposure to inhibiting drugs during a hazard window immediately preceding the outcome were compared to odds during a referent window 30 days prior. In the SCCS, outcome rates during person-time exposed to inhibiting drugs were compared to rates during unexposed person-time. We adjusted for possible bias associated with inhibiting drug by comparing DDI estimates to estimates from patients unexposed to the object drug (controls).
Results: The designs yielded similar estimates for simvastatin-clarithromycin DDI: odds ratios (ORs) 2.61 (95% CI 1.52 - 4.50) before and 1.29 (95% CI 0.73 - 2.28) after adjustment in CCO; incidence ratios (IRs) 2.67 (95% CI 1.82 - 3.91) and 1.32 (95% CI 0.89 - 1.96) in SCCS. Both designs showed no association between atorvastatin-valsartan exposure and muscle-related toxicity, either before or after adjustment. Due to small numbers of patients exposed to dabigatran and clarithromycin, we could not evaluate it using the CCO; the SCCS yielded IRs of 2.48 (95% CI 1.06 - 5.78) before and 1.20 (95% CI 0.51 - 2.82) after adjustment. Both designs showed no association between amiodarone or verapamil and bleeding while on dabigatran but revealed positive association in patients unexposed to oral anticoagulants (controls), leading to protective adjusted estimates.
Conclusions: We observed similar estimates from CCO and SCCS analyses of DDIs in real-world data, with SCCS displaying better efficiency. The use of control had a larger impact on the results than the choice of a

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

design, highlighting the importance of appropriate control group selection.

2472 | An FDA quality assessment tool for evaluation of real-world evidence observational studies

Marie C. Bradley, Wei Hua and Simone Pinheiro
FDA, Silver Spring, MD

Background: Recent legislation encourages the US Food and Drug Administration to evaluate the use of real-world evidence (RWE) in support of regulatory decision making. Assessing the quality of RWE observational studies to ensure they meet the FDA requirements for adequate and well-controlled studies is critical.
Objectives: To build an FDA specific quality assessment tool for observational studies based on a previous FDA quality assessment framework.
Methods: The 2012 FDA quality assessment framework (FDA framework) was evaluated against published quality assessment tools commonly used for observational cohort studies, including the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) and the GRACE checklist (GRACE), and in light of evolving observational study designs and methods for quality improvement. Important features of and gaps in the quality elements of the FDA framework were identified. These were used to inform the development of a more comprehensive FDA specific quality assessment tool.
Results: The main gaps identified in the FDA framework were: **Study design:** Use of a new user design and selection of participants based on variables assessed after index exposure were not addressed. **Exposure:** Adherence to treatment was not assessed. **Analytic approach:** Quantitative bias analysis or the appropriateness of methods to combine data from different sources was not addressed. Missing data for important confounders was not assessed. Important elements of the FDA framework that were not prioritized in the other tools included appropriateness of aims, study design and base population (denominator), exposure definition and measurement, extent of loss to follow-up, generalizability of findings and the inclusion of a statement on biologic plausibility or alternative explanations.
Conclusions: We identified several important features and gaps in the existing FDA quality assessment framework for observational cohort studies. To address these gaps, we built a comprehensive quality assessment tool for use in the evaluation of observational studies at FDA.

2530 | The state of real-world evidence in comparative effectiveness and safety studies based on healthcare insurance claims

Katsiaryna Bykov[1], Elisabetta Patorno[1], Mengdong He[1], Hemin Lee[1], Elvira D'Andrea[1], Jennifer S. Graff[2] and Jessica M. Franklin[1]
[1]*Brigham and Women's Hospital, Boston, MA;* [2]*National Pharmaceutical Council, Washington, DC*

Background: There is growing interest in broader use of real-world data (RWD) to inform decision-making, however, concerns about the validity of RWD analyses continue to detract from their utility. Some of these concerns may be attributable to mistakes in study design and analysis, but the relative contribution of these avoidable problems is not known.
Objectives: To evaluate the quality of observational studies on the comparative safety and effectiveness of medications conducted using US health insurance claims data.
Methods: Using a systematic PubMed search (January 2010 - May 2019), we identified published observational studies (cohort or case-control design) that were conducted using US healthcare claims and evaluated the comparative effectiveness or safety of medications in the therapeutic areas of cardiovascular diseases, diabetes, asthma or chronic obstructive pulmonary disease, and osteoporosis. A random sample of 75 studies (10 case-control and 65 cohort studies) was selected for evaluation. We developed a questionnaire to identify major methodological issues in published real-world evidence (RWE) studies, focusing on time-related biases, adjustment for causal intermediaries, biases due to depletion of susceptible individuals, reverse causation, residual confounding, differential surveillance (detection bias), and informative censoring, as well as exposure and outcome misclassification. Each study was evaluated by two reviewers; discordance was resolved through consensus within the overall team.
Results: We present interim results for 10 case-control and 30 cohort studies; complete results will be available by the time of presentation. Potential for time-related biases was the most common methodological issue and was identified in 60% of cohort studies (immortal person-time) and 80% of case-control studies (time-window bias). Half of the reviewed studies (52%) adjusted for variables measured during follow-up without appropriate statistical methods; 47% had the potential for bias due to depletion of susceptible individuals, 37% due to reverse causation, 25% due to detection bias, and 10% due to informative censoring. In only 45% of studies a new user design was implemented; 45% used an active comparator.
Conclusions: The prevalence of well-known design and analysis flaws that may lead to biased results is high among RWE studies on medication safety and effectiveness. Recognizing and avoiding known methodological pitfalls could substantially improve the quality and validity of RWD studies, ultimately increasing the confidence in evidence generated from them.

2658 | When decisions can't wait: Delivering rapid real world studies

Xavier Kurz[1], Simone Pinheiro[2], Sabine Straus[3], Marcel Kwa[3], Peter Rijnbeek[4], Katia Verhamme[4], Judith Maro[5]
[1]*European Medicines Agency, Amsterdam, Netherlands;* [2]*Us Food & Drug Administration, Washington, DC;* [3]*Medicines Evaluation Board, Utrecht, Netherlands;* [4]*Erasmus Medical Centre, Rotterdam, Netherlands;* [5]*Harvard Pilgrim Health Care Institute, Boston, MA*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Regulatory decisions on medicinal products often require valid and generalisable real-world evidence on their utilisation and risks. In some conditions, data are needed within a few weeks or months, such as for identification of the population at risk of serious adverse effects or targeted for risk minimisation, rapid surveillance and prevention of potential safety concerns, or management of public health emergencies (e.g. pandemic influenza). In such cases, multiple challenges need to be met with regard to study design, data access, collection and analysis and result integration, and some of these steps must be accelerated to support timely decisions without affecting internal and external validity. Given the increasing public expectation for fast regulatory decisions, solutions may need to be further developed and introduced in routine practice.

Objectives: This symposium will present regulatory circumstances in the EU and the US where rapid real-world studies were needed and will describe the challenges to be addressed and some available solutions. It will contribute to define the infrastructure, research environment, methodological approaches and the analytical system necessary for rapid studies, and benefit regulators, researchers and industry who need to quickly answer regulatory questions.

Description: Xavier Kurz (Data Analytics and Methods Task Force, EMA) will introduce the topic and moderate the panel. Sabine Straus (MEB, Chair of the EU Pharmacovigilance Risk Assessment Committee) will present examples of questions from the PRAC Pilot on rapid data analytics and how they were addressed. Marcel Kwa (Senior assessor, MEB) will explain the need for timely data in the situation of the EU Referral procedure on H2 receptor antagonists assessing the potential risk associated with N-nitrosodimethylamine (a human carcinogen). Peter Rijnbeek and Katia Verhamme (Department of Medical Informatics, Erasmus Medical Center) will present the challenges met and solutions found for an EMA-funded multi-centre study from 5 EU countries on this topic which was completed within 4 months, and will discuss the opportunities of this approach to answer other types of regulatory questions. Simone Pinheiro (Office of Surveillance and Epidemiology, CDER, FDA) and Judith Maro (Harvard Pilgrim Health Care Institute) will discuss how the Sentinel system is used in situations where rapid analyses are needed, including sequential surveillance, cohort definition and acceleration of time segments for different study phases. The panel will discuss the types of questions amenable (or not) to rapid studies and the research environment supporting them.

2677 | Prevalent new users: When is time not enough?

Michael Webster-Clark and Rachael Ross
University of North Carolina, Chapel Hill, NC

Background: The prevalent new user design estimates causal effects of initiating a new drug (Drug A) by matching initiators of A to non-initiators on time since initiating an older drug (Drug B). Initiators of A may switch directly from B (direct switchers) or start A after a period off B (delayed switchers).

Objectives: We aimed to describe when matching only on time since initiating B may be biased.

Methods: We simulated 40,000 individuals initiating B at time 0 and followed for 4 units of time or until "death". After time 0, individuals could switch to A (direct switchers), stay on B, or discontinue B. Discontinuers of B could then restart B or start A (delayed switchers). Stopping, switching, or restarting were a function of three covariates (two binary and one continuous) such that approximately 50% of A initiators were direct switchers and 50% were delayed switchers. We present the results of two illustrative scenarios here. In scenario 1, outcomes depended on time since starting B (RR: 1.1 per unit time). In scenario 2, outcomes depended on total exposure to B (RR: 0.70 per total exposure). Outcomes were also a function of current treatment and the three covariates. In each scenario, we estimated a hazard ratio (HR) of death had the A initiators instead continued on or restarted B. We implemented two analytic approaches to estimate standardized morbidity ratio weights to adjust for confounding. In the first, we fit logistic regression models stratified by time since starting B (analogous to matching on time since starting B). In the second, the models were stratified by full treatment history (analogous to matching on B treatment history, accounting for stopping and restarting). We estimated mean values and 95% confidence intervals (CIs) from the 500 replicates.

Results: When time since B initiation was a cause of the outcome (scenario 1, true HR: 0.60, crude HR: 0.76, 95% CI 0.72-0.79), both analytic approaches were unbiased (time-stratified: 0.60, 95% CI 0.57-0.63; treatment history-stratified: 0.60, 95% CI 0.57- 0.63). When total exposure to B was a cause of the outcome (scenario 2, true HR: 0.93, crude HR: 1.26, 95% CI 1.19-1.34), however, time-stratified analysis was biased (HR: 1.03, 95% CI 0.97-1.10) and analysis that stratified on treatment history was not (HR: 0.93, 95% CI 0.87, 1.00).

Conclusions: If outcomes depend only on measured covariates and time since starting B, conditioning on time since B initiation and adjusting for confounders estimates an unbiased treatment effect in initiators of A. If outcomes depend on past treatment in other ways (e.g. total exposure to B, recently restarting B, or time spent off treatment), matching only on time since initiating B is insufficient.

3733 | Drug-drug interaction research: Twice the fun (or More!)

Katsiaryna Bykov[1], Charles E. Leonard[2], Anton Pottegård[3], Meijia Zhou[4], Sean Hennessy[2]
[1]*Brigham and Women's Hospital, Boston, MA;* [2]*University of Pennsylvania, Philadelphia, PA;* [3]*University of Southern Denmark, Roskilde, Denmark;* [4]*Johnson & Johnson, Boston, NJ*

Background: Real-world data provide a valuable opportunity for generating evidence on health outcomes of potential drug-drug interactions (DDIs) as they occur in clinical practice and identifying new, previously unknown, interactions. However, these data present many challenges to researchers, and observational studies of DDIs must account for numerous sources of bias that are particularly salient in the setting of two or more exposures.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To present and discuss challenges, solutions, best practices, and future directions in observational DDI research. Researchers, regulators, DDI compendia/knowledge base editors, and other stakeholders concerned about interacting drugs or interested in conducting studies of DDIs would benefit from attending. Participants will leave the session better equipped to evaluate or design population-based DDI studies.

Description: This symposium will convene panelists from different research organizations who have considerable experience with and have advanced the methodology of DDI studies in real-world data. Anton Pottegård will introduce the topic and describe how the current state of evidence on most DDIs is insufficient to guide treatment decisions. Meijia Zhou will provide an overview of major challenges when conducting observational DDI studies in electronic healthcare data. Charles Leonard will present how these challenges can be addressed in a cohort study, using an empirical case example. Katsiaryna Bykov will present how real-world data can be harnessed to identify DDIs using high-throughput screening and self-controlled design. Finally, Sean Hennessy will provide the audience with a brief overview of dissemination efforts to bring DDI research into practice and will open the floor for discussion. We will reserve at least 10 minutes for audience participation and further response and interaction among panelists. The proposed symposium is particularly pertinent for this year's ICPE given the society's recent approval of a DDI Special Interest Group. **Moderator: Sean Hennessy**, Professor of Epidemiology and Director of the Center for Pharmacoepidemiology Research and Training, University of Pennsylvania, USA. **Panelists: Anton Pottegård,** Professor, University of Southern Denmark, Denmark; **Meijia Zhou,** Post-Doctoral Fellow, Johnson & Johnson, USA; **Charles E. Leonard**, Assistant Professor of Epidemiology, University of Pennsylvania, USA; **Katsiaryna Bykov**, Instructor in Medicine, Brigham and Women's Hospital and Harvard Medical School, USA

3776 | Challenges in the analyses of time-to-event data in cohort studies based on exposure definitions

Beatriz Seoane Nuñez[1], Mario Ouwens[2], Rosa Lamarca[1], Satya Sanikommui[3], Noman Lateef[3] and Annalisa Rubino[4]

[1]*AstraZeneca, Barcelona, Spain;* [2]*AstraZeneca, Gothenburg, Sweden;* [3]*AstraZeneca, Gaithersburg, MD;* [4]*AstraZeneca, Cambridge, United Kingdom*

Background: Unlike randomized controlled trials (RCTs), cohort studies often evaluate the association of drug use with the outcomes of interest by comparing current/recent/past *vs* never use of drugs. This leads to exposure being defined as a time-dependent variable in the treatment but not in the comparator (never use) cohort.

Objectives: To assess if the exposure definitions current/recent/past *vs* never use of drug as applied in cohort studies provides correct estimates of the exposure-outcome association.

Methods: Using RCTs data, we estimated the mortality risk of active vs placebo. Adjusted HR (95% CI) were computed with Cox regression. Current use defined ongoing use, or use ended within 1-5 days; Recent and past use indicated that use ended within 6-60 or over 60 days, respectively. We compared HRs obtained with these exposure definitions applied to both active and placebo and to the active arm only. We modelled exposure definitions as time-dependent variables.

Results: When exposure definitions were applied to both active and placebo arms, adjusted HRs for mortality were 0.53 (95% CI: 0.10, 2.91), 0.88 (95% CI: 0.41, 1.85) and 0.45 (95% CI: 0.21, 0.96) for current, recent and past use, respectively. These estimates were comparable to the mortality estimate in the original RCT analysis (adjusted HR: 0.94; 95% CI: 0.57,1.55). Comparing current/recent/past of active *vs* never use of placebo led to a raised mortality risk strongly associated with recent (adjusted HR: 13.17, 95% CI: 6.92, 25.1) and past (adjusted HR: 2.83; 95% CI: 1.37, 5.84) use.

Conclusions: Discrepancies were observed when applying the definition of current/recent/past use to both active and placebo or only to active. These observations indicate that the comparisons of current/recent/past use versus never use, as applied in cohort studies is likely to lead to biased results.

3789 | How many controls do you need?

Henrik Stovring[1], Anton Pottegård[2], Morten R. Hansen[2] and Jesper Hallas[2]

[1]*Aarhus University, Aarhus, Denmark;* [2]*University of Southern Denmark, Odense, Denmark*

Background: The precision of odds ratios estimated from case-control studies depends on the smallest number of exposed and unexposed cases and controls. In most applications, this is the number of exposed cases (NEC). While this count is often beyond the control of the investigator, the number of controls can be varied by the investigator, thereby preventing an undue variance contribution from the second smallest number.

Objectives: Investigate how many controls are needed to achieve a precision which is 90% of the theoretical maximum for a given number of exposed cases.

Methods: We set up a simulation study in which we varied the average NEC (5, 10, 50, 100 and 1,000), the number of controls per case (1, 2, 5 or 10), the proportion of exposure among cases (5% and 10%) and the true odds ratio of exposure (1, 2, 5 or 8). For each setting, we generated 2,500 datasets and estimated the ratio of the upper to the lower bound of the 95% confidence interval of the odds ratio of exposure among cases versus controls. We compared this to the corresponding theoretical minimal ratio based on the average number of exposed cases. In a supplementary simulation study, we repeated the above, but kept the NEC fixed at its true value in each simulated dataset to address situations, where the exact NEC of a study is known in advance.

Results: When the BNC was five with 5% of cases being exposed, the target of at least 90% relative precision could be reached by including

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

at least 10 controls per case with an OR of 1. With an OR of 2 this was only possible with a NEC of 50 and 10 controls per case or alternatively a NEC of 100 and 5 controls per case. When the fraction of exposed cases increased to 10%, it was harder to achieve the precision target, but it could still be attained with a NEC of 50 and 5 or 10 controls per case (OR=1). With an NEC above 50, 10 controls per case were sufficient for an OR of 1 or 2 With higher ORs of 5 or 8, it was necessary with a NEC of 100 and 10 controls per case (OR=5) or even a NEC of 1000 (OR=8). All findings were virtually unchanged when the NEC was fixed in simulated datasets within each setting.

Conclusions: When possible, 10 or more controls per case should be included if the number of exposed cases is small. When the anticipated effect size is large (OR above 2) a high precision could only be achieved with a higher number of exposed cases and by maintaining 10 controls per case.

3820 | The basket or umbrella real-world observational study (BUROS) design for molecular cancer subtypes

Geoffrey Liu[1], Stavroula Raptis[2], Maryam Mirshams[1], Devalben Patel[1], Simren Chotai[1], Abraam Ghattas[1], Aein Zarrin[1], Audra Stitt[2], Patrick Moriarty[3] and Karen Pope[2]

[1]Princess Margaret Cancer Centre - University Health Network, Toronto, ON, Canada; [2]Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, ON, Canada; [3]Takeda Canada Inc., Toronto, ON, Canada

Background: Observational studies are difficult to conduct in rare cancer subpopulations, whether as multiple molecular subtypes of one cancer (i.e., lung cancer with *EGFR*, *ERBB2*, *MET*, *BRAF*, *ROS1* and *ALK* alterations) or as a single molecular subtype across many disease sites (e.g., *NTRK* fusions).

Objectives: To compare a new study design potentially useful in observational pharmacoepidemiology for rare cancer subtypes to traditional study designs.

Methods: We describe the BUROS design of CARMA-BROS (CAnadian CAncers with Rare Molecular Alterations Basket Real-world Observational Study), comparing its design to alternative study designs consisting of Multiple Single-Marker (MSM) studies, Retrospective Chart Reviews (RCRs) or a Single Site-specific Registry (SSR). Through 4 national meetings of lung oncologists in 2017-2019, impact of each study design on centre staff, patients, and cost were assessed through a survey and qualitative directed-discussions (mixed methods analysis).

Results: CARMA-BROS (NCT04151342) is using an ambispective BUROS design to perform retrospective chart reviews on deceased patients and prevalent cases, and conduct a prospective observational study with patient-reported data on incident and prevalent cases. Eligible lung cancer cases have one of several molecular subtypes, each with (multiple) targetable agents: *EGFR* exon 20 and *BRAF* V600 mutations; *ROS1* and *ALK* translocations; each subtype forms its own cohort. When compared to MSM studies, there was significant cost and logistical efficiency (by 2-3 fold improvement) and greater site acceptability for BUROS. RCRs were the least expensive format; however, RCRs collected no patient-reported data, and cannot capture the contemporary, dynamic treatment and outcome landscapes of these subtypes. Although SSR was the preferred lung oncologists' study design, funding this model required significant resources. Because ~75% of Canadian lung cancers do not have a targetable drug agent, this format was deemed too inefficient when focusing on rare molecular subtypes; cost and logistical efficiency was improved by 3-4 fold when using a BUROS design instead. BUROS was also the only design that could expand across multiple disease sites (e.g., for patients with *NTRK* fusions, which affect >20 different disease sites), which is out-of-scope for a SSR. In contrast, the 12-14 CARMA-BROS sites will cover >70% catchment area for Canada efficiently.

Conclusions: We report cost and logistical benefits of a BUROS design for rare cancer subtypes using, as an example, the development and acceptance of CARMA-BROS.

3827 | Immeasurable time bias in case-only designs

Han Eol Jeong[1], In-Sun Oh[1], Hyesung Lee[1], Kristian B Filion[2,3] and Ju-Young Shin[1]

[1]Sungkyunkwan University (SKKU), Suwon, Republic of Korea; [2]McGill University, Montreal, QC, Canada; [3]Lady Davis Research Institute - Jewish General Hospital, Montreal, QC, Canada

Background: Pharmacoepidemiologic studies using healthcare databases that are missing in-hospital prescriptions may result in immeasurable time bias. The impact of this bias has yet to be evaluated in case-only designs.

Objectives: To describe the impact of the immeasurable time bias in case-crossover (CCO), case-time-control (CTC), and case-case-time-control (CCTC) designs and to assess methodological approaches to mitigate its effect.

Methods: We conducted three case-only analyses in a case study of β-blocker use and mortality among patients with incident heart failure (HF) using Korea's healthcare database, which has both in- and outpatient drug data. The index date was defined as the date of death for cases in CCO analysis or an inherited date for control person-moment in CTC and CCTC analyses. Exposure to β-blockers was assessed in the hazard and control windows of 1-30 and 91-120 days before the index date, respectively. We defined the gold standard using all drug data (including both in- and outpatient prescriptions) and a pseudo-outpatient setting using outpatient data only. We assessed 10 approaches of adjustment, stratification, or weighting on factors related to hospitalization to evaluate the ability of these approaches to reduce bias. We estimated the odds ratio (OR) with 95% confidence intervals (CI) using conditional logistic regression and the magnitude of the bias using the relative difference in OR estimates of the two settings.

Results: Our study cohort included 14,550 patients with HF, of which 3,264 died during follow-up. The immeasurable time bias had the greatest impact in the CCO analysis, where the estimates had a relative difference of 0.74 (gold standard: OR 1.62, 95% CI 1.32-1.99

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

vs. pseudo-outpatient setting: 0.93, 0.71-1.22), followed by a relative difference of 0.34 in the CTC analysis (1.11, 0.75-1.65 vs. 0.83, 0.52-1.33), and a relative difference of 0.26 in the CCTC analysis (0.78, 0.46-1.34 vs. 0.62, 0.32-1.19). The CCO analysis found discordant results between the two settings, while concordant results were found in the CTC and CCTC analyses. Overall, stratifying on the proportion of hospitalized time in each window best approximated the gold standard estimate in the CCO (1.70, 1.03-2.80), CTC (1.19, 0.62-2.30), and CCTC (0.85, 0.32-2.25) analyses.

Conclusions: Immeasurable time bias overestimated the benefits of β-blocker therapy on mortality in the CCO analysis while having a more modest impact in the CTC and CCTC analyses. Stratifying on the proportion of hospitalized time was effective at repairing the immeasurable time bias in the CCO analysis.

3848 | Is your sibling design biased?

Buket Öztürk, Vera Ehrenstein, Henrik T. Sørensen and Lars Pedersen
Aarhus University Hospital, Aarhus, Denmark

Background: The sibling design is commonly used in prenatal epidemiology to remove unmeasured confounding by shared genetic or environmental factors. However, recent methodological studies showed that if siblings are more similar with regards to the exposure under study than to unmeasured confounders, the "within-pair" estimate from the sibling design will always be more confounded than the unpaired estimate. To our knowledge, no study has addressed this limitation in observational studies.

Objectives: We aimed to examine the impact of unmeasured confounding in the sibling design when estimating the association between prenatal exposure to antidepressants and the risk of attention deficit hyperactivity disorder (ADHD) in childhood.

Methods: Using simulation, we mimicked an observational study estimating the association between prenatal exposure to antidepressants and the risk of ADHD in childhood, where the prevalence of prenatal antidepressant exposure was 2%, and the between-siblings Pearson correlation of the exposure was 0.37. We explored the impact of unmeasured confounding in the sibling design by introducing a hypothetical unmeasured non-shared confounder and by varying the level of non-sharedness of the confounder determined by the between-sibling correlation of the confounder. The unconfounded unpaired odds ratio (OR) was set to 2.00 and the confounded unpaired OR was set to 1.00. We estimated the OR for each level of between-sibling correlation of the confounder by using a sibling design.

Results: When the between-sibling Pearson correlation of the confounder was 0.10, 0.30, 0.50 and 0.90, then the ORs from the sibling design were 0.70, 0.91, 1.14 and 1.76, respectively. When the between-sibling correlation of the confounder was 0.37 (the same as the between-sibling correlation of the exposure), then the sibling design estimate was equal to the confounded unpaired estimate (OR=1.00).

Conclusions: In our example, the OR estimate from the sibling design was more biased than the confounded unpaired estimate, if the between-sibling correlation of the unmeasured confounder was less than 0.37. The OR estimate from the sibling design was less biased than the confounded unpaired estimate, if the between-sibling correlation of the unmeasured confounder was more than 0.37. Our study demonstrated that it is important to consider the correlation of exposure and unmeasured non-shared confounders before applying a sibling design.

3943 | Predicting the best achievable precision of a register-based case-control or cohort study: A "bottleneck count" analysis

Jesper Hallas[1], Morten R. Hansen[1], Anton Pottegård[1] and Henrik Støvring[2]
[1]*University of Southern Denmark, Odense, Denmark;* [2]*University of Aarhus, Aarhus, Denmark*

Background: Most power calculations address a study's ability to produce a statistically significant result. However, in register-based studies, the sample size is usually given and cannot be enlarged. In that setting, a decision on whether or not to conduct a study can be based on estimates of the achievable precision.

Objectives: To present a simple approach to estimate the achievable precision of the final effect estimate in a cohort or case-control study. In addition, an empirical example will be given.

Methods: If there is a large availability of untreated persons and of persons without the outcome in the data source, the achievable precision is constrained by the number of treated subjects who experience the outcome, i.e., the "bottleneck count" (BNC). This can be assumed to follow a Poisson distribution, whose confidence intervals are inherited by the study's effect estimate.

We present an empirical case with a hypothetical study of the association between systemic retinoids and peptic ulcer bleeding. Using publicly available age- and sex-specific incidence rates of the outcome and prevalence of treatment, we calculated the BNC, i.e., the expected annual number of treated outcomes. From this, we estimated the expected precision of a study, while assuming a null association. The precision was expressed as the ratio between the upper and lower confidence limit (ULCL).

In addition, we reviewed 126 effect estimates from papers published in Pharmacoepidemiology and Drug Safety. The relationship between the expected (based on BNC) and the achieved precision was analyzed.

Results: The annual number of retinoid-treated Danish residents who experience a peptic ulcer bleeding was estimated at 9.8. Assuming a null association, the estimated ULCL for a study with a one-year recruitment window study was 3.84, and 1.79 for a five-year study.

The review of Pharmacoepidemiology and Drug Safety papers showed a very strong association between expected and achieved precision (R squared = 0.8796 for log-transformed values). There was a near-linear association between log(BNC) and log(log(ULCL)). Most estimates (81%) of expected precision were slightly too optimistic, and the median achieved/expected ULCL ratio was 1.07. This achieved/expected ratio did not depend on choice of case-control or cohort design

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: The precision of a register-based study can easily and reliably be predicted provided there are available population data on frequency of exposure and outcome. Such estimates represent the best achievable precision and may be too optimistic, particularly if the design is suboptimal.

3970 | A self-controlled analysis of cumulative drug effects, a simulation study based on real-world prescriptions

Lars Christian Lund[1], Malcolm Maclure[2], Anton Pottegård[1] and Jesper Hallas[1]
[1]*University of Southern Denmark, Odense, Denmark;* [2]*University of British Columbia, Vancouver, BC, Canada*

Background: Self-controlled designs are useful in pharmacoepidemiology because they inherently adjust for time-invariant confounders. To our knowledge, approaches to self-controlled analyses of cumulative drug effects have not been described. These are drug effects that build up with long-term exposure, for example drug-cancer associations.
Objectives: To demonstrate how cumulative drug effects can be analysed using a self-controlled design.
Methods: We conducted a self-controlled analysis using simulated outcomes with real-world antidepressant prescriptions from the Danish OPED database from 2014 through 2017. Outcomes were simulated using a simple proportional relationship between cumulative dose and outcome rate. In addition, we introduced between-person confounding by assigning higher outcome rate at baseline for those who eventually accrued high cumulative doses.
We used a bi-directional case-crossover design with four random referent points that could be sampled anywhere in the individuals' full history, including after the simulated outcome, i.e., from start of the first prescription to end of study period. We used a log-transformed cumulative dose at referent points and at the simulated outcome date as independent variable in a conditional logistic regression. The effect measure was the OR associated with a doubling of cumulative dose.
In addition, we analysed a scenario where outcomes prevented further exposure to the drug, thereby addressing the design's sensitivity to post-outcome modification of drug-exposure. Finally, we conducted a conventional case-control analysis to demonstrate that between-person confounding would bias the case-control estimate while the self-controlled analysis would be immune. Bias was expressed by the log(measured/injected) value.
Results: 38,538 users of citalopram were included. In the main case-control and case-crossover analysis, the injected drug effects were reproduced with little or no bias (bias -0.02, CI -0.02 - 0.00 and -0.01, CI -0.02 - 0.00). The case-crossover analysis was immune to between-person confounding (bias -0.02, CI -0.02 - -0.01) in contrast to the case-control analysis (bias +0.14, CI 0.13-0.14). The scenario with no further exposure after an outcome resulted in a moderate upward bias in the case-crossover analysis (bias +0.10, 0.09-0.11).
Conclusions: Cumulative drug effects can be analysed using a bi-directional case-crossover design with random referent dates. This approach is robust to between-person confounding but is moderately biased if the outcome prevents further exposure.

4042 | Risk of acute kidney injury during antibiotic treatment: A self-controlled screening study utilising biochemical data

Lars Christian Lund, Jesper Hallas and Daniel P. Henriksen
University of Southern Denmark, Odense, Denmark

Background: Acute kidney injury (AKI) is mostly asymptomatic but increases the risk of subsequent chronic kidney disease. Due to the lack of subjective symptoms, laboratory data are needed to detect AKI. Use of laboratory data can introduce surveillance bias, which is difficult to address. Furthermore, antibiotics are prescribed to individuals with an infection, which increases the risk of AKI. This phenomenon, confounding by indication, may require use of active comparators, even in self-controlled designs.
Objectives: To investigate the association between antibiotic exposure and biochemical AKI using multiple self-controlled designs and whether using an active comparator (AC) reduces surveillance bias and mitigates confounding by indication.
Methods: Self-controlled case series (SCCS), case-crossover (CC) and symmetry analysis (SA) studies were conducted using data on prescriptions and creatinine measurements for all individuals tested in Funen area in 2001-2015. AKI was defined according to Kidney Disease Improving Global Outcomes criteria. Exposure periods were defined as the fill date of an antibiotic prescription until 7 days after end of treatment (SCCS/CC) or first fill date (SA). Window size for SA was +-28 days. Exposure to any antibiotic was used as an AC.
Results: 13,508 individuals, 117,751 prescriptions, 19 antibiotics and 18,879 events were included in the analysis. Median estimates of incidence rate ratio (IRR) were 2.19 [IQR: 2.03-2.40] (SCCS) and 1.80 [IQR: 1.66-2.09] (CC). When using an AC, median estimates were 1.17 (SCCS) and 1.00 (CC), with trimethoprim being the only outlier (IRR 2.75/2.74). SA results resembled the AC estimates, even without use of such, but had larger variance due to a lower number of outcomes.
Conclusions: Trimethoprim increases the risk of biochemical AKI. Literature suggests that creatinine levels are elevated while renal clearance is unaffected. Use of an AC effectively reduced surveillance bias and confounding by indication in SCCS and CC. We did not identify unknown nephrotoxicity for any antibiotic.

4118 | ISPE RWE task force: Current status and future directions

Wei Zhou[1], Almut Winterstein[2], Shirley Wang[3], Mehmet Burcu[1], Mary E. Ritchey[4] and Helga Gardarsdottir[5]
[1]*Department of Pharmacoepidemiology, Merck Research Laboratories, West Point, PA;* [2]*Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL;* [3]*Department*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [4]RTI Health Solutions, Research Triangle Park, NC; [5]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, Netherlands

Background: ISPE's new strategic plan has tasks related to supporting real-world evidence (RWE) methods development, enhancing outreach to other scientific disciplines involved in RWE, and emphasizing the prominence of pharmacoepidemiology in this space. Part of this strategic initiative is to form a longer-term task force that takes responsibilities for these goals, and promotes the scientific methods, education, and policies related to the development, use, and interpretation of real-world data and RWE. ISPE sought volunteers from all members and formally created a RWE Task Force at the end of 2019. In this symposium, we will invite ISPE leadership, co-leads of the Task Force, and several sub-groups within the Task Force to share the background, current status, and future directions of ISPE's effort to strengthen its leadership in the "science of RWE". This symposium will also be an opportunity to gather input from ISPE members.

Objectives: • To provide an overview of the rationale and objectives of the ISPE RWE Task Force and its 11 sub-groups

• To share the progress, current status, future plans, opportunities and challenges of the ISPE RWE Task Force

• To discuss how to best coordinate expertise from ISPE members and build collaborations with external stakeholders.

• To solicit additional input and engagement from ISPE members on the next steps of the RWE Task Force

Description: • The symposium will start with a short introduction of the panel members and topics and continue with presentations from 5 speakers. The workshop will end with an interactive discussion between the audience and the panelists. Scheduled presentations and speakers are listed below:

Outline

a. Opening remarks and history of the ISPE RWE Task Force (5 min, Almut Winterstein)

b. Overview of the mission, structure, and current plan of the ISPE RWE Task Force (Helga Gardarsdottir, 15 min)

c. Showcase #1: Collaboration with ISPOR on ISPOR on RWE reproducibility and transparency (Shirley Wang, 15 min)

d. Showcase #2. Strategic plan for RWE manuscript development: who, what, where? (Mehmet Burcu; 15 min)

e. Showcase #3. How to engage with external societies and promote ISPE as key resource for RWE methods----Medical Device example (Mary Beth Ritchey, 15 min)

f. Panel discussion (25 min, Facilitated by Wei Zhou)

4143 | Assessment of immortal time bias in a retrospective study of exenatide use and pancreatic and thyroid cancers

Caihua Liang[1], Monica L. Bertoia[1], C. Robin Clifford[1], Yan Ding[1], Qing Qiao[2], Joshua J. Gagne[3,4] and David D. Dore[5,6]

[1]Optum Epidemiology, Boston, MA; [2]Medical Evidence and Observational Research, AstraZeneca, Gothenburg, Sweden; [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA; [4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA; [5]Research & Development, UHG, Boston, MA; [6]Department of Health Services, Policy & Practice, Brown University School of Public Health,, Providence, RI

Background: Preferentially selecting patients with specific drug use into an exposed cohort even when they have earlier use of the comparator drug can result in immortal time bias in observational studies of drug safety.

Objectives: To assess and quantify immortal time bias in a retrospective cohort study comparing the incidence of pancreatic and thyroid cancers among users of exenatide versus other antidiabetic drugs (OADs).

Methods: A retrospective cohort study was performed to estimate the incidence of pancreatic and thyroid cancers in patients with type 2 diabetes mellitus who initiated exenatide compared to OADs in 2005-2015 using health insurance claims data. In this study, initiators of exenatide were preferentially assigned to the exenatide cohort even if OADs had been initiated earlier. This preferential cohort formation was conducted in order to increase the sample size of the exenatide cohort, and achieve adequate statistical power. For patients who initiated OADs earlier than exenatide, the time between OAD initiation and exenatide initiation is immortal. As a sensitivity analysis, we applied the approach presented by Suissa to quantify the amount of immortal time bias introduced by this hierarchical cohort selection. In this analysis, the event-free person-time from the earlier, eligible OAD initiation until exenatide initiation was included in the OAD cohort. The estimated incidence rates (IRs) and incidence rate ratios (IRRs) were recalculated and compared before and after excluding the immortal time.

Results: Originally, the pancreatic cancer IR was 0.34 per 1,000 person-years among exenatide initiators and 0.45 among OAD initiators, yielding a crude IRR of 0.76 (95% CI: 0.48 -1.21). A total of 14,306 exenatide initiators qualified for OAD initiation earlier corresponding to a total of 18,479 person-years of event-free person-time added to the OAD cohort. The pancreatic cancer IR was reduced to 0.38 per 1,000 person-years among OAD initiators, with a corresponding crude IRR of 0.90 (95% CI: 0.57 -1.43). The thyroid cancer IR was 0.62 per 1,000 person-years among exenatide initiators and was reduced from 0.44 to 0.37 per 1,000 person-years among OAD initiators, with a corresponding crude IRR increasing from 1.43 (95% CI: 0.97- 2.13) to 1.70 (95% CI: 1.15 - 2.53). Inclusion of this immortal time in the OAD cohort changed the point estimates for pancreatic and thyroid cancers by less than 20%.

Conclusions: Observational studies of drug safety that apply hierarchical cohort selection should quantify and report immortal time bias that might result.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4164 | Dulaglutide proactive safety surveillance program (PSSP)

Ayad K. Ali
Eli Lilly and Company, Indianapolis, IN

Background: Dulaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1-RA) indicated to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).
Objectives: This PSSP aims at periodically detecting postmarketing safety signals of drug-event combinations (DEC) in relation with dulaglutide exposure in real-world practice settings. The methodology and preliminary results of the first run are introduced.
Methods: The PSSP applies high-dimensional propensity score (HdPS) adjustment algorithm to compare the incidence of DEC in adults (≥18 years old) with T2DM who initiated dulaglutide with those who initiated other long-acting GLP-1-RA and those who initiated insulin therapy in the IBM® MarketScan database. The DEC were defined by ICD-9/10 diagnosis codes and CPT procedure codes compiled according to the Clinical Classification Software (CCS) of AHRQ, which includes multi-level and single-level classification schemes. For the purpose of this analysis, multi-level broad classification was used. Cox proportional hazards regression with stratification, by quintiles, on the propensity score was applied to estimate quintile-specific and average hazard ratios (HRs). Potential signals that warrant further review are defined as DEC with HR≥2.0 and lower limit of 95%CI>1.0.
Results: Between 2014 and 2018, a total of 13,780 dulaglutide initiators met PSSP selection criteria (34,831 other long-acting GLP-1-RA initiators, and 130,081 insulin initiators). Mean age±SD and mean duration of T2DM±SD: 54±10 years and 4.2±3.3 years (dulaglutide initiators); 53±10 years and 4.0±3.2 years (other long-acting GLP-1-RA initiators); and 56±14 years and 4.7±3.6 years (insulin initiators), respectively. During the analysis period, the following DEC have met the signal threshold for dulaglutide vs. other long-acting GLP-1-RA: 'rheumatoid arthritis and related disease' (HR=4.22, 95%CI=1.67-10.7); and 'complications of surgical procedures or medical care' (HR=2.06, 95%CI=1.21-3.51). No DEC have met the threshold for dulaglutide vs. insulin; however, the following DEC had statistically non-significant HR≥2.0: 'tonsillitis' (HR=2.46, 95%CI=0.59-10.3); 'hip fracture' (HR=2.31, 95%CI=0.14-37.5); 'leukemias' (HR=2.07, 95%CI=0.13-33.8); and 'developmental disorders' (HR=2.0, 95%CI=0.28-14.4).
Conclusions: Preliminary results did not show new safety signals for treatment with dulaglutide compared to treatment with other long-acting GLP-1-RA or insulin. This PSSP supplements ongoing pharmacovigilance activities for dulaglutide by bridging the gap between clinical trials and spontaneous reporting systems.

4182 | Handling of statistical heterogeneity in meta-analyses of comparative effectiveness studies: A systematic review

Jean-Francois Nepveu[1,2], Tiffany Cristarella[1,2], Teigna Arredondo Bisono[2], Franziska Schmidt[2], Mareva Faure[2] and Yola Moride[1,2,3]
[1]University of Montreal, Montreal, QC, Canada; [2]YolaRX Consultants, Montreal, QC, Canada; [3]Rutgers University, New Brunswick, NJ

Background: Meta-analysis of comparative effectiveness studies is a main source of evidence for policy and decision-making. The pooling of results from individual studies in the presence of statistical heterogeneity can, however, lead to spurious conclusions. Currently, there are no clear thresholds or guidelines for the handling of statistical heterogeneity in meta-analyses of comparative effectiveness studies of therapeutic interventions.
Objectives: i) To develop a standardized decision tree to evaluate the appropriateness of the methods of handling statistical heterogeneity; ii) To review and describe how statistical heterogeneity has been assessed in meta-analyses of comparative effectiveness studies; iii) To identify methodological gaps in the handling of statistical heterogeneity.
Methods: The decision tree was developed using the Cochrane Collaboration mandatory aspects of core methods for conducting a meta-analysis and involved: i) the quantification of statistical heterogeneity using Chi^2 or I^2 tests and; ii) the implementation of subgroup or sensitivity analyses, when heterogeneity was considered moderate or high (I^2 ≥ 30 %). A systematic review of meta-analyses of comparative effectiveness studies of drug interventions was conducted using MEDLINE and Embase between 01 January 2018 and 09 December 2019. Pragmatic searches of the grey literature were also conducted.
Results: Of the 838 sources identified, 61 were reviewed in depth and 39 were retained. Based on the predefined decision tree, only 12.8% (n=5) used appropriate strategies for handling of statistical heterogeneity. All studies assessed heterogeneity of estimates, with 84.6% (n=33) of sources using both Chi^2 and I^2 tests. The majority of studies (87.2%, n=34) pooled estimates despite high heterogeneity (I^2 ≥ 50%), the remaining (12.8%, n=5) pooled in the presence of low or moderate heterogeneity (I^2 < 50 %). Regardless of the level of heterogeneity, the estimates were pooled using a random effect model in 76.9% (n=30) of meta-analyses and 17.9% (n=7) of studies used a random effect model when heterogeneity exceeded 50% (I^2 ≥ 50%). Estimates pooled in the presence of high heterogeneity tended to be closer to the null value with broader confidence intervals compared to those pooled in presence of low heterogeneity.
Conclusions: Estimates from individual comparative effectiveness studies are often pooled regardless of statistical heterogeneity. Impact on comparative effectiveness conclusions will be discussed. Operational guidances on thresholds of heterogeneity for the pooling of estimates are much needed.

4264 | Differential lags in treatment information in electronic health record derived databases

Anne-Marie Meyer[1,2], Jessica Davies[3], Michael Taylor[4] and Charlotta Fruechtenicht[1]
[1]F. Hoffmann-La Roche, Basel, Switzerland; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]F. Hoffmann-La Roche, Welwyn, United Kingdom; [4]Genetech, San Francisco, CA

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Data recency is key to real-world data (RWD) but must be balanced against maturity. RWD are entered and refreshed through multiple systems introducing potential lags in information. In contrast to claims data, little guidance on lags exist for many of the EHR-based systems.

Objectives: Explore data recency and maturity in EHR-derived RWD.

Methods: We observed treatment timing across database refreshes in two datasets from the Flatiron Health EHR-derived de-identified database: metastatic Breast Cancer (mBC) and Diffuse B Cell Lymphoma databases (DLBCL) patients diagnosed between 2011 and 2019. Using mortality data, we differentiated between prospective patients who were still alive when entering the database vs retrospective patients who had already died. In prospective patients we calculated lag for accruing (prospective) treatment from treatment administration date until entry in the database, and retrospective treatment lag from the time the patient entered the database to the first refresh capturing the treatment. Lags for retrospective patients were calculated from the time they entered the database to the database refresh capturing the treatment.

Results: Over two-thirds of both cohorts were defined as prospective upon entry in the database (mBC 67.4% ; DLBCL 77.3%). The absolute number of patients with structured treatment data 2+ months late was higher (35.7% mBC, 18.6% DLBCL) relative to the overall fraction of treatments affected by 2+ months lag (18.1% mBC, 5.4% DLBCL). Lags of 2+ months were greater in prospective patients (20.6% in mBC, 5.1% in DLBCL). Yet, retrospective patients still had treatment lagged 2+ months (6.8% in mBC, 6.3% DLBCL) with a long tail (>24 months). Unexpectedly, in prospective patients, the retrospective treatment had greater lags compared to prospective treatment received after entry. In mBC 12.6% of structured prospective treatments were 2+ months lagged vs. 26.2% of retrospective treatments, in DLBCL this was 4.6% vs. 16.9% respectively. As expected, abstracted treatment had greater lags than structured treatment. For example, in prospective DLBCL patients 37.8% of abstracted administrations (63.6% of antineoplastic treatments) were 2+ months lagged vs. 5.1% structured administrations (1.9% of antineoplastic treatments).

Conclusions: Information lags in EHR-derived datasets may vary depending on the type of data and the processing pipeline. RWD researchers need to be aware of the lags in information and potential impact on bias. More systematic comparisons across RWD information types could perhaps inform best practices for using RWD.

4297 | Open cohorts and ghost-time bias in real world data

Anne-Marie Meyer[1,2], Jessica Davies[3], Michael Taylor[4] and Charlotta Fruechtenicht[1]

[1]F. Hoffmann-La Roche, Basel, Switzerland; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]F. Hoffmann-La Roche, Welwyn, United Kingdom; [4]Genetech, San Francisco, CA

Background: The open nature of RWD means that cohorts may be a mix of patients whose treatment and outcome information is complete and others for whom it is still accruing. This does not just affect exposures and outcomes but can also affect denominators through misspecified person-time. Decades of claims research has led to specific methods but less information is available for EHR-derived studies.

Objectives: We sought to quantify ghost time bias from EHR-derived cohorts.

Methods: We used the Flatiron Health EHR-derived de-identified database to create two open cohorts of metastatic breast cancer (mBC) patients, n=20,446 and diffuse large B-cell lymphoma (DLBCL), n=6,002 who were treated at some point in the network from 1/2011 to 11/2019. Using mortality data, we calculated the proportion of patients who were retrospective versus prospective when they entered the database and whose treatment and outcome information was still accruing. We compared across data refreshes and contrasted date of events (death or progression) against when the information arrived in the database. Event dates were set to the beginning of the month in lieu of date granularity. Ghost-time was defined as any person-time contributed to the dataset 2+ months after the event date. We then quantified lags in mortality and progression ascertainment.

Results: In both indications, we observed a mix of both retrospective (mBC 22.7%; DLBCL 22.7%), and prospective (mBC 67.4%; DLBCL 77.3%;) patients. Separately a third group was identified who were misclassified as prospective but were in fact dead upon database entry (mBC patients, 11% but <1% DLBCL). The vast majority of all deaths were captured within the next monthly data refresh however, a very long tail of lagged data capture persisted (>24 months). In mBC 13% of deaths were lagged 2+ months while in DLBLC only 5% were lagged ≥2 months. Progression in mBC also demonstrated significant lags, overall 67.2% of events were found ≥2 months after the event date. In prospective patients this rose to 76.5% with 2+ months and 41% with ≥7 months. In retrospective patients 50% of progressions were lagged 2+ months though dropped to 26.1% with ≥7 months. Lags were not consistent over time, and improvements to ascertainment (spikes) were clearly visible and likely associated with database enhancements.

Conclusions: While EHR-derived databases have unique strengths (e.g., depth of clinical data), they also present unique challenges to the field of pharmacoepidemiology. Patient maturity, complexity of clinical data sources and necessary linkages need to be considered in study designs to minimize bias and accommodate the reality of real-world data processing.

4361 | Plotting daily incidence of influenza vaccine reactions among patients with end-stage renal disease to inform study design decisions

J. Bradley Layton[1], Leah J. McGrath[2], John M. Sahrmann[3], Vikas R. Dharnidharka[3], Caroline A. O'Neil[3] and Anne M. Butler[3]

[1]RTI Health Solutions, Research Triangle Park, NC; [2]NoviSci, Durham, NC; [3]Washington University School of Medicine, St. Louis, MO

Background: Evaluation of incident outcomes requires excluding patients with prevalent disease. The appropriate length of the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

lookback period to define prevalent disease may vary depending on the outcome; chronic conditions may require all available data, but acute or recurrent conditions may require shorter periods.

Objectives: To inform decisions about the length of prevaccination lookback periods, we investigated daily incidence of diagnoses of outcomes relative to vaccination.

Methods: Patients with end-stage renal disease receiving hemodialysis were identified in the United States Renal Data System (2010-2016) on the date of influenza vaccination. For each adverse reaction (anaphylaxis, angioedema, seizure, encephalopathy, urticaria/hives, rash, pain in limb, cellulitis, myalgia/myositis, fever, nausea and vomiting, and syncope), we plotted daily incidence rates of recorded diagnoses relative to the vaccination date, from 180 days before to 180 days after vaccination. Multiple diagnoses per patient were permitted.

Results: Among 520,876 vaccinations from 216,843 unique patients, daily incidences of many outcomes exhibited clear periodicity, frequently corresponding to regular health care interactions such as monthly comprehensive physician encounters or hemodialysis sessions every 2-3 days. Daily incidence rates of the following outcomes at least doubled in recurrent, 30-day spikes before and after vaccination: anaphylaxis, cellulitis, myalgia/myositis, nausea/vomiting, and fever. For example, daily incidence rates of fever were approximately 140-150 cases/10,000 patients for most days but were elevated to approximately 250-350 cases/10,000 patients in narrow spikes around days 30, 60, 90, 120, and 150 before and after vaccination. Both syncope and seizure outcomes exhibited weekly spikes in incidence; pain in limb, rash, diarrhea, and angioedema exhibited spikes occurring every 2-3 days. Plots of outcomes requiring hospitalization (e.g., encephalopathy, secondary outcomes of hospitalized fever, nausea/vomiting, diarrhea) did not demonstrate the same periodicity observed in nonhospitalized events.

Conclusions: Diagnoses for recurrent, minor, or sustained conditions may be routinely recorded at regularly occurring health care encounters. The duration of baseline washout periods should account for diagnostic patterns in special populations, such as end-stage renal disease, with regular patterns of health care utilization (e.g., extending washout periods to > 30 days to capture the previous month's comprehensive physician visit).

4436 | Real-world endpoints to support regulatory decision-making

Jennifer B. Christian, Edward J. Warren and David Cameron
IQVIA, Chapel Hill, NC

Background: The passage of the 21st Century Cures Act in 2016 signaled a shift in the role of real world evidence (RWE) in regulatory decision-making. However, the precise role of RWE including the selection of real world (RW) endpoints that will be sufficient for regulatory decisions largely remains unclear.

Objectives: To identify and describe what RW endpoints have been successfully used to support regulatory decisions regarding clinical effectiveness of new treatments and how those endpoints compare to those of traditional RCTs.

Methods: We compiled a series of regulatory decisions between 2017 - 2019 from the literature where regulators mentioned that observational RWE supported their decision for an approval, conditional approval, or label expansion. Decisions included those made by the FDA, EMA, or NMPA for any therapeutic area. We noted what primary and secondary endpoints were used from RW studies and compared them with trial endpoints, when applicable.

Results: Fifteen regulatory decisions using observational RWE were identified for 10 different medicines between 2017 - 2019. All treatments were indicated for patients with rare disease or cancer. Types of RWE endpoints assessed varied by treatment and disease, ranging from clinical response, overall survival, biomarker changes, and others. Definitions of response varied by observational RWE study, such as using objective response rate, complete response, tumor size, clinical judgment, and/or audited RECIST 1.1. For RW external comparator studies, ascertainment and definitions of RW outcomes frequently differed from trial definitions, and—even where similar—data collection methods often varied.

Conclusions: Our findings suggest that there is great variability in the types of RW endpoints that have been used for regulatory decision-making. Differences in endpoint definitions and data collection methodologies were observed when defining RW response across RWE studies and when used to compare to trials.

4540 | Who are we missing?: Underrepresentation of data sources used for pharmacoepidemiology research in the United States

Suzanne Landi[1], Pardiss Kaviani[2], Aaron McKethan[1], M. Alan Brookhart[1] and Leah McGrath[1]
[1]*NoviSci Inc., Durham, NC;* [2]*Montgomery College, Rockville, MD*

Background: Research using healthcare databases often includes patients frequently excluded from clinical trials, with the goal of increasing generalizability of results to a broader population in the United States (US). However, it is unknown if commonly used data sources adequately represent the overall population or include understudied sub-populations.

Objectives: We aimed to examine population representativeness from data sources used in recent pharmacoepidemiologic research studies in the US.

Methods: We identified data sources from abstracts accepted to the 34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. The final sample included research studies using one or more data sources from the US. We classified data sources broadly as claims, linkage, electronic health records (EHR), survey, distributed data network, and other. Studies using claims and EHRs were further classified into more specific categories (e.g. insurance type, source of electronic records). We noted if the study focused on a special population of interest (e.g. children, pregnant women).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: We reviewed 1,142 published abstracts, of which 961 abstracts were classified as original research. Of these, 356 (31.2%) included at least one US-based data source and were included in the final sample. The majority of research studies used claims data (n=200, 56.2%), followed by data linkages (n=47, 13.2%), and EHR data (n=39, 11.0%). Almost half (49.3%) of claims-based studies used commercial claims data sources, followed by Medicare (22.3%), Medicaid (10.9%), and Medicare Supplemental (6.1%). Approximately half of the studies using Medicaid data pertained to pregnancy (n=12). Only 14.9% of all research studies, regardless of data type, included children in the study population (n=53), and only 7.6% focused on a pediatric topic (n=27).

Conclusions: Certain populations in the US are under-represented in pharmacoepidemiology, particularly Medicaid enrollees and children. Researchers should strive to utilize data sources that may be more representative of the US population, particularly vulnerable population sub-groups.

4608 | Multi-database studies in the post-authorisation setting: A review the EU PAS register

Janet Sultana[1], Mariana Almas[2], Ippazio Antonazzo[3], Esme Baan[4], Claudia Bartolini[3], Maria Paola Bertuccio[1], Salvatore Crisafulli[1], Fedele Bonifazi[5], Antonella Didio[5], Vera Ehrenstein[6], Carmen Ferrajolo[7], Remy Francisca[4], Annie Fourrier-Reglat[8], Joan Fortuny[9], Rosa Gini[3], Giulia Hyeraci[3], Christel Hoeve[10], Valentina Isgro'[1], Christos Kontogiorgis[11], Panagiotis Lalagkas[11], Deborah Layton[12], Annalisa Landi[5], Silvia Narduzzi[12], Leonardo Pereira[13], George Poulentzas[11], Concita Rafaniello[7], Simona Ravera[5], Giuseppe Roberto[3], Giulia Scondotto[1], Liberata Sportiello[7], Maddalena Toma[5], Massoud Toussi[14], Katia Verhamme[4], Elisabetta Volpe[5] and Gianluca Trifiro'[1]

[1]University of Messina, Messina, Italy; [2]Real World Solutions Department, IQVIA, Lisbon, Portugal; [3]Agenzia Regionale di Sanita' Della Toscana, Florence, Italy; [4]Erasmus Medical Centre, Rotterdam, Netherlands; [5]Teddy European Network of Excellence for Paediatric Clinical Research, Bari, Italy; [6]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [7]University of Campania "Vanvitelli", and Campania Regional Center of Pharmacovigilance and Pharmacoepidemiology, Naples, Italy; [8]University of Bordeaux, Bordeaux, Italy; [9]RTI Health Solutions, Barcelona, Spain; [10]Erasmus Medical Centre, Messina, Netherlands; [11]University of Thrace, Thrace, Greece; [12]Real World Solutions Department, IQVIA, London, United Kingdom; [13]Utrech Medical Centre, Utrecht, Netherlands; [14]Real World Solutions Department, IQVIA, Paris, France

Background: The European post-authorisation study (EU PAS) register is a repository, launched in 2010, where all PAS requested by the European Medicines Agency must be registered. Multi-database studies (MDS) have become an important strategy to conduct PAS in recent years.

Objectives: To analyse post-authorisation studies in the EU PAS register, with focus on MDS.

Methods: Studies in the EU PAS Register from inception to 31st December 2018 were described concerning transparency, regulatory obligations, type of data and study type (observational study, clinical trial, survey, review/meta-analysis and miscellaneous), objectives and population. MDS were defined as studies conducted through secondary use of >1 data source not linked at patient-level. Data extraction was carried out independently by 13 expert centres, using publicly available information in the EU PAS register and PAS protocol, whenever available, using a standardised data collection form. For validation purposes, a second revision of key fields for a 15% random sample of studies was carried out by a different centre. The inter-rater reliability (IRR) was then calculated.

Results: Overall, 1,426 studies were identified. Clinical trials (N=30; 2%), systematic reviews/meta-analyses (N=16; 1%) and miscellaneous study designs (N=46; 3%) were much less common than observational studies (N=1,227; 86%). The protocol (indicator of transparency) was available for 63% (N=360) of observational studies requested by regulators. Overall, 31% (N=376) of observational studies were based on primary data collection. Of 726 observational studies based on secondary use of data, 319 (26%) were MDS. There was an increase of MDS over time (1 in 2010 vs. 42 in 2018). Overall, 59% and 57% of MDS and non-MDS conducted risk assessment, respectively (p-value: 0.50). As compared to non-MDS, MDS were more commonly used for drug utilization studies (41% vs. 34%; p-value: <0.05) and less commonly for effectiveness studies (17% vs. 34%; p-value: <0.05). Special populations (hepatic/renal impairment, pregnant/lactating women, immunocompromised persons) were included in less than 10% of MDS or non-MDS. The IRR for classification of study type was 94%, while for MDS this was 77%.

Conclusions: Observational studies were the most common type of studies in the register, but 30% used primary data, which is more resource-intensive. One quarter of observational studies were MDS. MDS hold untapped potential to investigate special populations. The IRR suggests that MDS information in the EU PAS register is sometimes unclear.

4628 | Risk of neuropsychiatric adverse events associated with varenicline treatment for smoking cessation: A prescription sequence symmetry analysis

Yuanyuan Wang[1], Job F.M. van Boven[2], Jens H.J. Bos[1], Catharina C.M. Schuiling-Veninga[1], H. Marike Boezen[3], Bob Wilffert[1] and Eelko Hak[1]

[1]Groningen Research Institute of Pharmacy, University of Groningen, Groningen, Netherlands; [2]Groningen Research Institute for Asthma and COPD (GRIAC), University of Groningen, Groningen, Netherlands; [3]University Medical Center Groningen, University of Groningen, Groningen, Netherlands

Background: Varenicline is an effective treatment for smoking cessation. While clinical trials did not confirm a causal role, case reports suggested a possible link of varenicline with neuropsychiatric adverse drug events (NPAEs).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To investigate the risk of NPAEs associated with varenicline initiation among the general population in a real-world setting.

Methods: We conducted a prescription sequence symmetry analysis (PSSA) based on the University of Groningen IADB.nl prescription database. We selected incident users of both varenicline and marker drugs for NPAEs, including depression, anxiety and sleep disorder within different time-intervals. Adjusted sequence ratios (aSR) were calculated for each time-interval.

Results: Within 365-days' time-interval 1,066 patients were incident users of both varenicline and NPAE marker drugs. In total, 505 patients were prescribed varenicline before NPAE marker drugs and 561 vice versa (crude sequence ratio (cSR) 0.90, 95% CI: 0.80-1.02). After adjustments for trends in prescriptions, overall a null association was found (aSR 1.00, 95% CI: 0.89-1.13). Regarding specific NPAEs, no increased risks were found for depression nor anxiety within any time-interval. A small transient increased risk was found for sleep disorders, particularly in earlier time-intervals 3 and 6 months (aSRs 1.52, [1.10, 2.11] and 1.45, [1.15, 1.83], respectively). Stratified analyses by age and gender, and several sensitivity analyses yielded similar results.

Conclusions: Varenicline initiation was not associated with an increased risk of taking anti-depressants nor anti-anxiety drugs. Yet a small, but statistically significant, transient association with drugs for sleep disorders was noticed, possibly associated with withdrawal symptoms caused by smoking cessation.

4811 | Feasibility of addressing family burden of disease through variable linkage in US claims data

Hannah Furby[1] and Athanasios Siadimas[2]

[1]Roche Pharmaceuticals, Welwyn Garden City, United Kingdom; [2]Roche Pharmaceuticals, Basel, Switzerland

Background: Understanding the impact of chronic illness on family members is valuable for addressing the indirect burden of disease and assessing cost-effectiveness. The 'EFAMID' variable has been available in Marketscan Commercial Claims and Medicare insurance data since 2011. Relationship to the patient can further be determined through the 'EMPREL' variable.

Objectives: To explore the feasibility of using the 'EFAMID' for linking family members to patient cases in insurance claims data (Truven Marketscan).

Methods: To demonstrate feasibility, we defined a patient cohort with at least one relevant diagnostic code for Huntington's Disease (ICD-9/10=333.4/G10) between 1st Jan 2011 - 31st Dec 2018 in Marketscan Commercial claims and Medicare. To explore feasibility, we calculated the number of HD patients with >1 family member on their plan age >18years. Using the 'EMPREL' variable, we calculated the proportion of these family members who were spouses, parents or children.

Results: Of 125,957,476 patients enrolled in the Marketscan Commercial claims and Medicare database, we identified 5,299 HD cases during the observation period. Using the EFAMID variable we identified 3,189 (60%) who had at least one family member with the same family ID i.e. on the same family plan. In 1,267 cases (40%) the HD patient was the primary beneficiary. A total of 4,532 family members were identified, of which the majority of family members identified were spouses (62%; N=2,824), 1067 were children (24%), 133 were parents (3%) and the remainder were unknown.

Conclusions: Large scale data from insurance claims are commonly utilised to describe the burden of the disease on the patient (e.g. comorbidities, procedures and treatments) and associated healthcare costs. To our knowledge this is the first time feasibility of linking patients to family members via the EFAMID variable has been demonstrated for addressing this question. This could be of relevance across multiple therapeutic areas.

4821 | Using real world data for hypothesis strengthening to support early discovery activities: Examining associations between patients with treated autoimmune conditions and incident Parkinson's disease

Jolyon Fairburn-Beech[1], Usha Gungabissoon[1], Marni Stott Miller[1] and Paul Wilson[2]

[1]GlaxoSmithKline, London, United Kingdom; [2]GlaxoSmithKline, Stevenage, United Kingdom

Background: Reported associations can provide a good starting point to explore potential new drug targets using existing knowledge of disease mechanisms and pathways. Additional evidence from 'real world data' may help to corroborate or refute biological hypotheses, aiding in decision making.

Objectives: We sought to develop a standard approach to evaluate disease-disease or disease-drug associations, and to test the hypothesis that individuals with selected autoimmune conditions are at an increased risk of Parkinson's Disease, in an attempt to validate previous findings.

Methods: We used the IBM® MarketScan US Claims Database and employed a matched case-control study design. Cases (incident Parkinson's disease) were defined as those with two Parkinson's Disease codes (ICD10: G.20 or ICD9: 332.0) with no prior code in previous year and controls without any occurrence of the outcome of interest in their record. Cases and controls were matched 1:3 on age, sex, region and length of enrolment prior to index date defined as incident diagnosis in cases and prior to a random medical claim in the same time period for controls. Pre-index exposure was assessed from patient entry into the database until index date. We examined the exposure as four diseases separately (Ulcerative Colitis, Crohn's Disease, Irritable Bowel Disease (IBD) and Rheumatoid Arthritis) and combined. In our adjusted analysis we controlled for Charlson Score, healthcare utilisation, age and sex.

Results: In our matched case (n=22,475) and control (n=62,301) cohorts, proportion of patients with any autoimmune condition was similar (6.3 v 5.4%) and parity remained when the cohorts were subset

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

by individual condition. Our modelling results showed no association between the prior history of each autoimmune condition and the outcome (Adjusted OR: 0.98 (95% CI - 0.92-1.05). We did observe a trend of decreasing odds of Parkinson's Disease with increased length of prior use of immunosuppressants, across all individual diseases studied. In IBD patients, with prior immunosuppressant exposure for 3 years or more, we observed an adjusted odds ratio of 0.85 (95% CI: 0.80-0.90) against no prior exposure.

Conclusions: Our application of a standard approach for evaluating associations in large real-world data sets did not produce definitive evidence of an association between autoimmune disease and Parkinson's Disease. There is an opportunity to apply this design at scale across several potential biological associations.

4822 | A comparison of sampling methods to select real-world relapsed/refractory (R/R) diffuse large-cell B-cell lymphoma (DLBCL) patients with multiple eligible index dates

Paul Dillon[1], Andy Surinach[2], Felipe Castro[1], Nathalie Spielewoy[1], James A. Black[1], Aijing Shang[1] and John Radford[3]
[1]*F. Hoffman-La Roche AG, Basel, Switzerland;* [2]*Genesis Research, Hoboken, NJ;* [3]*University of Manchester and the Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Real world data provide rich longitudinal information on the entire cycle of care for patients, however sampling R/R DLBCL patient is challenging due to the presence of multiple eligible index dates per patient. In the epidemiological literature, potential sampling methods include to select: 1) the first index, 2) a random index, or 3) all index dates and statistically adjust for within-patient correlation in outcome models.

Objectives: To apply three sampling methods to a retrospective real world cohort of R/R DLBCL patients and to evaluate differences of five patient characteristics between each sample by comparing to a reference sample of R/R DLBLC patients enrolled in the control arm of a historic clinical trial (NCT02257567).

Methods: Clinical notes from The Christie NHS Foundation trust in the UK were retrospectively abstracted using a standardized data collection form for 90 patients with R/R DLBCL, aged 18 or older, histologically confirmed DLBCL, at least one prior anti-lymphoma treatment, who collectively received 192 lines of therapy between 2011-2018. The index date was the start date of each line of therapy. Characteristics included gender, age at index, no. of prior treatment lines, refractory disease, and history of stem-cell transplant; the latter four can vary within patient per eligible index date. The trial enrolled R/R DLBCL patients, of which 39 participants were randomised to the control arm. The trial eligibility criteria were applied to the Christie data resulting in a cohort of 73 patients with 122 eligible index dates. The three sampling approaches were applied to the eligible cohort, and the standardized mean difference (SMD) of the patient characteristics in comparison to the reference sample calculated.

Results: In each sample the SMDs were similar for gender (≈0.05), index age (≈0.16), and prior transplants (≈0.22); while the all-index sample yielded the lowest SMDs for refractory disease (0.61) and no. of prior lines (0.60) in comparison to the reference sample. Probability sampling of a single index to match the distribution of the no. of prior lines from the trial was additionally performed, further reducing SMDs for refractory disease (0.10) and no. of prior lines (0.46) with similar SMDs to the other samples for the remaining variables.

Conclusions: Each method yielded samples with differences in patient characteristics, reflected in varying SMDs in comparison to a reference sample. Thoughtful consideration should be given to sampling R/R DLBCL patients that should reflect the purpose of the study.

4837 | Potential bias in matched cohort studies when the referent exposure group lacks a clearly defined time origin for follow-up

Samantha R. Eiffert[1], Virginia Pate[1], Jennifer L. Lund[1], Andrew W. Roberts[2], Til Stürmer[1] and Alan C. Kinlaw[1]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC;* [2]*Kansas University Medical Center, Kansas City, KS*

Background: When active comparators are unavailable, identifying a reasonable index date to begin follow-up of a referent population is challenging. Matched cohort studies in this setting may exhibit differential selection from all eligible index events into the matched cohort, especially when matched sets need to have similar continuous enrollment prior to follow-up for the outcome.

Objectives: To quantify differential selection of index event patients into matched cohort studies when there is not a classic active comparator treatment, using simulated and empirical claims data.

Methods: First, we simulated 1000 cohorts (n=10 000) mimicking individuals with and without colorectal cancer (CRC), using US census and SEER data on the joint distribution of age, sex, and race. Second, we augmented this simulation using recently published data (Butler et al., doi 10.1002/pds.4750) to predict disenrollment from commercial insurance claims, restricted to ages 18-64. We matched CRC and non-CRC patients 1:1 without replacement on exact age and sex. Finally, in an empirical analysis, we used IBM Watson Health MarketScan claims data (2000-2018) to identify incident CRC patients based on Setoguchi's algorithm (n=74 265). We matched CRC and non-CRC patients 1:1 without replacement on exact age, sex, and region, and varied the requirement of continuous enrollment prior to index date. For each matched cohort, we evaluated how many CRC patients were lost in matching, and whether selection into matched cohorts was differential by baseline covariates and required prior enrollment.

Results: In the initial simulation, 2.7% of cancer patients were lost when matched on age and sex. In the augmented simulation that addressed disenrollment, 14.5% of cancer cases were lost in matching. Unmatched patients remained older than matched (mean age 56 vs 51 years); in addition, given the correlation between sex and disenrollment, matching led to differential loss of women (7.0%) versus men (20.6%) from the cancer group. In the empirical analysis of MarketScan data, 31.0%, 47.0%, and 63.6% of incident CRC patients were

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

lost in matching using continuous enrollment criteria of 183, 365, and 730 days, respectively.

Conclusions: Increasing dimensionality of matching criteria led to notable and differential loss of patients with the index event from the final matched cohort. When the target population of interest is the population with the index event, and the unexposed group does not have its own well-defined index date, matched cohort studies may not represent the target population.

4843 | Comparison of the prevalent new user and active comparator new user designs for assessing the real-world safety and effectiveness of NSAIDs and COX-2 inhibitors

John Tazare[1,2], Daniel C. Gibbons[2], Liam Smeeth[1], M. Sanni Ali[1], Elizabeth Williamson[1], Ian J. Douglas[1] and John Logie[2]
[1]*London School of Hygiene & Tropical Medicine, London, United Kingdom;* [2]*GlaxoSmithKline, London, United Kingdom*

Background: Evidence of real-world safety and effectiveness is vital when a drug enters the market. The active comparator new user (ACNU) study has become the gold standard for conducting these studies and typically compares incident new users of the study drug with incident new users of a comparator. Restricting comparisons to treatment naïve patients excludes a potentially large clinically and pharmacoepidemiologically relevant subset who switch from the comparator to the study drug. The prevalent new user (PNU) design aims to address this limitation by incorporating initiators of the study drug that previously received the comparator. In this study we provide an assessment of the potential for PNU designs to recover on-treatment observation time that would have been lost under an ACNU design, using the example of users of non-steroidal anti-inflammatory drug (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors. Future work will use results obtained from a comparison of ACNU and PNU designs assessing gastrointestinal bleeding risk between NSAID and COX-2 inhibitor users to illustrate differences between these designs and to inform discussion of the utility of these designs.

Objectives: To explore the potential increase in on-treatment observation time of the PNU design compared to the ACNU design.

Methods: As part of a wider study comparing the performance of PNU and ACNU study designs, we identified a cohort of NSAID and COX-2 inhibitor users between 2000 and 2005 from the UK Clinical Practice Research Datalink and compared the on-treatment person-time under the ACNU and PNU designs. We assumed a prescription length of 30 days for all treatments and allowed for 60 days between prescriptions to define continuous treatment.

Results: 100995 patients received a prescription for either COX-2 inhibitors or NSAIDs. Of the 75007 who received NSAIDs, 13956 switched from NSAIDs to COX-2 inhibitors. 25988 patients were incident new users of COX-2 inhibitors. The potential person-time available under an ACNU design is 27684 person-years for NSAID users and 12869 person-years for COX-2 inhibitor users. Implementing the PNU design increases the potential on-treatment person-time for COX-2 inhibitor users by 6568 person-years.

Conclusions: Here, the PNU design added 6568 person-years of observed COX-2 exposure, equivalent to a 51% increase in on-treatment time that would otherwise be omitted under an ACNU design. This additional information can aid a more comprehensive understanding of a drug's effectiveness and help detect safety signals earlier in its lifecycle.

4848 | External comparators supporting regulatory submissions: 2017-2019

Joan A. Largent[1] and Priscilla Velentgas[2]
[1]*IQVIA, Mission Viejo, CA;* [2]*IQVIA, Cambridge, MA*

Background: The increased use of single-arm trials (SATs) in regulatory decision making in recent years has driven the need to contextualize outcomes using real-world, external comparators (ECs) obtained from data on typical care. This novel approach has developed in the space of targeted therapies in oncology and rare diseases where randomization to standard of care or placebo is either impractical and/or unethical. No practical guidance has been established to date by regulators regarding proper design, analysis and application of this approach, yet there is increasing use of this approach even without guarantee of acceptance.

Objectives: Review and summarize the use of ECs in regulatory submissions to FDA and EMA from 2017-2019 including successful and unsuccessful submissions.

Methods: We reviewed publicly available regulatory documents (FDA briefing documents, EPAR assessments, product labels), and literature for regulatory submissions where ECs were either successfully or unsuccessfully accepted as part of evidence submission for marketing authorizations between 2017-2019. Specifics of the EC designs were summarized according to type of submission, indication, source(s) of the EC, analytic techniques utilized, and regulatory assessment.

Results: Eleven cases of regulatory submissions for 8 unique product-indication (P-I) submissions including ECs were identified: this included overlap of successful submissions between FDA and EMA in 6 cases and 2 unsuccessful submissions where ECs were not accepted. Type of submission for successful acceptances were FDA initial approval (n=3), FDA label expansion (n=1), EMA conditional approval (n=1) and EMA approval (n=4). For the 8 unique P-I combinations, indications were in oncology (n=6), and rare pediatric indications (n=2). Sources of ECs were identified as registries/observational studies (OS) (n=2), pooled OS and clinical trials (n=2), electronic health records (EHR) (n=2), and chart review (n=2). Analytic comparisons were direct (n=4), benchmark (n=3), and indirect (n=1) among the unique P-I combinations. Assessments by regulators included importance of pre-specifying design and analysis plans, careful matching on inclusion and exclusion criteria of the index trial, comparability and validity of endpoints, and analytic methods appropriate to account for confounding.

Conclusions: Regulatory submissions including ECs between 2017-2019 were primarily in oncology and rare pediatric indications. There are varied approaches to the use of ECs and a need in the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

industry for guidance on methodologic approaches using ECs to evaluate new therapies where only SATs are feasible.

4905 | Visual space: Using visualization in pharmacoepidemiology to design and disseminate valid real-world evidence in a structured framework

Jeremy A. Rassen[1], Shirley V. Wang[2], Nicolle M. Gatto[1,3] and M. Alan Brookhart[4,5]

[1]*Aetion, New York, NY;* [2]*Brigham & Women's Hospital, Boston, MA;* [3]*Columbia University, Mailman School of Public Health, New York, NY;* [4]*NoviSci, Inc, Durham, NC;* [5]*Duke University, Durham, NC*

Background: Credible RWE depends on transparency throughout all the stages of a study, from designing the study and disseminating the findings to decision-makers evaluating the validity and quality of the results. Visualization reduces the risks of implementing poor study designs or misinterpreting results. However, other than recommendations to include graphical representations for the study design and patient attrition, the field lacks specific guidance on how visualizations can support transparency. To develop an approach to pharmacoepidemiology visualizations, the panelists received ISPE funding to develop a manuscript and will share the current thinking of the working group.

Objectives: (1) To examine the use of visualization in study design, including evaluating database quality, study design time windows, covariates, and complex variable measurements in a patient's longitudinal timeline

(2) To identify sources of bias and misclassification through visual representations

To solicit input from ISPE members and attending audience on visualization guidance Researchers and decision-makers using RWE would benefit from attending this symposium.

Description: This symposium will provide an opportunity to learn about graphically representing methods and results for secondary database studies.

(1) First, we will provide an overview of the SPACE framework, focusing on the role of visualization in the overall study design framework (**Nicolle Gatto**).

(2) Next, a visual approach and taxonomy for representing the patient timeline and events will be introduced and we will examine visualizations to determine database quality, such as patterns of data missingness (**Alan Brookhart**).

(3) The third section will discuss visually representing study designs (cohort, case-control, case-crossover) and temporal anchors to increase transparency and reproducibility, building upon the standards set forth by the ISPE-ISPOR Task Force (**Shirley Wang**).

(4) The final section will focus on the visual communication of study findings and understanding how complex study results can be effectively communicated to scientific and non-scientific audiences (**Jeremy Rassen**).

Case examples will be provided to illustrate opportunities to improve the study design and implementation as well as avoid potential pitfalls (e.g., misclassification and immortal time bias).

MY01 | At the intersection of frailty and pharmacoepidemiology: Foundations, applications, and future directions

Dae Kim[1], Scott Martin Vouri[2]

[1]*Department of Medicine/Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School;* [2]*Department of Pharmaceutical Outcomes & Policy, UF College of Pharmacy*

Description:

This symposium will provide participants with an overview of frailty as an important concept in pharmacoepidemiology. We will present aspects pertaining to measuring frailty as a clinically relevant outcome, as well as an important confounder, or effect modifier. We will address challenges of measuring frailty from secondary data sources (i.e., claims data) in studies evaluating medication use, safety and effectiveness in vulnerable populations.

Goals and Objectives:

The main objectives of the symposium are: (1) to provide an overview on the concept of frailty and its measurement as applied in pharmacoepidemiologic studies, (2) to discuss the challenges related to defining, identifying, and measuring frailty from different data sources in vulnerable populations, and (3) to discuss future directions in addressing existing methodological challenges in incorporating measures of frailty in pharmacoepidemiologic studies. This symposium will provide useful insights to researchers involved in or seeking additional expertise in conducting pharmacoepidemiologic studies in vulnerable populations. Participants will have the opportunity to engage in discussions with the speakers and other attendees.

Topics and Speakers:

- **5 W's of Frailty: who, what, when, where and why**
- Todd Manini, Associate Professor, Institute on Aging, Department of Aging and Geriatric Research, University of Florida
- **You may know frailty when you see it, but how do you measure it?**
  - Daniela Moga, Associate Professor, Department of Pharmacy Practice and Science, University of Kentucky
- **How to Incorporate Frailty in Pharmacoepidemiology, in Just 5 Applications**
  - Andrew Zullo, Assistant Professor of Health Services, Policy and Practice, Assistant Professor of Epidemiology, Brown University
- **Current Methodological Challenges and Future Directions for Frailty Measurement in Pharmacoepidemiology**
  - Jennifer Lund, Associate Professor, Department of Epidemiology, University of North Carolina at Chapel Hill

4909 | Tools for assessing the validity of non-randomized studies: A systematic review. Recommendations by the International Society for Pharmacoepidemiology Comparative Effectiveness Research Special Interest Group (CER SIG)

Elvira D'Andrea[1], Lydia Vinals[2], Elisabetta Patorno[1], Jessica M. Franklin[1], Dimitri Bennett[3], Joan A. Largent[4], Daniela C. Moga[5], Hongbo Yuan[6], Xuerong Wen[7], Andrew A. Zullo[8], Thomas P.A. Debray[9] and Grammati Sarri[2]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [2]Evidence Synthesis, Modeling & Communication, Evidera, London, United Kingdom; [3]Epidemiology, Takeda, Boston, Massachusetts, USA and Perelman School of Medicine, Adjunct, University of Pennsylvania, Philadelphia, PA; [4]Real-World Solutions, IQVIA, Mission Viejo, CA; [5]Department of Pharmacy Practice and Science, College of Pharmacy, University of Kentucky, Lexington, KY; [6]Canadian Agency for Drugs and Technologies in Health, Ottawa, ON, Canada; [7]Department of Pharmacy Practice, University of Rhode Island, Kingston, RI; [8]Departments of Health Services, Policy and Practice and Epidemiology, Brown University School of Public Health, and the Center of Innovation in Long-term Services and Supports, Providence VA Medical Center, Providence, RI; [9]University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

Background: Real world evidence from non-randomized studies (NRS) is becoming a key source to support clinical and regulatory decisions on pharmacological therapies. However, due to the observational nature, its capability to produce valid results depends on the implementation of rigorous research design and analysis. An evaluation of whether existing tools allow to adequately assess the validity of NRS on the comparative safety and effectiveness of medications is lacking.

Objectives: To systematically identify existing assessment tools and to determine whether they address aspects that may affect the validity of NRS on the comparative safety and effectiveness of medications.

Methods: We searched Pubmed, Embase, Google®, and bibliographies of reviews, for tools that evaluated the validity of NRS, from inception to November 2019. In parallel, we conducted a Delphi survey among the CER SIG to identify the key methodological challenges (domains) for NRS on comparative safety and effectiveness. Tools identified through the search were evaluated against the methodological domains recommended by the CER SIG using a pre-piloted framework.

Results: Of 43 tools reviewed, 47% assessed multiple NRS designs and 30% also assessed randomized control trials. Case-control and cohort studies were assessed by 28% and 25% of the tools, respectively. Most tools included items related to the methods for selecting study participants (98%); definition and measurement of exposure, outcomes, covariates and follow-up (91%); and measurement and control of confounding (91%). Design-specific sources of bias, mainly recall, loss to follow-up, and observer biases, were assessed by most tools (91%). Very few tools included important sources of bias such as immortal time bias (4%), detection bias (9%), lack of new-user design (4%), or active comparator design (0%). One-third of the tools addressed the appropriateness of statistical analyses (33%). Almost half included methods for assessing uncertainty in the findings (47%). Few tools addressed methods for assessing internal (35%) or external validity (26%).

Conclusions: Although existing tools address well-known threats to validity of NRS, major challenges such as new-user design, active comparator design, immortal time bias, and statistical assessment of internal validity, remain poorly addressed. Including these critical elements to existing tools may ultimately improve the validity of NRS on the comparative safety and effectiveness of medications.

5019 | Innovation and pragmatism in retrospective chart review methodology for post-approval drug utilization studies

Delphine Saragoussi[1], Alice Rouleau[1], Philippe Capart[2], Claudia C. Deveras[2], Neil R. Brett[3], Raphael Ognar[2], Henry Gazay[2] and Krista Payne[3]

[1]Evidera, Paris, France; [2]Medimix, Miami, FL; [3]Evidera, Montreal, QC, Canada

Background: Studies of real-world drug utilization, safety and effectiveness are frequently executed using administrative claims or electronic medical records data. There are significant limitations associated with this approach due to data sources not available in all geographies, and not uniformly containing drug exposure data of interest (e.g. hospital administration; adverse event grading, radiological response). To resolve these data gaps, traditional site-based retrospective chart reviews are an alternative, but are associated with extended timelines, greater site burden and funding requirements. Methods that leverage real-world direct to physician networks for the collection of standardized drug utilization, safety and effectiveness data are warranted.

Objectives: To present pilot study performance metrics of a direct to physician drug utilization study designed to address FDA post-market requirements that leverages an existing on-line research infrastructure.

Methods: A retrospective chart review pilot study was designed and executed in the US, using an existing physician network accessed remotely through an existing pre-screened panel infrastructure. Study execution was governed by a robust and IRB-approved study protocol that required the identification of eligible patient charts selected from within a defined eligibility period (2016 to 2019) and minimum per patient follow-up period of 6 months. Study variables for this historical cohort study included patient characteristics, treatment prescriptions dates and treatment patterns. Physicians from a large panel of HCP treating several conditions were selected using a stratified sampling frame based on the disease and patients required for the study. Data were entered by physicians into a data platform that allowed for tailored validation and edit checks. Data were reviewed by the team and queries issued as needed.

Results: Ninety-one physicians within the therapeutic area were contacted, with 43 (47.3%) participating and 24 (26.4%) providing data for participants who fit the inclusion criteria. In 2 months, medical chart data for 153 patients were abstracted and screened, with 119 patients included in the study. Queries to physicians were answered in 3-5 days on average. There was less than 1% of missing data in the final dataset.

Conclusions: IRB-approved, direct-to-physician on-line chart review methodology is a cost and time-efficient approach to the collection of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

robust real-world data, offering an alternative to secondary data sources or traditional chart review approaches for historical cohort designs.

5053 | Characteristics of network meta-analyses presented at ICPE and ISPOR

Nicole Fusco, Thrudur Gunnarsdottir, Alisa Wilson, Laura C. Morgan and Kristina Lindsley
IBM, Cambridge, MA

Background: As statistical methods have developed and become more accessible, network meta-analysis (NMA), also known as indirect or multiple treatment comparison, has become an accepted technique for comparing treatments that may not have been evaluated directly in head-to-head trials.

Objectives: To describe the characteristics of NMAs presented at two epidemiologic conferences.

Methods: Two independent reviewers screened abstracts presented at International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) or International Society for Pharmacoeconomics and Outcomes Research (ISPOR) from 2015 to 2019; a third reviewer resolved conflicts. We identified and included all abstracts that presented the results of an NMA. One reviewer extracted data about the author affiliation (categorized as industry, research company/organization, academic institution, or government agency), literature review methods, primary research question, and clinical condition under study. A second reviewer verified the extracted data; a third reviewer resolved all conflicts.

Results: We identified 13,964 abstracts presented at ICPE (5405 abstracts, 39%) and ISPOR (8559 abstracts, 61%). Of these, 127 (1%) were NMAs. Only 3/127 (2%) had at least one author affiliated with a government agency. Most abstracts had authors affiliated with industry (73/127, 57%), a research organization (81/127, 64%), and/or an academic institution (61/127, 48%). Most abstracts (78/127, 61%) had authors from more than one category. NMAs were typically conducted in conjunction with another type of literature-based research (108/127, 85%): systematic reviews (SRs, 87/127, 69%), non-SRs (18/127, 14%), pairwise meta-analysis (18/127, 14%), and umbrella reviews (2/127, 2%). More abstracts addressed questions of intervention effectiveness alone (62/127, 49%) than safety alone (11/127, 9%); 45/127 (35%) reported both. Methodological details were often unreported, likely due to space limitations. Nearly half (61/127, 48%) did not report search methodology; 115/127 (91%) did not report assessing risk of bias or study quality. The most commonly studied disease categories were oncology (27%), cardiology (12%), and endocrinology (10%).

Conclusions: Most NMAs were conducted in conjunction with an SR, the most comprehensive means of identifying studies; however, 36% of NMAs were not conducted within an SR. As the number of treatment options grows, statistical methods such as NMA can be used to evaluate the comparative effectiveness and safety of multiple treatments to better guide healthcare decision-makers.

5145 | Review of oncology real-world comparator arm submissions in support of effectiveness claims in 2019 FDA original approvals reveals label-grade real-world study best practices

Ilker Oztop, Wesley Eddings, Amanda Patrick, Pattra Mattox, Christina Purpura and Nicolle Gatto
Aetion, New York, NY

Background: In 2019, FDA has reviewed several real-world comparator arm submissions in support of single-arm trials for novel oncology products. For each submission, FDA publishes a Multidiscipline Review (MDR) upon approval. The MDRs discuss in detail the real-world study protocol, evaluates the methodology behind generating and analyzing the real-world comparator arm, and calls out whether the RWD meets substantial evidence requirements, thus qualifying it label-grade, or not. To date, there has not been a comprehensive review of RWD submissions to FDA that systematically analyzed respective FDA statistical reviews.

Objectives: Identify a comprehensive list of 2019 oncology real-world comparator arm submissions supporting effectiveness in FDA original approvals. Identify criteria FDA statistical review boards use to determine methodological limitations and evidentiary status of RWD. Summarize methodological standards for executing principled real-world studies to generate label-grade RWE.

Methods: Identified 2019 FDA novel drug approvals in oncology. Identified MDRs including RWD submissions supporting effectiveness. Classified RWD based on descriptive vs. comparative statistical methodologies. Analyzed RWD based on (where available): fit-for-purpose data, real-world efficacy endpoints, real-world cohort selection criteria, epidemiological methods to mitigate confounding bias, matching methodologies, transparency, and whether RWD was referenced on the label

Results: Five of 11 submissions included RWD in support of effectiveness. In 2 of these 5 submissions, RWD only served descriptive purposes. The remaining 3 RWD submissions included real-world comparator arms, analyzing overall survival, progression-free survival, and time-to-treatment-discontinuation endpoints. All 3 RWD submissions were deemed non-evidentiary by the FDA and RWD was not referenced in approved labels. The following methodological issues were cited: post-hoc analyses (n=2), selection bias (including improper control selection; n=3), immortal time bias (n=1), confounding bias (n=2), and lack of transparency/misclassification of treatment definitions (n=1).

Conclusions: Until FDA finalizes their detailed RWE guidance (anticipated in 2021), publicly available FDA statistical reviews of RWD submissions provide a valuable resource for identifying real-world study best practices. These reviews highlight the importance of adopting a principled epidemiological approach to avoid common pitfalls in real-world studies.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5148 | Use of anti-diabetic medications and fatal traffic crashes: A case-based analysis

Ye-Jee Kim[1], Xue-Mei Jin[2], Bo Ram Yang[3], Byungkwan Hwang[4], Nam-Kyong Choi[5], Sun-Young Jung[6], Byung-Joo Park[7] and Joongyub Lee[8,9]

[1]Asan Medical Center, Seoul, Republic of Korea; [2]Lixiang Eye Hospital of Soochow University, Suzhou, China; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Keck School of Medicine of USC, University of Southern California, Los Angeles, CA; [5]Ewha Womans University, Seoul, Republic of Korea; [6]Chung-Ang University, Seoul, Republic of Korea; [7]Seoul National University College of Medicine, Seoul, Republic of Korea; [8]Inha University Hospital, Incheon, Republic of Korea; [9]School of Medicine, Inha University, Incheon, Republic of Korea

Background: There are few studies focused on oral hypoglycemic agents and risk of motor vehicle accidents and no data on newly approved glycemic treatment agents for the risk of road traffic accidents.

Objectives: We evaluate whether the use of anti-diabetic medications and the risk of road traffic death in a case-based analysis.

Methods: We used a Korean national road traffic authority database linked with a national health insurance database between January 1, 2010 and December 31, 2014 and applied a case-crossover design. The study subjects were drivers in South Korea who died from traffic accidents and who had prescriptions for anti-diabetic medications within 1 year prior to the date of the accident. We compared the status of prescription for anti-diabetic medications with the hazard period and four matched control periods using conditional logistic regression, adjusting for other drug use. When anti-diabetic medication shows an obvious increase in the exposure trend, the case-case-time-control design was applied to adjust the effect of the exposure trend on the risk estimate.

Results: A total of 1032 anti-diabetics-using drivers were included. In the case-crossover analysis, the odds ratio of total anti-diabetics was 3.61 (95% CI: 2.68-4.88) adjusting for the use of narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, and hypnotics. In the case-crossover analysis by the class of anti-diabetics, insulin (aOR: 5.81, 95% CI: 4.36-7.75) and a fixed-dose combination of metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor (aOR: 2.51, 95%CI: 2.68-4.88) showed significantly increased risk of accident. The risk between the fatal crash and total anti-diabetics (1.07, 0.95-1.22), DPPi+MET (1.02, 0.67-1.55) was negligible and statistically insignificant in the case-case-time-control analysis to adjust effect of the utilization trend.

Conclusions: There was no increased risk of fatal traffic accidents with the use of newly approved glycemic treatment agents after considering the trends of anti-diabetic medication prescription and utilization.

Molecular Epidemiology/ Biomarkers/ Pharmacogenetics

62 | Medication errors and pharmacogenetic factors as possible causes of therapeutic failures and adverse drug reactions in a group of Colombian epilepsy patients

Carlos Calderon-Ospina[1,2], Jubby-Marcela Gálvez-Bermúdez[1,3], Claudia López-Cabra[1], Natalia Morales[1], Juan-David Cala[1], Jesús Rodríguez[3,4], Fabio Aristizábal[2], Alberto Vélez-Van Meerbeke[1] and Dora Fonseca-Mendoza[1]

[1]Universidad del Rosario, Bogota, Colombia; [2]Universidad Nacional de Colombia, Bogota, Colombia; [3]Hospital Universitario Mayor - Mederi, Bogota, Colombia; [4]Fundación Cardioinfantil, Bogota, Colombia

Background: Epilepsy is a serious health problem worldwide. Despite the introduction of new antiepileptic drugs (AEDs) almost 30% of epilepsy patients have drug-resistant forms of the disease (DRE), with a significant increase in morbi-mortality.

Objectives: Our objective was to assess the impact of pharmacogenetic factors and medication errors (MEs) as possible causes of therapeutic failures (TFs) and adverse drug reactions (ADRs) in 77 adult Colombian epileptic patients (41 cases and 36 controls).

Methods: We conducted an analytical, observational, prospective case-control study to screen four polymorphisms in pharmacogenes: *CYP2C9*2* c.430C>T (rs1799853), *CYP2C9*3* c.1075A<C (rs1057910), *ABCB1* c.3435T>C (rs1045642) and *SCN1A* IVS5-91 G>A (rs3812718), and their association with treatment response. Patients were followed during one year to confirm the existence of DRE and ADRs. Every time that at least a single criterion of the Schumock and Thornton criteria was met, we consider the existence of a ME.

Results: 53% of patients displayed DRE and 87% of them used phenytoin. Patient's genetic factors were associated to ADRs in 30% of cases and we found an association between polymorphic alleles of *CYP2C9* and vestibular-cerebellar ADRs (p = 0,001). However, there was no association between the genetic variants evaluated and DRE. 69% of ADRs and 36.6% of TFs could be explained by MEs and could actually correspond to "pseudo-resistance."

Conclusions: MEs were identified in more than the third part of TFs and almost 70% of ADRs. Active pharmacovigilance and clinical pharmacokinetics programs are essential in order to optimize the quality in health care of epilepsy patients.

2340 | Bronchial airway inducible expression and methylation QTL mapping identifies a single nucleotide polymorphism predicting inhaled corticosteroids response heterogeneity in childhood asthma

Elise M.A. Slob[1], Alen Faiz[2], Susanne J.H. Vijverberg[1], Cristina Longo[1], Merve Kutlu[1], Patricia Soares[3], Fook Tim Chew[4], Esther Herrera-Luis[5], Antionio Espuela Ortiz[5], Maria Pino-Yanes[5], Esteban G. Burchard[6], Uroš Potočnik[7], Colin Palmer[8], Cyrielle Maroteau[8],

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Steve Turner[9], Katia Verhamme[10], Leila Karimi[10], Somnath Mukhopadhyay[11], Wim Timens[12], Pieter Hiemstra[13], Mariëlle W. Pijnenburg[14], Maarten van den Berge[15], Anke-Hilse Maitland-van der Zee[1] and Gerard H. Koppelman[15]

[1]Amsterdam University Medical Centers, Amsterdam, Netherlands; [2]University of Technology Sydney, Sydney, Australia; [3]Royal Alexandra Children's Hospital, Brighton, United Kingdom; [4]National University of Singapore, Singapore, Singapore; [5]Universidad de La Laguna, Santa Cruz de Tenerife, Spain; [6]University of California San Francisco, San Francisco, CA; [7]University of Maribor, Maribor, Slovenia; [8]University of Dundee, Dundee, United Kingdom; [9]University of Aberdeen, Aberdeen, United Kingdom; [10]Erasmus Medical Center, Rotterdam, Netherlands; [11]Royal Alexandra Children's Hospital, Brighton, United Kingdom; [12]University Medical Center Groningen, Groningen, Netherlands; [13]Leiden University Medical Center, Leiden, Netherlands; [14]Erasmus Medical Center - Sophia Children's Hospital, Rotterdam, Netherlands; [15]University Medical Center Groningen, Groningen, Netherlands

Background: Approximately 35% of the asthma patients respond poorly to inhaled corticosteroids (ICS). It has been hypothesised that molecular mechanisms underlying poor response to ICS might be similar in asthma and chronic obstructive pulmonary disease (COPD).

Objectives: We aimed to identify genetic variants affecting gene expression and methylation changes in airway wall biopsies of COPD patients before and after ICS and investigate whether these are associated with poor response to ICS in children with asthma.

Methods: Candidate single nucleotide polymorphisms (SNPs) were selected based on steroid inducible expression and methylation. Quantitative Trait Locus (QTL) Mapping profiling of paired bronchial biopsies from 42 COPD patients, participating in the longitudinal GLUCOLD study, was performed prior to and 6 months post ICS use. The window size was 1Mb flanking the gene limits and the false discovery rate was used to adjust for multiple comparisons using the R package MatrixEQTL version 2.2. Association between SNPs and gene expression (eQTL) or gene methylation (meQTL) changes upon ICS use was evaluated. Subsequently, a candidate-gene study was conducted in asthma patients treated with ICS within the PiCA consortium to investigate whether these SNPs are associated with ICS response. Poor ICS response was defined as the presence of exacerbations despite ICS use in the last 6-12 months. Logistic regressions adjusted for age and gender were used to test the association with ICS response. Significance threshold was adjusted by means of Bonferroni correction.

Results: In the COPD study, 18 eQTL and 57 meQTL SNPs were identified to be associated with ICS response. When these SNPs were tested in asthma patients (3,722 children were included for eQTL SNPs and 1,166 children for the meQTL SNPs), the only significant variant was the meQTL SNP rs7220099, an intergenic variant at locus 17q12 with an allele frequency of 33%. The G allele increased the risk of exacerbations (pooled OR: 1.39 95%CI 1.19-1.63, p-value = 2.4 x 10^{-5}).

Conclusions: Our results show that gene expression and methylation profiling prior and post ICS use are quite different between asthma and COPD but still may help to find functional SNPs predicting ICS response. The G allele of rs7220099, a lung eQTL for *TBC1 domain family member 3D*, was associated with increased risk of exacerbations in children treated with ICS and higher methylation.

2542 | Association between genetic variants and cisplatin nephrotoxicity: A genome-wide approach

Zulfan Zazuli[1,2], Wei Xu[3], Susanne Vijverberg[1], Rosalinde Masereeuw[4], Maryam Mirshams[5], Khaleeq Khan[5], Bayardo Ordonez-Perez[6], Shao Hui Huang[5], Anna Spreafico[5], Aaron Hansen[5], David Goldstein[5], Scott Bratman[5], Andrew Hope[5], Bruce Carleton[7], Anke Hilse Maitland-van der Zee[1] and Geoffrey Liu[5]

[1]Amsterdam UMC, location AMC, Amsterdam, Netherlands; [2]School of Pharmacy, Bandung Institute of Technology, Bandung, Indonesia; [3]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [4]Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]University Health Network, Toronto, ON, Canada; [7]University of British Columbia, Vancouver, BC, Canada

Background: The association between genetic variants and cisplatin nephrotoxicity has been studied previously using candidate gene approach but consistent results are lacking.

Objectives: To improve our understanding of genetic risk factors for cisplatin nephrotoxicity by identifying previously unreported genetic associations.

Methods: We conducted a meta-analysis of three genome-wide association studies (GWAS) of high-dose cisplatin-treated adults. Patients were diagnosed with head and neck cancer (n=557) and esophageal cancer (n=168) and recruited at the Princess Margaret Cancer Centre, Toronto, Canada. Nephrotoxicity was assessed between start of treatment and 90 days after cisplatin treatment had completed. Nephrotoxicity was based on following criteria: (i) increased serum creatinine according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 for acute kidney injury (AKI-CTCAE) and (ii) decreased estimated glomerular filtration rate (eGFR). Three different Illumina arrays were used for genotyping and standard quality control pre- and post-genotype imputation was applied.

Results: More than 6 million single nucleotide polymorphisms (SNPs) from 608 patients of European ancestry were evaluated. Five SNPs reached genome-wide significance ($p<5x10^{-8}$). Rs4388268 (minor allele frequency, MAF=0.229), an intron variant SNP in the *BACH2* gene was the most consistent single nucleotide polymorphism associated with increased risk of cisplatin nephrotoxicity in both outcomes and across the genotyping platforms: meeting genome-wide significance (β =-8.37, 95%CI -5.38 - -11.36, $p=3.85x10^{-8}$) for decreased eGFR outcome and reaching near-significance level (OR=3.92, 95%CI 2.28-6.74, $p=7.36x10^{-7}$) for AKI-CTCAE outcome. However, we couldn't replicate the findings of our previously published candidate gene study although the association went to the same direction.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: We found that rs4388268 in *BACH2* increases the risk of nephrotoxicity nearly 4-folded in cancer patients treated with cisplatin. So far, polymorphisms in *BACH2* gene are known to be associated with several autoimmune diseases. Replication in an independent cohort of similarly-treated patients and functional or pharmacokinetic validation are now needed before these findings can be utilized to personalize high-dose cisplatin therapy.

2632 | Finnished geneness: Linking biobank with electronic health record data - TRK fusion in a predefined Finnish cancer cohort

Wei Zhang[1], Jihong Zong[1], Bahman Farahmand[2], Mikko Tukiainen[3], Merja Perälä[3], Sebastian Bender[4], Arndt Schmitz[4] and Renate Schulze-Rath[4]

[1]Bayer US LLC, Whippany, NJ; [2]Bayer Sweden, Solna, Sweden; [3]Auria Biopankki, Turku, Finland; [4]Bayer AG, Berlin, Germany

Background: Selective tropomyosin receptor kinase (TRK) inhibitors, indicated for patients with solid tumors harboring a gene fusion involving one of the three neurotrophic TRK genes (*NTRK*1-3), are now approved in the US and Europe. However, systematic estimates of *NTRK* gene fusion frequency and knowledge on its disease characteristics in each tumor entity are limited. This type of study, which requires linkage of genetic testing data with patients' electronic health records (EHR), is currently lacking.

Objectives: This study aims to evaluate the ability to characterize biobank samples with linkage to secondary care EHR to: 1. Describe the *NTRK* gene fusion frequency amongst papillary thyroid carcinoma (PTC) cohort. 2. Describe patient demographics, natural history of disease, and clinical journey.

Methods: The Southwest Finland province is home to 470,000 residents of Caucasian descent with minimal migration and comprehensive cancer care within the hospital. A retrospective cohort of histologically-confirmed PTC patients with research-consented archival formalin-fixed paraffin-embedded tumour samples were obtained from Auria Biobank. All samples were first stained for pan-TRK protein expression by immunohistochemistry (antibody clone EPR17341) followed by next generation sequencing using the Illumina TruSight170 kit. Characterized genomic data were linked to the Turku University Hospital EHR. Observation period began 1 year prior to diagnosis till end of record/death to describe *NTRK* gene fusion, other gene alterations, patient demographics, and clinical journey.

Results: EHR data is available from 1993 but most complete from 2005 onwards, therefore a cohort of 234 adult PTC patients, diagnosed between 2005 - 2017, were identified. Complete structured data providing information on dates, therapies, and corresponding results are linkable and available for patient demographics, tumour characteristics, comorbidities, operations, chemotherapy, radiotherapy, drugs, lab tests, hospitalizations, and overall survival datasets. More detailed clinical information such as lifestyle risk factors and treatment responses are in unstructured format.

Conclusions: Linking biobank and EHR data in a Finnish cohort provides the non-interventional platform needed to study natural history of gene-driven tumour entities. Additional data linkages, such as Statistics Finland and Finnish Cancer registry, is possible. High-level information can be readily found in structured format while more detailed clinical information may require further manual data extraction.

2644 | Tailoring type II diabetes treatment: Effect of 5-HTT polymorphism on HbA1c levels after metformin initiation

Taichi Ochi[1], Petra Denig[2], Hiddo Heerspink[2], Eelko Hak[1] and Bob Wilffert[1]

[1]University of Groningen, Groningen, Netherlands; [2]University of Groningen, University Medical Center Groningen, Groningen, Netherlands

Background: The serotonin transporter (5-HTT) has been associated with metformin intolerance and may play a role in its efficacy. Tailoring metformin dosage depending on 5-HTT polymorphisms is a potential step towards personalizing the treatment for patients with type 2 diabetes.

Objectives: To investigate the effect of 5-HTT polymorphisms on change in HbA1c levels six months after metformin initiation.

Methods: Participants of PROVALID (PROspective cohort study in patients with type 2 diabetes mellitus for VALidation of biomarkers) within the GIANTT (Groningen Initiative to Analyse Type 2 Diabetes Treatment) cohort who initiated metformin were genotyped for combined SERT 5-HTTLPR/rs25531 (L*L*, L*S* and S*S*) and 5-HTT VNTR (STin 2.12, 12/- and 10/-) polymorphisms, respectively. Differences in distribution of patient characteristics by 5-HTTLPR genotype tested by ANOVA or Chi-square. Multiple linear regression was conducted to determine change in HbA1c level from baseline to six months, adjusted for differences at start in age, sex, 5-HTTLPR/VNTR genotype groups, triglyceride level, low density lipoprotein level, serum creatinine, comorbidities and use of medications that may affect the outcome.

Results: Data on 320 participants, 184 men and 136 women, were analyzed. Mean age was 58.6 ± 8.8 years and index HbA1c was 58.72 ± 14.43 mmol/L. 5-HTTLPR was characterized as L*L*, L*S* and S*S* in 94, 150 and 76 patients. 5-HTT VNTR was categorized as STin2.12, STin2.12/- and STin2.10/- in 74, 157 and 89 patients. Compared to the reference group of L*L*, patients with S*S* had lesser change in HbA1c (B = -6.26, p = 0.044). However, significance was lost after adjusting the regression analysis for further confounders (proton pump inhibitor prescription, low density lipoprotein, serum creatinine), but an effect remains (B = -5.25, p = 0.07). 5-HTT VNTR STin2 polymorphisms were not found to be a significant predictor for difference in HbA1c in six months. Of note, sex and triglyceride level at index were found to be significant covariates in difference in HbA1c levels for the six-month period.

Conclusions: Change in HbA1c after metformin initiation may be smaller in patients with S*S* genotype. Other 5-HTT genotyping for

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

polymorphisms did not provide evidence towards its influence on HbA1c change over the course of six months.

2647 | Danish population prescription drug use and related actionable drug-gene interactions

Carin A.T.C. Lunenburg[1,2], Alexander S. Hauser[3], Kazi Ishtiak-Ahmed[1,2] and Christiane Gasse[1,2]

[1]Aarhus University Hospital Psychiatry, Aarhus, Denmark; [2]Aarhus University, Aarhus, Denmark; [3]University of Copenhagen, Copenhagen, Denmark

Background: Many commonly used drugs have great variability in drug metabolism and response. Pharmacogenetics (PGx) studies genetic variation linked to drug efficacy and adverse events, aiming to improve drug therapy using the individual patients' genetic make-up. Little is known about the potential impact of PGx on the population level, possibly hindering clinical implementation of PGx.

Objectives: To determine the impact of PGx on the population level, we investigated how many patients use actionable PGx drugs, have actionable geno- or phenotypes and which patients could benefit the most of PGx testing.

Methods: In this cross-sectional study, we included PGx recommendations from two international PGx consortia (CPIC and DPWG) and identified all actionable PGx drugs. Actionable PGx refers to drugs, geno- or phenotypes for which dosing recommendations in PGx guidelines exist. The number of users per actionable prescription PGx drug among the total Danish population in 2017 was extracted from the Danish Register of Medicinal Product Statistics (MEDSTAT), stratified by sex and age. We estimated frequencies of actionable geno- or phenotypes based on reported frequencies from literature. For each drug-gene interaction (DGI) we identified 1] total number of drug users, 2] total estimated number of users with an actionable geno- or phenotype, 3] the estimated prevalence of actionable geno- or phenotypes (also per age group) and 4] sex ratio.

Results: We mapped 68 actionable PGx drugs, of which 41 unique drugs (49 DGIs) were identified in prescription drug users in primary care in Denmark. The number of drug users varied from 10-341,395 users in 2017. The estimated median frequency of actionable geno- or phenotypes among prescription drug users was 25% (interquartile range: 7-26%). Six out of 41 drugs were used more than twice as much in females. Actionable PGx drugs were most frequently used by 45-79 year olds (62%), followed by 25-44 year olds (18%). Only 4% of the users of the included drugs were aged below 17 years. Almost half of the actionable PGx drugs (19/41) were psychotropics.

Conclusions: PGx testing can have a substantial impact on the population, as a median of one in four prescription drug users has an actionable geno- or phenotype for which a dose recommendation is provided. These patients could thus benefit from PGx testing, if followed by a dose adjustment to improve drug effectiveness and reduce the risk of adverse events. We advocate for prospective panel-based PGx testing at the time of the first PGx drug prescription ('as needed'), with PGx results ready to be applied prior to start of the first, and all future, therapies.

3778 | The needs of many vs the needs of few: Is society willing to pay for stratified medicine?

Marco Boeri[1], Alan McMichael[2], Jonathan J. Rolison[3] and Frank Kee[2]

[1]RTI Health Solutions, Belfast, United Kingdom; [2]Queen's University Belfast, Belfast, United Kingdom; [3]University of Essex, Essex, United Kingdom

Background: Stratified medicine aims to use genotype or other individual characteristics to predict risk of disease or response to treatment. Patients who receive stratified medicine treatments often have better treatment outcomes; however, these treatments can be substantially more expensive than other treatments available in general health care. In the United Kingdom (UK), much of the cost of health care is borne by society in tax contributions.

Objectives: In this study, we aimed to quantify, using a discrete choice experiment, the benefits the general public would receive by knowing that stratified medicine is funded by society. This is achieved by estimating their willingness to accept an annual increase in tax to help fund this policy.

Methods: We used a discrete choice experiment (DCE) to assess whether a representative sample (n=2804) of members of the UK general public were in favour of implementing a stratified medicine health policy for one or both of two conditions, cystic fibrosis and depression. The stratified medicine health policy was characterised by four attributes: "Proportion of patients who will receive the stratified medicine treatment;" "Potential effectiveness of the stratified medicine treatment;" "Supportive services available to all patients, carers and their family in addition to medical treatment;" and "Additional cost to each tax payer." Respondents were randomly assigned to consider one of the two conditions and asked to assume they were voting in a referendum to decide whether to develop a stratified medicine health care system or to maintain the current general health care system. Data were analysed using random-parameters logit.

Results: : Respondents were more likely to favour implementing a stratified medicine health policy if it benefitted more patients (OR=.02; 95%CI .02-.02) or if the treatment was more effective than currently funded treatments. Reduction in non-medical services (OR=-72; 95%CI=-.79:-.65) or annual increase in taxation (OR= -.03; 95%CI=- -.04:-.03) reduced the likelihood of favouring the stratified health policy. Respondents were more likely to favour implementing the stratified policy for cystic fibrosis than the one for depression.

Conclusions: Results imply that the general public may be willing to support implementing a stratified medicine health policy, but only if treatments are highly effective or benefit many patients.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3894 | Mineralocorticoid receptor as a novel therapeutic target for alcohol use disorder? Preliminary evidence in rodents and humans

Christopher T. Rentsch[1,2], Mehdi Farokhnia[3,4,5], Janet P. Tate[2,6], Brendan J. Tunstall[4], Adriana Gregory-Flores[4,5], Kendall J. Bryant[5], George F. Koob[4], Leandro F. Vendruscolo[4], David A. Fiellin[6,7], Lorenzo Leggio[4,5] and Amy C. Justice[2,6,7]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]VA Connecticut Healthcare System, West Haven, CT; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [4]National Institute on Drug Abuse, Baltimore, MD; [5]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD; [6]Yale School of Medicine, New Haven, CT; [7]Yale School of Public Health, New Haven, CT

Background: A growing body of evidence suggests that the hormone aldosterone and its mineralocorticoid receptor (MR) may play a role in alcohol seeking and consumption. Accordingly, the MR antagonist spironolactone may represent a potential pharmacotherapy for alcohol use disorder (AUD).

Objectives: To examine the effects of treatment with spironolactone on alcohol-related outcomes in both rodents and humans.

Methods: For the first study, Wistar rats were made alcohol-dependent (n=7) via alcohol vapor exposure; non-dependent rats (n=9) were exposed to air. Operant alcohol (0.1 mL, 10% w/v EtOH) self-administration was measured in bi-weekly, 30-min sessions (fixed-ratio 1); procedures were performed during acute withdrawal in alcohol-dependent rats. Spironolactone (50 mg/kg dissolved in 4% Tween 80 in saline) was administered intraperitoneally 1h before the test session. For the second study, real-world data from the Veteran Birth Cohort were used to investigate the association between spironolactone use (prescribed for any indication) and alcohol consumption in humans aged 40 to 70 years. Spironolactone-exposed individuals (n=10,726) were propensity-score matched to five unexposed individuals. Multivariable linear regression models estimated changes in Alcohol Use Disorders Identification Test - Consumption (AUDIT-C) scores before and after spironolactone exposure.

Results: Results showed that alcohol-dependent rats developed escalated alcohol self-administration. Spironolactone (50 mg/kg) significantly reduced alcohol self-administration in both dependent and non-dependent rats (treatment effect: p=0.0003). Among substance use disorder treatment-seeking patients, AUDIT-C scores decreased 0.34 points (95% CI: 0.16, 0.52) more among those exposed than unexposed to spironolactone (p=0.0003). This observation was stronger among individuals who had baseline AUDIT-C scores ≥ 8 [0.55 (0.25, 0.86), p=0.0003] and those who were exposed to ≥ 50 mg/day of spironolactone [0.89 (0.56, 1.22), p<0.0001]. There were no substantial demographic or clinical differences between spironolactone exposed and matched unexposed Veterans (all standardized differences <0.1).

Conclusions: Together, these results support recent findings on the role MRs in the neurobiology of alcohol consumption and suggest that MR antagonists should be further studied as potential pharmacotherapy for AUD.

3895 | Polygenic risk for alcohol consumption predicts drinking response to a mineralocorticoid receptor antagonist

Christopher T. Rentsch[1,2], Rachel L. Kember[3,4], Mehdi Farokhnia[5,6,7], Brendan J. Tunstall[6], Henry R. Kranzler[3,4], Adriana Gregory-Flores[6,7], Kendall J. Bryant[7], George F. Koob[6], Leandro F. Vendruscolo[6], Amy C. Justice[2,8,9], David A. Fiellin[8,9], Lorenzo Leggio[6,7] and Janet P. Tate[2,8]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]VA Connecticut Healthcare System, West Haven, CT; [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [4]VISN 4 MIRECC, Crescenz VA Medical Center, Philadelphia, PA; [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [6]National Institute on Drug Abuse, Baltimore, MD; [7]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD; [8]Yale School of Medicine, New Haven, CT; [9]Yale School of Public Health, New Haven, CT

Background: There is growing evidence that the mineralocorticoid receptor (MR) antagonist spironolactone is a potential pharmacotherapy for alcohol use disorder (AUD).

Objectives: To determine whether spironolactone, prescribed for any indication, is associated with reduced alcohol consumption, and whether effectiveness is predicted by genetic liability for alcohol consumption.

Methods: We used real-world data from the Million Veteran Program to identify patients with Alcohol Use Disorder Identification Test - Consumption (AUDIT-C) scores >0 who received >1 pharmacy fill of spironolactone from 2009 to 2018. We compared them to 1:5 propensity score-matched, spironolactone-unexposed patients. Index date was considered receipt date of first spironolactone prescription for exposed and a randomly selected outpatient visit date for unexposed. Post-index AUDIT-C scores were defined as the closest measure to end of exposure or within 30 days of end of follow-up. Change in pre- and post-index AUDIT-C scores were compared using difference-in-difference linear regression. Polygenic risk scores (PRS) for AUDIT-C were calculated for European-ancestry MVP patients using genome-wide association study summary statistics from the UK Biobank. We examined association between spironolactone exposure and change in AUDIT-C in the overall sample and by drug dose and quartile of PRS.

Results: There was no differential change in AUDIT-C scores between 1,418 spironolactone-exposed and 4,794 unexposed individuals in the full sample (p=0.32) or in the lower three PRS quartiles (all p>0.70). However, among patients in the top PRS quartile (i.e., with the greatest genetic risk of alcohol consumption), AUDIT-C scores decreased 0.26 points (95% CI: 0.01, 0.52) more among those exposed to spironolactone (p=0.044). Differential changes in AUDIT-C scores were greater among individuals exposed to ≥50mg/day of spironolactone in the full sample [0.43 points (0.15, 0.72),

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

p=0.003]. This effect was observed among those in both the bottom PRS quartile [0.74 points (0.15, 1.33), p=0.01] and the top PRS quartile [0.82 points (0.28, 1.35), p=0.003]. There were no substantial demographic or clinical differences between spironolactone-exposed and matched, unexposed Veterans (all standardized differences <0.1).

Conclusions: Spironolactone treatment for any indication, particularly at doses ≥50mg/day or to those with high genetic liability for alcohol consumption, is associated with significant decreases in AUDIT-C scores in real-world patients of European ancestry.

3997 | Predictors for malignancy in pulmonary nodules

Hong Qiu[1], Meng Shu[2], Hao Huang[2], Xiaoyan Fang[2] and Wenhua Liang[3]

[1]*Epidemiology, Janssen Research and Development, New Jersey, NJ;* [2]*Epidemiology, Janssen Research and Development, Shanghai, China;* [3]*The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China*

Background: Screening to detect pulmonary nodules (PN) was associated with reduced lung cancer mortality in the National Lung Cancer screening trial in the US. However, few data are available that describe PN features and predictors of malignancy among PNs from China.

Objectives: To describe characteristics of PNs identified from chest computerized tomography (CT) scans; to identify predictors of malignancy in PNs in a Chinese population.

Methods: A retrospective database study was performed using electronic medical records from the First Affiliated Hospital of Guangzhou Medical University, a general hospital with specialized care for respiratory diseases. PNs were identified from chest CT reports. A PN cohort was constructed from adult patients with a single PN of less than 30 mm from January 1, 2010 to June 30, 2018. PNs were classified as either solid nodule or ground-glass opacification (GGO). Nodule characteristics, including size, location, morphology (mixed vs. pure GGO), as well as patient demographics (age, gender, residency, marriage status), smoking status, and comorbidities were captured. Among patients who underwent pulmonary surgery within 3 months after the nodule detection, potential predictors of malignancy were evaluated using logistic regression analyses.

Results: The study cohort consisted of 2,361 patients with a solid nodule and 1,748 patients with a GGO; 70.3% of patients with GGO demonstrated pure components and the remainder contained a solid part (mixed GGO). The mean ages were similar among patients with solid nodules (54.3 years old) and those with GGO (52.5 years old). Around one-half of patients were male (55.2% in solid PN and 49.3% in GGO). The average diameter of solid nodules and GGO were 5.5mm (±4.9 mm) and 7.9 mm (± 6.4 mm), respectively. Lung surgery was performed on 142 patients with solid nodules and 240 patients with GGO within 3 months after detection of the PN, among which 47.1% of solid nodules and 72.9% of GGO were malignant. Nodule size was a strong predictor for malignancy in patients with GGO: The risk of malignancy was increased by 8.05-fold (95% CI 1.42 - 45.67) in GGO with a diameter of 8 - 10 mm, and by 3.21-fold (95% CI 1.10 - 9.36) when the diameter was 10 - 30 mm, compared to GGO with diameter <5 mm. There were no statistically significant predictors of malignancy identified among patients with solid nodules.

Conclusions: The diameters of GGO were larger than that of solid nodule among CT detected PNs. Nodule size was a strong predictor for malignancy in GGO, but this association was not seen among patients with solid nodules.

4004 | Pharmacogenetics and prescription psychotropic drug use in the Danish population

Carin A.T.C. Lunenburg[1,2], Alexander S. Hauser[3], Kazi Ishtiak-Ahmed[1,2] and Christiane Gasse[1,2]

[1]*Aarhus University Hospital Psychiatry, Aarhus, Denmark;* [2]*Aarhus University, Aarhus, Denmark;* [3]*University of Copenhagen, Copenhagen, Denmark*

Background: Pharmacogenetic (PGx) dosing guidelines are available for psychotropic drugs, aiming at improving drug effectiveness and reducing adverse events. Yet PGx is rarely applied in psychiatric care. The potential impact of PGx in psychotropics on the population level is unknown.

Objectives: To determine the impact of PGx of psychotropic drugs at the population level, we investigated the PGx recommendations for psychotropic drugs, the related geno- or phenotypes and the frequency of drug users and their characteristics.

Methods: We executed a cross-sectional study in the total Danish population of 5,7M inhabitants in 2017. PGx recommendations from two international PGx consortia (CPIC and DPWG) were used to identify all psychotropic PGx drugs which are considered actionable (i.e. for which dosing recommendations in PGx guidelines exist). Using literature, we estimated the frequency of related actionable geno- or phenotypes. The number of users per actionable psychotropic PGx drug was extracted from the publicly accessible sales data of the Danish Register of Medicinal Product Statistics (MEDSTAT), stratified by sex and age. For each drug-gene interaction (DGI) we estimated the proportion of users with an actionable geno- or phenotype by age and sex.

Results: We identified 23 actionable psychotropic PGx drugs from PGx recommendations, of which 19 (corresponding to 24 DGIs) were identified in MEDSTAT in 2017. The genes linked to the identified DGIs were HLA-A, HLA-B and CYP2C9 for anti-epileptics, CYP2C19 for antidepressants and CYP2D6 for antidepressants, antipsychotics and psychostimulants. The average number of users per PGx drug was 22,800. Sertraline had the highest (100,920) and fluvoxamine had the lowest (180) number of users. The estimated median frequency of actionable geno- or phenotypes among psychotropic prescription drug users was 25% (interquartile range: 5-26%). Citalopram and escitalopram, both linked with CYP2C19, had the highest estimated proportion of actionable users (50%, corresponding to N=50,152 and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

N=12,028 users, respectively). Fifteen of the included drugs (79%) were used more often by females. Only carbamazepine, oxcarbazepine, pimozide and atomoxetine were used more often by males. On average, actionable psychotropic PGx drugs were used most often by 45-64 year olds (35%) and least by ≤17 year olds (4%).

Conclusions: PGx testing could contribute to the improvement of drug effectiveness and safety at a median of 1 in 4 users of actionable psychotropic PGx drugs, and 1 in 2 users of the antidepressants (es-) citalopram.

4201 | Association between NR1I2 polymorphisms and the susceptibility to anti-tuberculosis drug-induced hepatotoxicity in a Chinese Han population: A case-control study

Miaomiao Yang, Wenpei Liu, Bilin Tao, Hua You, Honggang Yi and Shaowen Tang

Nanjing Medical University, Nanjing, Jiangsu, China

Background: Anti-tuberculosis drug-induced hepatotoxicity (ATDH) is a serious adverse drug reaction, and its pathogenic mechanism is still largely unknown. Pregnane X receptor (PXR, encoded by *NR1I2* gene) is a ligand-dependent transcription factor and rifampicin is a human PXR specific activator. Rifampicin and isoniazid co-therapy targets porphyrin biosynthesis via PXR and results in hepatic protoporphyrin IX accumulation and subsequently liver injury.

Objectives: The present study aimed to investigate the associations between genetic polymorphisms in *NR1I2* and ATDH in a Chinese Han population.

Methods: A 1:4 matched case-control study was conducted using 146 ATDH cases and 584 controls. Seven tag single-nucleotide polymorphisms (tagSNPs) were detected and analysed. Multivariate conditional logistic regression analysis was used to estimate the association between genotypes and risk of ATDH by the odds ratios (ORs) with 95% confidence intervals (CIs), with liver diseases history, hepatoprotectant use, smoking history and drinking history as covariates.

Results: Patients carrying GG genotype of rs7643645 were at a higher risk of ATDH than with AA genotype (OR=1.864, 95%CI: 1.106-3.141, P=0.020), and significant differences were also found under recessive model (P=0.029) and additive model (P=0.021). Patients with a polymorphism at rs2276707 were at a reduced risk of ATDH under the recessive model (OR=0.600, 95%CI: 0.364-0.988, P=0.045). Subgroup analysis confirmed the relationship in mild hepatotoxicity cases under the additive model (rs7643645, OR=1.429, 95%CI: 1.027-1.988, P=0.034) and recessive model (rs2276707, OR=0.478, 95CI: 0.253-0.902, P=0.023). Functional annotation using ENCODE data also indicated that rs2276707 and rs7643645 were located in the histone modification regions targeting enhancers (H3K4Me1, H3K4Me3 and H3K27Ac).

Conclusions: Based on this case-control study, tagSNPs rs7643645 and rs2276707 in *NR1I2* may contribute to the susceptibility to ATDH in Chinese Han anti-TB treatment patients. Further studies in larger varied populations are needed to validate our findings.

4380 | Impact of tumour genomic characteristics on healthcare resource utilisation and real-world outcomes in patients with non-small cell lung cancer: A real world study using linked whole genome-clinical databases

Fiona Grimson[1], Sudhir Venkatesan[1], Lorena Cirneanu[1], Svetomir Hitov[2], Valeria Lascano[1], Mounika Parimi[1], Rosalind Polya[1] and Benjamin Bray[1]

[1]*IQVIA, London, United Kingdom;* [2]*IQVIA, Sofia, Bulgaria*

Background: Non-small cell lung cancer (NSCLC) is a leading cause of mortality worldwide, accounting for 85% of the total lung cancer deaths. The aim of this study was to establish this feasibility of using the Genomics England database (GE), to generate real world evidence about patients with cancer to support the development of targeted therapies. The database contains somatic and germline whole genome sequencing data from patients with cancers and rare diseases in the UK, linked to real-world clinical databases.

Objectives: To use linked genomic-clinical data to describe the association between genetic features and outcomes (Overall survival and healthcare resource utilisation) in patients with non-small cell lung cancer.

Methods: A retrospective cohort study of participants with a NSCLC diagnosis between 2015-2017 and whole genome sequencing in the GE database, with clinical information from the Cancer Outcomes and Services Dataset (COSD), Systemic Anti-Cancer Therapy Dataset (SACT) and Hospital Episode Statistics Dataset (HES). Tumour mutational burden (TMB), a measure of somatic mutations in the tumour DNA, was calculated for all study participants. Participants were classified as "high" and "low" TMB by the median TMB value in the study population. Descriptive statistics and Kaplan-Meier analyses for overall survival were performed.

Results: A cohort of 647 participants with whole genome sequencing and NSCLC as primary tumour was identified (median age 69 years, 48% female). The study cohort comprised predominantly early stage NSCLC (1A: 27%, 1B: 22%, 2A: 17%). Median follow-up time was 24.5 months [Interquartile range (IQR):20-30] in HES, and 93.5 months (IQR: 59-132) in SACT. There were a median 5 hospitalisation episodes per participant (IQR: 3-11), and 164 (25%) participants were SACT-treated. The median TMB score was 5.9 (IQR: 3-10). Participants with high TMB compared to low TMB, on average, had slightly lower survival times (14.9 v 19.8 months for stage 3B-4) within the same stage and in the overall population.

Conclusions: Longitudinal epidemiological studies using linked genomic-clinical data from the Genomics England database are feasible. Further studies with this database could include drug efficacy and safety studies, biomarker testing, and drug discovery.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4386 | Association of proton pump inhibitor use with endothelial function and metabolites of the nitric oxide pathway: A cross-sectional study

Michael Nolde[1,2], Martin Bahls[3,4], Nele Friedrich[3,4], Marcus Dörr[3,4], Tobias Dreischulte[5], Stephan B. Felix[3,4], Ina-Maria Rückert-Eheberg[1,2], Nayeon Ahn[1,2], Ute Amann[2], Edzard Schwedhelm[6,7], Henry Völzke[3,4], Markus M. Lerch[3], Jakob Linseisen[1,2], Christa Meisinger[1,2] and Sebastian E. Baumeister[1,2]

[1]LMU München, Augsburg, Germany; [2]Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; [3]University Medicine Greifswald, Greifswald, Germany; [4]German Centre for Cardiovascular Research (DZHK) partner site Greifswald, Greifswald, Germany; [5]LMU München, Munich, Germany; [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]German Centre for Cardiovascular Research (DZHK) partner site Hamburg/Kiel/Lübeck, Hamburg, Germany

Background: Proton pump inhibitors (PPIs) might increase the risk of cardiovascular events through inhibition of the cardiovascular enzyme dimethylarginine dimethylaminohydrolase (DDAH). This would elevate the endothelial level of asymmetrical dimethylarginine (ADMA), resulting in reduced production of nitric oxide (NO) and endothelial dysfunction. So far, this mechanism has not been confirmed in vivo.

Objectives: Instead of plasma ADMA, plasma citrulline concentrations might be the preferred biomarker for disturbed endothelial NO synthesis. We analyzed the association between regular daily PPI intake and flow-mediated dilation (FMD) of the brachial artery as well as plasma citrulline.

Methods: We analyzed cross-sectional data from 1,298 participants from two independent cohorts of the population-based Study of Health in Pomerania. Data collection took place between 2008 and 2012 and included ultrasound examinations of the brachial artery, the analysis of non-fasting plasma samples as well as interviews on drug intake. We estimated the association between regular daily PPI intake (Anatomical Therapeutic Chemical (ATC) code A02BC) and FMD as well as plasma citrulline using inverse probability weighting to adjust for confounding and censoring.

Results: 5.9% of male and 7.5% of female study participants were regular daily PPI users. In the fully adjusted models, statistically significant associations were identified for FMD and plasma citrulline concentrations. PPI users revealed a 0.99% (95% CI: -1.96 to -0.02) lower FMD and 3.03 μmol/l (95% CI: -4.96 to -1.10) lower plasma citrulline levels as compared to non-users.

Conclusions: Our data provide evidence that regular daily intake of PPIs might inhibit human DDAH activity, and thereby impair endothelial NO production and vascular endothelial function. Chronic disruption of endothelial NO synthesis may explain an increased risk for major adverse cardiovascular events among long-term users of PPIs, as reported in some previous cohort studies.

4396 | What counts as a cancer diagnosis in real world data? Cohort identification and oncology endpoints in a linked genomic-clinical database

Sudhir Venkatesan[1], Fiona Grimson[1], Lorena Cirneanu[1], Svetomir Hitov[2], Valeria Lascano[1], Mounika Parimi[1], Rosalind Polya[1] and Benjamin Bray[1]

[1]IQVIA, London, United Kingdom; [2]IQVIA, Sofia, Bulgaria

Background: Cohort identification when combined with record linkage can serve to consolidate information from different sources to generate a more comprehensive dataset. However, an evaluation of the level and quality of the linkage is necessary to understand the types of research questions that can be addressed using such datasets.

Objectives: To explore cohort identification approaches for non-small cell lung cancer (NSCLC) patients in the linked Genomics England (GE) database, evaluate the level of linkage with clinical databases and its impact on oncology endpoints.

Methods: Records of participants with whole genome sequencing from the GE database were linked to the Cancer Outcomes and Services Dataset (COSD), Systemic Anti-Cancer Therapy Dataset (SACT) and Hospital Episode Statistics Dataset (HES). Diagnosis information from multiple sources was combined to identify NSCLC diagnoses between 2015 and 2017. Overall survival (OS) was the primary clinical endpoint. The impact on OS from using endpoints defined from HES and SACT data vs. COSD data was assessed and analyses were stratified by cancer staging (Kaplan-Meier analysis).

Results: There were three potential sources of diagnosis data in the linked database: registry diagnosis (COSD), hospital diagnosis (HES) and diagnosis recorded by GE. ICD-10 cancer diagnosis with morphology and behaviour codes were only available in COSD and unavailable in HES and GE. In the HES and GE databases, diagnoses were entered as ICD-10 (3 & 4 character) codes and text descriptions (cancer type and subtype) respectively. In total 647 NSCLC patients in the GE database were identified using diagnosis data from COSD. While diagnosis of NSCLC in COSD agreed with a diagnosis of 'lung cancer' in GE data in 98.3% of study participants, more discrepancies were found with cancer subtype. Nearly all study participants (~100%) had linkage with HES, and 164 (25.4%) were recorded as having received chemotherapy in the SACT database. Using data from SACT and HES in defining OS, 599 patients were included in the analysis and median survival in stage IIIB-IV patients was estimated at 18.7 months. Using COSD data in defining OS, 647 were included in the analysis and median survival in stage IIIB-IV patients was estimated at 16.6 months.

Conclusions: Linked databases often contain multiple sources of information, each with a different provenance. The most detailed and validated cancer diagnosis information is available in the COSD linkage data. GE data linked with the COSD, HES and SACT provide a rich dataset well-suited for use in genomic-clinical studies.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4556 | Data sources for studying genetic factors of chronic obstructive pulmonary disease (COPD)

Anokhi Kapasi, Sharmila A. Kamani and Judith K. Jones
DGI, LLC, Fairfax, VA

Background: Genome-wise association studies are the first step in detecting genetic loci associated with risk of disease. Findings must be confirmed with high-powered, large-scale gene-disease association studies. It is critical to know which population healthcare databases (HC DBs) are available, what data are captured, and their strengths/limitations. B.R.I.D.G.E. TO DATA® (BRIDGE, www.bridgetodata.org), an international compendium of HC DB profiles, may be a unique genetic epidemiology resource.

Objectives: To show how genetic epidemiologists identify and compare genetic HC DBs through a case study relevant to drug developers.

Methods: A drug developer has identified new genetic variants associated with reduced lung function. The researcher must now confirm potential COPD targets via genetic HC DBs. A search was conducted in BRIDGE: *Keyword = COPD*; *DB Type = Tissue/Blood/Genetic/Pharmacogenetic; Age = Yes; Gender = Yes; Diagnosis = Yes; Genotype/Polymorphism = Yes;* and *Allele Frequency = Yes*. Search results were manually reviewed and selected for comparing data attributes. Feasibility of cross-study analysis to achieve sufficient power was assessed.

Results: The search yielded relevant hits (>70%), including Women's Health Initiative (WHI; USA) and UK Biobank, which contain genetic data linked to medical, demographic (e.g., ethnicity), and lifestyle (e.g., smoking) information. Both DBs consist of clinical trial participants, but WHI is limited to postmenopausal women. UK Biobank reports small nucleotide polymorphisms (SNPs), insertions/deletions, allele frequencies, and supports public access. Some SNPs in WHI are publicly available (dbGaP), while other data are restricted to WHI investigators. Combining both study cohorts is not ideal given the major differences in study aims, sampling, and demographics.

Manual review of lower relevancy-ranked profiles (≤70%) identified additional DBs with the potential to provide genetic data and link to COPD outcomes. Maccabi Health Services (MHS) COPD Registry (Israel) is a subset of MHS Clinical DB; biospecimens from adults in MHS are being collected for eventual genetic analyses. Big3 (Sweden) and PHARMO (Netherlands) may allow genotyping of existing or prospectively obtained blood samples, respectively, with special authorization.

Conclusions: This case study demonstrates how BRIDGE supports DB selection for gene-disease association studies. It was successfully used to identify genetic HC DBs, compare attributes, and assess potential for pooling cohorts. While BRIDGE is still growing, it may be a tool for standardizing HC DBs, including genetic data.

4640 | Effect modification by BMI in association of PHOSPHO1 gene methylation with the change in HDLC response to simvastatin

Juanlin Fan[1], Shanqun Jiang[1] and Scott Venners[2]
[1]*School of Life Sciences, Anhui University, Hefei, China;* [2]*Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, Canada*

Background: Genetic variants only explain limited inter-individual variations of statin treatment, the residual response to statins could be attributed, in part, to epigenetic alternative.

Objectives: Our aim was to detect the effect of DNA methylations in phosphoethanolamine/phosphocholine phosphatase (PHOSPHO1) gene on the therapeutic efficacy of simvastatin.

Methods: We used an extreme sampling approach by selecting 211 individuals from approximately the top and bottom 15% of adjusted lipid-lowering response residuals to simvastatin (n=104 for the high response group and n=107 for the low response group) from a total of 734 subjects with hyperlipidemia. They were treated orally with 20 mg/d simvastatin for eight consecutive weeks. DNA methylation loci at the PHOSPHO1 gene were measured by high-throughput NGS-based sequencing technology. Fasting serum lipids were measured at baseline and after eight weeks of simvastatin treatment.

Results: Mean PHOSPHO1 DNA methylation had significantly negative correlation with HDL-C variation (β=-0.014, P=0.045) in the high response group. After stratification by BMI, the associations between the PHOSPHO1 DNA methylations and the change in HDL-C response to simvastatin were more significant in obese subjects with BMI≥25 kg/m^2. Moreover, mean PHOSPHO1 methylation together with traditional predictors could explain up to 24.7% (adjusted R^2) of the change in HDL-C response in obese patients. In addition, there was statistically significant additive interaction term (interaction P=0.028) between BMI and mean PHOSPHO1 methylation in the model of the change in HDL-C response to simvastatin.

Conclusions: Our findings suggest that the PHOSPHO1 DNA methylations are associated with the change in HDL-C response to simvastatin treatment, especially dependent on the extent of obesity of patients.

4653 | GWAS of antidepressant treatment non-response in depression

Christiane Gasse[1], Janne P. Thirstrup[1], Søren D. Østergaard[1], Thomas D. Als[1], Ole Köhler-Forsberg[1], Merete Nordentoft[2,3], Ole Mors[1,3] and Anders Børglum[1,3]
[1]*Aarhus University, Aarhus, Denmark;* [2]*Copenhagen University, Copenhagen, Denmark;* [3]*Lundbeck Foundation Initiative For Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark*

Background: Depression is a highly complex disorder with a lifetime prevalence of around 14%. A recent Genome-wide association study (GWAS) identified 44 risk variants strongly enriched among gene-targets of antidepressant medications (Wray & Sullivan, 2017). These findings increase the prospects of identifying genetic variants affecting the response outcomes to antidepressant treatment as a further step towards personalized medical treatment.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: We aimed at 1) identifying genetic variants associated with treatment non-response in depression in a population-based cohort; 2) obtaining an estimate of SNP heritability of treatment non-response in depression.

Methods: We conducted a population-based cohort study based on Danish national registries and biobanks from 1981 to 2018. The study population comprises all individuals born between 1981 and 1995, with depression according to ICD-10 (F32-F33) diagnosed at psychiatric hospitals between 1995 and 2012 (index date) and treated with antidepressants (AD, ATC code: N06A). We excluded patients with comorbid schizophrenia or bipolar disorder (n=1586). The study population was genotyped using the custom array by Illumina (PsychChip). Quality control and imputation were performed using standard procedures. Non-response (NR) to AD was defined by applying an algorithm considering number of switches between AD drugs, augmentation therapy and (re-) hospitalisation. Patients were followed from the date of first AD prescription within two years prior to the index hospital contact until two years after this date, NR, eimigration, or death, whichever came first. We conducted GWAS of AD NR using logistic regression analysis and adjusted the analysis for sex, genetic population structure, and wave information. We created Manhattan plots based on GWAS summary statistics. SNP-heritability was estimated using univariate genome-based restricted maximum likelihood approaches. Heritability (h^2_{SNP}) was estimated on the liability scale assuming population prevalence for depression of 15 %.

Results: Among 12,189 individuals with hospital diagnosed depression and treated with AD, we identified 2953 (24.2%) individuals with NR. In the GWAS analysis of NR, no SNPs reached the significance level of 5e-08. The estimated h^2_{SNP} of NR in individuals with depression treated with AD was 0.0853 (SD: 0.0377).

Conclusions: We did not identify any SNPs associated with antidepressant non-response defined by a register-based algorithm at genome-wide significance. The proportion of phenotypic variance of antidepressant non-response explained by all SNPs was low.

5090 | Pharmacogenetics-based preliminary model improves prediction of infection in patients receiving cytotoxic chemotherapy for hematological malignancies

Matias F. Martinez[1], Enzo Alveal[1], Tomas Soto[1], Eva Bustamante[2], Ivonne Flores[2], Claudia Benavides[2], Fernanda Avila[3], Scarlette Jara[1], Ricardo Morales[2], Nelson M. Varela[1] and Luis A. Quinones[1]

[1]University of Chile, Santiago, Chile; [2]Arturo Lopez Perez Cancer Institute, Santiago, Chile; [3]Clinical Hospital of the University of Chile, Santiago, Chile

Background: Infections in hematological cancer patients in treatment are common and usually life-threatening. Genetics could help to predict their incidence.

Objectives: To estimate the effect of genetic variables in the performance of a preliminary pharmacogenetic-based algorithm in the prediction of infections in patients undergoing chemotherapy, compared with a non-genetic algorithm.

Methods: We carried out a prospective cohort study in >18 years old patients receiving cytotoxic chemotherapy for the treatment of leukemia, lymphoma or myeloma; in two hospitals in Chile. We built the predictive model using multivariate logistic regression. We assessed for inclusion into the model 6 non-genetic variables and 13 genetic polymorphisms, nine of them related to pharmacokinetic processes and 4 related to immune response. Variables were incorporated into the model depending on their statistically significant association in a univariate model. Pseudo-R^2 was used to select the best model. Calibration and discrimination of the models was assessed by the Hosmer-Lemeshow (HL) goodness-of-fit test and area under the ROC curve (AUC-ROC), respectively.

Results: We analyzed 201 chemotherapy cycles in 50 enrolled patients (mean age 47.8±16.1; 56% women), mainly with acute lymphoblastic (13(26%)) and acute myeloblastic (12(24%)) leukemia. Infection was present in 40.8% (82) chemotherapy cycles in 80.0% (40) patients. For the non-genetic algorithm, we incorporated chemotherapy type and cycle, diagnosis, days in neutropenia, age and sex. The Pseudo-R^2 was 0.23, the p-value of the HL test was 0.29 and the AUC - ROC was 0.82. For the Pharmacogenetics-based algorithm we included three pharmacokinetics-related polymorphism, CYP3A4 rs2242480C>T (p = 0.04 for CC), the organic anion transporter 4 (OAT4) rs11231809T>A (p = 0.006 for AT and 0.002 for TT) and the ATP-binding cassette Subfamily C member 2 (ABCC2) rs12762549G>C (p = 0.067 for GG). Inflammatory response-related polymorphisms were the Toll-like receptor 2 (TLR2) rs4696480T>A (p = 0.01 for TT), the interleukin 6 (IL6) rs1800796G>C (p = 0.027 for GG and GC) and the interleukin 1β (IL-1β) rs1143627G>A (p = 0.128 for AG/GG). The Pseudo-R^2 was 0.56, the p-value of the HL test was 0.98, and the AUC - ROC was 0.93.

Conclusions: To include genetic variables improved the prediction of infections, the calibration and the discrimination of the model. Our results could help to prevent infections in patients undergoing chemotherapy and optimize limited resources. This model should be validated in a larger prospective study.

5112 | Genome-wide pathway analysis identifies biological pathways related to treatment response in metastatic colorectal cancer patients given cetuximab: A secondary analysis of clinical trials data

Lidija Latifovic[1], Wei Xu[2], Rayjean Hung[3] and Geoffrey Liu[2]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; [2]University Health Network, Toronto, ON, Canada; [3]Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada

Background: The use of genetic information to improve treatment selection is an emerging approach in precision medicine. We consider the possibility that multiple, modestly associated genetic variants from

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

common biological pathways explain differences in response to the targeted drug cetuximab.

Objectives: To identify biological pathways related to overall survival (OS) and progression-free survival (PFS) in metastatic colorectal cancer (mCRC) patients given cetuximab +/- brivanib alaninate.

Methods: A genome-wide scan (GWAS; 439,894 SNPs) was conducted on 573 KRAS wild-type chemo-refractory mCRC patients from the Canadian Cancer and Australasian Gastrointestinal Trials Groups' CO.20 multi-centre phase III trial that randomized cetuximab +/- brivanib alaninate. Analyses adjusted for treatment, principal components for ancestry, sex, number of metastatic sites, tumor grade, side of primary tumour and lactate dehydrogenase levels. Genome-wide pathway analysis based on GWAS p-values utilized GSA-SNP2, a competitive method based on the random set model Z-statistic adjusted for gene size and the number of genes analyzed, to identify pathways enriched in associated genetic variants. False discovery rate was controlled by the Benjamini-Hochberg method.

Results: Five pathways were associated with OS and one with PFS ($q<0.05$). Pathways related to OS included: arrhythmogenic right ventricular cardiomyopathy, extrinsic component of cytoplasmic side of plasma membrane, cell-cell adherens junction, fat cell differentiation and extrinsic component of plasma membrane. PFS was related to hemophilic cell adhesion via plasma membrane adhesion molecules. Many of these pathways are involved in cell-cell interaction, suggesting that genetic variation that affects cell response to the drug-target complex may affect cetuximab efficacy. Several of the top scoring genes were common to more than one pathway and may explain some of the pathway-level associations [CTNNA3 (cell-cell adhesion), ACTN1 (cell adhesion; endothelial cell contacts), ATP2A2 (rearrangements of the cytoplasmic and transmembrane domains), GNG2 (signaling mechanisms across membranes), FERMT2 (integrin-mediated cell adhesion on extracellular matrix; cell spreading), RGS6 (regulates signaling cascades), STYK1 (focal adhesion), CADM1 (cell-cell adhesion)].

Conclusions: Our findings provide insight into the biological mechanisms associated with cetuximab efficacy. These findings are being replicated in the CO.17 cetuximab trial.

Pediatric Pharmacoepidemiology

30 | Androgen therapy and longitudinal outcomes for hypospadias repair procedures in the United States

Julia B. Ward[1,2], Brian R. Matlaga[3], Kevin C. Abbott[4], Tamara Bavendam[4], Ziya Kirkali[4], John Lim[1], Erline E. Martinez-Miller[1,5], Casey Pierce[1] and Lydia Feinstein[1,2]

[1]Social & Scientific Systems, Durham, NC; [2]University of North Carolina, Chapel Hill, Chapel Hill, NC; [3]Johns Hopkins University School of Medicine, Baltimore, MD; [4]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; [5]University of Texas Southwestern Medical Center, Dallas, TX

Background: Hypospadias is the most common variation of urethral development among male infants and is often treated with a surgical repair procedure. Some patients receive neo-adjuvant androgen therapy prior to surgery in order to enlarge the surgical area. However, nation-wide trends in prevalence of hormonal therapy prior to surgery remain understudied. Further, longitudinal assessments of surgical outcomes and the influence of androgen therapy on these outcomes are virtually non-existent.

Objectives: As part of the Urologic Diseases in America project, we assessed 12-year trends in hypospadias repair procedures, use of preoperative androgen stimulation (PAS), and surgical outcomes among a large, national pediatric population.

Methods: We utilized 2004-2016 Optum© Clinformatics® Data Mart, a de-identified adjudicated insurance claims database of 15-18 million individuals covered annually by commercial insurance. Among 316,152 males continuously enrolled in private insurance from birth through two years of life, we utilized medical and pharmacy claims to estimate the annual prevalence of hypospadias, hypospadias-related repair procedures, and use of PAS. Among 2,356 hypospadias patients with a repair procedure, we used the Kaplan-Meier estimator to calculate the 18-month cumulative probability of repeat procedures and postoperative complications (urethral fistula, stricture, or diverticulum). Analyses were conducted overall and stratified by use of PAS and procedure location.

Results: Average annual hypospadias prevalence was 1%. Overall, 57% of hypospadias patients had a repair procedure by two years of age, most of which occurred in ambulatory settings. PAS was prescribed for 4% of patients with a repair procedure. Among those with an initial procedure, an average of 16% had a postoperative complication and 12% required a repeat procedure, most within 9 months of the initial procedure. The prevalence of repeat procedures decreased by 15% over the 12-year study period. Surgical complications and repeat procedures were both more common among patients receiving PAS and among those requiring an inpatient procedure.

Conclusions: The majority of male infants with hypospadias underwent a repair procedure early in life. Those with an inpatient procedure or PAS were more likely to have an adverse surgical outcome; however, the prevalence of repeat procedures decreased over the study period regardless of PAS status. Although PAS and inpatient procedures may be markers of hypospadias severity, awareness of these risk factors may allow urologists to better counsel and treat hypospadias patients.

78 | Comparative effect of four antimalarial treatments on haematocrit in children in Southwest Nigeria

Zacchaeus F. Olofin, Adebola E. Orimadegun and Catherine O. Falade

University of Ibadan, Ibadan, Nigeria

Background: Anaemia in malaria has both central (dyserythropoiesis) and peripheral causes (phagocytosis of both infected and uninfected

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

erythrocytes and haemolysis). However, it is often difficult to disentangle the anemia effect of malaria from its treatments.

Objectives: To compare the change in haematocrit following four antimalarial treatments among children of microscopically-confirmed Plasmodium *falciparum* infection.

Methods: Data were extracted from 313 case record forms of children that met the eligibility criteria aged 3-119 months enrolled in antimalarial clinical trials in Southwest Nigeria between 1998 and 2014. Study participants were followed up over a 28 day period according to the World Health Organization recommendation for treatment of malaria research participants. Enrollment criteria included symptoms compatible with acute uncomplicated malaria, including parasite density of at least 1000/μL and absence of chronic illness or danger signs of severe malaria. Change in haematocrit level from baseline through the treatment period and 28 days post treatment were compared among children treated with artemether-lumefantrine (82), artovaquone-proguanil (41), artesunate-amodiaquine (156) and chloroquine (34). Repeated measures analysis was done by fitting a general linear model (GLM).

Results: The median age of the study population was 25 months and 54% were males. The mean differences (95% CI) in haematocrit from baseline were 4.7 (95% CI = 3.6, 5.8), 4.4 (95% CI = 2.7, 6.0), 3.8 (95% CI = 3.0, 4.7) and 2.4 (95% CI = 0.5, 4.4), for artemether-lumefantrine, artovaquone-proguanil and artesunate-amodiaquine and chloroquine, respectively. Using the general lineal model, repeated measure analysis showed that there were significant differences in the mean haematocrit level over the 28-day follow-up among the four treatment groups ($p<0.05$).

Conclusions: All children experienced increases in haematocrit after treatment, with artesunate-amodiaquine appearing to result in a greater increase in haematocrit than other antimalarial drugs although not statistically significant, but might be significant with a larger sample size.

88 | Liver enzymes during and after antimalarial therapy in Nigerian children with uncomplicated *Plasmodium falciparum* infection

Zacchaeus F. Olofin, Adebola E. Orimadegun and Catherine O. Falade
University of Ibadan, Ibadan, Nigeria

Background: Derangement of liver enzymes is a known adverse event associated with antimalarial due to drug-induced liver toxicity. However, it remains unclear whether these changes in liver enzyme levels persist following the completion of antimalarial therapy.

Objectives: To determine the effect of artemether-lumefantrine on plasma levels of four liver enzymes, namely; alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and gamma glutamyl transpeptidase [GGT] in children with uncomplicated *Plasmodium falciparum* infection during and after completion of antimalarial treatment.

Methods: We reviewed the records of all children who participated in a clinical trial of antimalarial drug in Ibadan, Nigeria and 102 children who met the eligibility criteria for this analysis (i.e microscopically-proven *Plasmodium falciparum* infection treated with artemether-lumefantrine at the recommended age-specific dose for 3 days). Study participants were followed up on days 3, 7, 14, 21, and 28 according to the World Health Organization recommendation for treatment of malaria research participants. Inclusion criteria for the clinical trial included symptoms attuned with acute uncomplicated malaria, parasite density of at least 1000/μL, absence of chronic illness or signs of severe malaria. The results of ALT (U/L), AST (U/L), ALP (U/L) and GGT (U/L) at baseline (day 0), on day 3, and day 28 post-treatment were extracted and compared using Friedman two-way ANOVA at $p = 0.05$. Normal range for ALT 5-45U/L, AST 15-63U/L, ALP 145-420U/L and GGT 5-90U/L

Results: The median age of participants was 25 months (range = 3 to 119 months), and 49% were male. The mean ALT decreased from 25.8 (95% CI=15.5-36.0) at baseline to 23.1 (95% CI=16.4-29.8) on day-3 and 19.1 (95% CI=15.8-22.4) on day-28 ($p=0.219$), $p = 0.219$. The mean AST increased from 50.3 (95% CI=36.7-64.2) at baseline to 51.0 (95% CI=36.9-65.1) on day-3 and 55.2 (95% CI=37.5-72.9) on day-28; $p=0.198$. ALP decreased from 319.2 (95% CI=287.6, 250.7) at baseline to 308.3 (95% CI=279.7-336.8) on day-3 and increased to 373.8 (95% CI=327.9-419.8) on day-28; $p=0.042$. The GGT increased from 21.1 (95% CI=17.5-24.8) at baseline to 22.6 (95% CI=19.3-25.8) on day-3 and decreased to 18.7 (95% CI=1.9-14.9) on day-28; $p=0.001$.

Conclusions: Substantial rise in ALP and GGT suggesting liver injury during malaria treatment among Nigerian children. Further research is needed to identify the underlying mechanism responsible for this drug-induced liver toxicity.

120 | Changes in early life exposure to antibiotics: A comparison of birth cohorts based on German claims data

Oliver Scholle[1], Susann Grill[1] and Ulrike Haug[1,2]
[1]*Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany;* [2]*University of Bremen, Bremen, Germany*

Background: Antibiotic exposure in early life has been associated with an increased risk of chronic conditions such as childhood obesity as well as with negative effects on the gut microbiota. To avoid inappropriate antibiotic prescribing, antimicrobial stewardship programs have been implemented. However, detailed information on potential changes, e.g., regarding first antibiotic use in life, is lacking.

Objectives: To describe the time span between birth and first antibiotic prescription as well as the type of the first prescribed antibiotic agent in different birth cohorts in Germany (2004-2015).

Methods: Using the German Pharmacoepidemiological Research Database (GePaRD), covering ~17% of the German population, we identified children born between 2004 and 2015. Each newborn was followed until 2016 or end of enrolment in the database. Prescriptions

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of systemic antibiotics were identified based on outpatient drug dispensations. We estimated Kaplan-Meier curves to determine time to first antibiotic prescription in life and assessed the type of the first prescribed antibiotic agent.

Results: Among ~1.5 million newborns included overall, 55% received an antibiotic prescription before the age of two years. Children in more recent birth cohorts received the first antibiotic prescription later than those in less recent birth cohorts: The median age at first antibiotic prescription was 18 months for children born in 2004 and 24 months for those born in 2014. Across all birth cohorts, amoxicillin and the broad-spectrum antibiotic cefaclor were the most frequently prescribed first-in-life antibiotics, and their proportions rose between 2004 and 2014 (amoxicillin: from 31% to 37%; cefaclor: from 20% to 29%). An increasing proportion was also observed for the broad-spectrum antibiotic cefuroxime (2% in 2004 and 6% in 2014), whereas it decreased for the narrow-spectrum antibiotics erythromycin (13% in 2004 and 6% in 2014) and phenoxymethylpenicillin (7% in 2004 and 4% in 2014).

Conclusions: Our study showed that the age at first antibiotic prescription has increased over the years, but the proportion of broad-spectrum antibiotics prescribed as first-in-life antibiotic agents continues to be at a high and further increasing level. The appropriateness of this prescribing behavior requires further monitoring to ensure rational antibiotic prescribing in early life.

2317 | Maternal thyroid dysfunction during pregnancy and the risk of adverse outcomes in the offspring: A systematic review

Mengqin Ge, Miriam T.Y. Leung, C.L. Cheung and Ian C.K. Wong
The University of Hong Kong, Hong Kong, Hong Kong

Background: Maternal thyroid function plays an important role in optimal fetal development. However, thyroid dysfunction is among the most prevalent disorders in pregnant women. Previous studies suggested that maternal thyroid diseases may be associated with adverse neurocognitive outcomes and impair fetal other organ development.

Objectives: To review the available evidence for an association between maternal thyroid dysfunction during pregnancy and the risk of various adverse outcomes in offspring

Methods: We performed systematic literature searches in PubMed, EMBASE, and Cochrane. Studies were included if they investigated the association between maternal thyroid hormone function during pregnancy and the risk of adverse outcomes in their children. The Proffered Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed. The quality of the design and reporting of included studies was assessed using the Newcastle-Ottawa Scale (NOS).

Results: We identified 30 eligible articles: 22 studies of neurodevelopmental disorders and 8 studies of other disorders. All studies were based on a population-based prospective birth cohort or a national register-based screening cohort. The review found an association between maternal hypothyroidism and an increased risk of autism spectrum disorder (HR: 1.31, 95% CI: 1.17 - 1.47, p < 0.00001), epilepsy (HR: 1.22, 95% CI: 1.06 - 1.39, p = 0.004) and schizophrenia (OR: 1.70, 95% CI: 1.13 - 2.55, p = 0.010). Children born from mothers with higher free T4 levels are more likely to be diagnosed with depression (OR: 1.21, 95% CI: 1.00 - 1.14, p = 0.05), but the result did not attain a statistically significant level. The review also suggested a higher risk of other disorders in the offspring including pediatric endocrine morbidity (HR: 1.92, 95% CI: 1.08 - 3.4, p = 0.0263), congenital heart disease (OR: 1.68, 95% CI: 1.02 - 2.78, p = 0.0416), and asthma (HR: 1.37, 95% CI: 1.04 - 1.80, p = 0.0252) born from mothers with abnormal thyroid hormone levels. Overall, the quality of the studies is satisfied (60% "Good", 10% "Fair" and 30% "Poor"); however, most of the studies did not adjust for pregnancy-related complications and birth outcomes which may have an intermediary role in the association.

Conclusions: This systematic review suggests a possible association between maternal thyroid function and various disorders in the offspring. Future studies are needed to investigate the association with consideration of more confounding factors (e.g. thyroxine or antithyroid treatment).

2498 | The efficacy and safety of metformin for insulin resistance and obesity in children and adolescents: A systematic review and meta-analysis

Reem Masarwa[1,2], Vanessa C. Brunetti[1,2], Staphanie Aloe[2,3], Melanie Henderson[4,5], Robert W. Platt[2,3] and Kristian B. Filion[2,3]
[1]Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada; [2]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [3]McGill University Healthcare Center, Montreal, QC, Canada; [4]University of Montreal, Montreal, QC, Canada; [5]CHU Sainte-Justine Research Center, Montreal, QC, Canada

Background: The worldwide prevalence of childhood obesity and its complications has markedly increased over the last several decades. Metformin is prescribed "off-label" for the treatment of obesity and insulin resistance in children and adolescents. However, the efficacy and safety of metformin remains unclear.

Objectives: To compare the efficacy and safety of metformin in children and adolescents via systematic review of randomized controlled trials (RCTs) and observational studies and meta-analysis of RCTs, with a particular focus on body mass index (BMI), insulin resistance, and adverse effects.

Methods: We systematically searched PubMed, Embase, the Cochrane Library, Scopus and ClincalTrials.gov from inception to November 2019. We included all published RCTs and observational studies assessing the efficacy and safety of metformin monotherapy compared to lifestyle interventions in children and adolescents (4-19 years) with obesity, prediabetes, diabetes, or non-alcoholic fatty liver disease. We used the ROB-2 and ROBINS-I tools to assess the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

quality of RCTs and observational studies, respectively. The primary outcomes were changes in BMI, BMI z-score, and homeostatic model assessment insulin resistance (HOMA-IR), and the occurrence of gastrointestinal (GI) adverse effects. Observational studies were included in the qualitative systematic review only. Data were pooled across RCTs using DerSimonian and Laird random-effects models with inverse variance weighting, and amount of heterogeneity present was estimated using the I^2 statistic.

Results: Our systematic review included 25 RCTs (1,705 participants) and 5 observational studies (301 participants). Ages ranged from 4 to 19 years, and follow-up duration ranged from 2 months to 2 years. Compared with lifestyle interventions, metformin was associated with a greater decrease in BMI (weighted mean difference [WMD]: −0.69 kg/m^2, 95% confidence interval [CI] −1.28, −0.10, I^2: 76%), BMI z-score (WMD: −0.15, 95% CI −0.27, −0.04, I^2: 89%), and HOMA-IR (WMD: −0.92, 95% CI −1.71, −0.13, I^2: 68%). Sensitivity analyses restricted to higher-quality studies produced similar results for BMI z-score (WMD: −0.16, 95% CI, −0.33, 0.01, I^2: 86%), but attenuated effects for BMI (WMD: −0.25 kg/m^2, 95% CI, −0.98, 0.45, I^2: 77%) and HOMA-IR (WMD: −0.54, 95% CI, −1.77, 0.68, I^2: 43%). Metformin was associated with an increased risk of GI adverse effects (relative risk: 1.84, 95% CI 1.37, 2.49, I^2: 10%).

Conclusions: Metformin therapy has modest but favorable effects on weight, and insulin resistance, and a tolerable safety profile.

2531 | Development and validation of a pediatric comorbidity index to predict the risk of hospitalization in the ICD-10-CM era

Jenny W. Sun[1], Florence T. Bourgeois[2], Sebastien Haneuse[1], Sonia Hernández-Díaz[1], Brian T. Bateman[3] and Krista F. Huybrechts[3]
[1]Harvard T.H. Chan School of Public Health, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: Comorbidity scores are widely used for risk adjustment in pharmacoepidemiologic studies conducted in healthcare databases. Because a pediatric comorbidity index does not currently exist, comorbidity scores developed to predict all-cause mortality in adults are often used for risk adjustment in pediatric studies.

Objectives: To develop and validate a single numerical pediatric comorbidity index to predict the 1-year risk of hospitalization using administrative data from the tenth revision of the International Classification of Diseases, Clinical Modification (ICD-10-CM).

Methods: Within the IBM MarketScan database, we identified children (age 0-18 years) continuously enrolled between October 1, 2015-September 30, 2017. Patients were randomly allocated to the development (2/3 of patients) or validation cohort (1/3 of patients). Within the development cohort, logistic regression was used to predict the 1-year risk of hospitalization based on 27 predefined conditions and empirically-identified conditions derived from the top 250 most prevalent codes among patients with the outcome. Elastic net was used for variable selection. A single numerical index was created by assigning a weight to each condition based on its beta coefficient. We conducted internal validation of the pediatric index and compared its performance to existing adult comorbidity scores. The pediatric index was mapped to the ninth revision of ICD (ICD-9-CM) and validated in patients continuously enrolled between October 1, 2012-September 30, 2014.

Results: There were 1,934,703 patients (mean age: 10.3 years) in the development cohort, among which 27,492 (1.4%) had a hospitalization during follow up. The pediatric comorbidity index consisted of 24 conditions and achieved a c-statistic of 0.718 (95% CI: 0.714-0.723). The strongest predictors were diagnosis of malignancy (OR=4.06), epilepsy (OR=3.65), or diabetes mellitus (OR=3.36) in the previous year. C-statistics among age subgroups were as follows: 0.689 (95% CI: 0.674-0.695) for <6 years, 0.705 (95% CI: 0.694-0.715) for 6-11 years, 0.718 (95% CI: 0.712-0.723) for 12-18 years. The index outperformed adult comorbidity scores (Charlson index c-statistic: 0.568, 95% CI: 0.564-0.571; Elixhauser score c-statistic: 0.522, 95% CI: 0.517-0.527). Performance was similar after adapting the index to ICD-9-CM (c-statistic: 0.704, 95% CI: 0.701-0.706).

Conclusions: We propose a pediatric comorbidity index that provides a summary measure of underlying health status and can be used for risk adjustment in pediatric studies conducted in healthcare databases.

2558 | Assessment of parents knowledge attitude and practice towards vaccines that are not covered under expanded program on immunization in India

Juny Sebastian, Rechitha Mary Mathews, Haritha Gopal and Ashmy Jose
JSS College of Pharmacy, Mysuru, India

Background: Vaccines are safe, simple and one of the most cost-effective way to save the lives of children worldwide. In India emphasis is given to vaccines that are covered by the Expanded Program on Immunisation (EPI) even though India accounts for a large number of childhood deaths that can be prevented by proper utilisation of vaccines that are not covered by the EPI.

Objectives: To assess the knowledge, attitude and practice of parents towards Rotavirus, Pneumococcal, Influenza and Hepatitis A vaccines and to assess the factors contributing for non-vaccination.

Methods: A cross- sectional observational study using a validated questionnaire was conducted on parents of children between three to five years of age visiting the paediatric department of JSS Hospital, Mysuru. Median split method was used to classify the knowledge level to adequate or inadequate. Chi square test was used for the statistical analysis of the study.

Results: Out of 207 study participants, children of 97.58% parents were fully immunized according to the EPI schedule, but the non- EPI vaccine coverage was 22.34%. Among the study population, 41.88% of mothers and 63.82% fathers found to have inadequate knowledge of non-EPI vaccines and the study participants belong to upper socioeconomic

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

class demonstrated better knowledge (78.3%) whereas lower class demonstrated least (5.29%) knowledge. The higher rate of vaccination was observed with Hepatitis A (37.19%) followed by rotavirus vaccine (26.57%) among the vaccines under study. The knowledge level in the parents who have not vaccinated their children with non-EPI vaccines was found to be inadequate when compared with parents in the vaccinated group (76.36%). Lack of knowledge about non EPI vaccines (65.7%) among parents were the major constraint for not vaccinating their children. There was a significant association between the non-EPI vaccination coverage and urban residential area ($p<0.01$), having two or more kids ($p<0.05$), educational status of the parents($p<0.05$), socio-economic class of upper/upper lower/upper middle ($p<0.05$) and adequate knowledge on non-EPI vaccines($p<0.05$).

Conclusions: Most of the sampled parents were unaware of the non-EPI vaccines. As the parental knowledge, attitude and practice about non-EPI vaccines are important determining factors for the immunization status of their child, future efforts by providing education on non-EPI vaccines are required to improve the parents confidence on non-EPI vaccines and to decrease the non- EPI vaccine hesitancy.

2579 | Fluoroquinolone antibiotic exposure and risk of achilles tendon injury in adolescents in the United States 2000-2018

Rachael K. Ross[1], Jeffrey S. Gerber[2], Mackenzie M. Herzog[3], Michele Jonsson-Funk[1] and Alan C. Kinlaw[1]

[1]*University of North Carolina, Chapel Hill, NC;* [2]*Children's Hospital of Philadelphia, Philadelphia, PA;* [3]*IQVIA, Durham, NC*

Background: Fluoroquinolones, a class of broad-spectrum antibiotics, are associated with increased risk of Achilles tendon injury in adults. The only population-based study of this association in children was published 17 years ago.

Objectives: To estimate the 30-day risk difference of Achilles tendon injury associated with fluoroquinolone use compared to other broad-spectrum antibiotics among adolescents.

Methods: We conducted an active comparator, new user study using the IBM Watson Health MarketScan Commercial Claims and Encounters database 2000-2018. The cohort included children aged 12-18 years with prescription fills for fluoroquinolone or other broad-spectrum antibiotics (comparators) used for similar indications (amoxicillin-clavulanate, cefdinir, cefixime, nitrofurantoin, and sulfamethoxazole-trimethoprim). The outcome, Achilles tendon injury, was assessed using ICD-9/10 diagnosis codes and CPT codes for tendonitis, rupture, and surgical repair. We also assessed clavicle fracture as a negative control outcome, expecting it to be unassociated with fluoroquinolone exposure. Covariates, assessed in the 180 days prior to index fill, included demographics, indication, prior medication use, healthcare utilization, and comorbid conditions. We estimated risks standardized to population of fluoroquinolone users with bootstrapped 95% confidence intervals (CI), using the Kaplan-Meier cumulative incidence estimator and standardized mortality ratio weights.

Results: The cohort included 333,339 fluoroquinolone users and 3,481,109 users of comparator antibiotics. Fluoroquinolone users were older (median age 17 vs. 15) and more likely to be female (68% vs 57%) and have a urinary tract infection diagnosis (27% vs 9%). The standardized 30-day risk of Achilles tendon injury was 14.3 per 10,000 fluoroquinolone users (95% CI 10.5, 18.6) and 13.5 per 10,000 comparator users (95% CI 11.3, 16.0). The 30-day risk difference for fluoroquinolone use was 0.08 per 10,000 children (95% CI -0.35, 0.54). The risk of tendon injury was similar between exposure groups at multiple time points assessed up to 180 days after the index fill. The 30-day risk difference for clavicle fracture, the negative control outcome, was 0.11 (95% CI -0.33, 0.52).

Conclusions: We did not observe an association between fluoroquinolone use and increased risk of Achilles tendon injury compared to other antibiotics among adolescents. Regardless, given safety concerns about fluoroquinolones in adults and limited safety data in children, additional safety data to support evidence-based prescribing is needed.

2645 | Prevalence and effects of suicidal ideation diagnosis code position in claims on readmission rate estimates

Aram Babcock[1], Richard Moussa[2] and Vakaramoko Diaby[1]

[1]*University of Florida, Gainesville, FL;* [2]*Ecole Nationale Supérieure de Statistiques et d'Economie Appliquée, Abidjan, Côte D'Ivoire*

Background: Suicidal ideation (SI) is a major health concern in children, adolescents, and young adults (CAYA). Inaccurate estimates of SI-related hospital readmission rates may contribute to inappropriate allocation of resources for prevention of future readmission. The estimation of these readmission rates using claims data may be sensitive to the diagnosis code position used to establish analytic cohorts.

Objectives: The objectives of this research were to examine the prevalence (2010-2015) and effects of SI diagnosis code position on 30-day readmission rate estimates (2010) in a population of CAYA using the Nationwide Readmissions Database (NRD). Our null hypothesis (H_0) was that SI-related readmission rates are not sensitive to the diagnosis code position on the claim form, with the alternative (H_a) being that the readmission rates are sensitive to the diagnosis code position on the claim form.

Methods: We conducted a cross-sectional study using the NRD (2010-2015). We established six cohorts of hospitalized CAYA (5-24 years old) with diagnosis of SI based on different combinations of SI diagnosis code (ICD-9 code V62.84) positions in claims. The outcomes were the prevalence of SI and 30-day all-cause readmission rates following an SI discharge, reported per 100 and 1,000 discharges respectively. Prevalence of SI by year, quarter, and month was measured using frequency counts of SI diagnosis codes. Readmission was measured based on time between events of 30 days. Thirty-day hospital readmission rates following an index SI discharge were estimated for each cohort. Quarterly and monthly trends were assessed for seasonality using ANOVA. We tested the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

null hypothesis using a test for equality of proportions between the predefined SI cohorts.

Results: Prevalence of SI diagnosis codes increased yearly from 2.9% in 2010 to 5.8% in 2015. Quarterly (p=0.39) and monthly (p=0.35) trends were not significant. SI hospital readmission rates ranged from 0 to 41.1 per 1000 index events based on cohort definitions (i.e. diagnosis code positions). We rejected the null hypothesis that SI-related readmission rates are not sensitive to diagnosis code positions.

Conclusions: SI-related readmission rate estimates are sensitive to SI diagnosis code positions. Determining appropriate diagnostic positions can further improve readmission analyses for SI and its applications in healthcare policies.

3713 | Polypharmacy among hospitalized children in the capital region of Denmark

Thomas B. Jensen[1], Mia M. Nørgaard[1] and Jon T. Andersen[1,2]
[1]*Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark;*
[2]*University of Copenhagen, Copenhagen, Denmark*

Background: The prevalence of polypharmacy is increasing in both children and adults. The implications are not fully known, but it has amongst others been associated with drug-drug interactions, increased risk of adverse drug reactions, hospital admissions and increased costs. Previous studies have found the prevalence highly variable in terms of study design, patient population and time period.

Objectives: We therefore aimed to investigate the prevalence of polypharmacy in a Danish pediatric inpatient population.

Methods: Using the Danish National Patient Register we identified all children (between 1 and 17 years of age) hospitalized in the Capital Region of Denmark between January 1st, 2012 to May 15th, 2016. All in-hospital administrated drugs in the study period were identified from the administrative in-hospital drug use database in the Capital Region of Denmark. The register contains information on all in-hospital drug administrations on a personal level between January 1st, 2012 to May 15th, 2016 in the Capital Region of Denmark. Polypharmacy was defined as treatment with 5 or more drugs with different ATC-codes within the admission period.

Results: We identified 66,897 hospital admissions in the study period. The mean age of the hospitalized children was 8.3 years and 52.5 % were boys. The median number of admission days per admission was 2 (interquartile range [IQR] 2-4) and the median number of different drugs administrated per admission was 2 (IQR 0-5). 26.3 % of the children were treated with five or more different drugs during the admission. The prevalence of polypharmacy increased with age: 21.0 % (1-4 years), 23.5 % (5-8 years), 26.9 % (9-13 years) and 33.9 % (14-17 years). The most commonly administrated drug was acetaminophen (15.9 %).

Conclusions: Polypharmacy among hospitalized children within the Capital Region of Denmark is common and increases with age. Further investigation is warranted.

3752 | Association of antipsychotic medications with seizure in children and adolescent

Soo Min Jeon, Susan Park, Hae-Young Park, Sena An and Jin-Won Kwon
College of Pharmacy and Research Institute of Pharmaceutical Sciences, Kyungpook National University, Daegu, Republic of Korea

Background: Antipsychotics are the class of medications commonly prescribed to manage psychiatric disorder. Over past years, the prescription of antipsychotics was steadily increased with raising the number of psychiatric patients in pediatrics. The antipsychotics are well known to lower the seizure threshold and increase seizure, however, there is lack of empirical evidence in pediatric patients.

Objectives: We aimed to evaluate seizure risk in user of antipsychotics in Korea using a time-dependent approach in a large population based claim database.

Methods: We conducted a retrospective cohort study using the claims data of Health Insurance Review and Assessment (HIRA) from 2008-2018 in Korea. We identified the pediatric patients who prescribed antipsychotic medication, and the first date of prescription of antipsychotics was defined as index date. The main outcome was the incident of seizure, and they were followed until the incidence date of seizure, the year 21 years old or the end of follow-up. The exposure of antipsychotic medication was measured as time-dependent value for exposure status (non-user, user), average daily dose (in chlorpromazine equivalent dose) and polypharmacy (non-user, mono user and multiple user). We used a 1 month of interval time to code time-dependent measures. The association between antipsychotic use and seizure was analyzed using time-dependent Cox regression.

Results: There were 17,945 children and adolescent who initiated antipsychotic medication treatment, with a mean (SD) age of 13.3 (3.73) years and mean (SD) follow up of 4.79 (2.96) years. During follow-up, the period of antipsychotics use had significantly higher risk of seizure incidence compared with the period of non-use (HR 3.94, 95% CI 3.46 - 4.48). Moreover, we observed the intensified risk of seizure with increasing average daily dose (HR 1.83, 95% CI 1.67 - 2.02 for medium dose; HR 2.75, 95% CI 2.47- 3.05 for high dose). The risk of occurring seizure was significantly greater in multiple antipsychotics versus non user (HR 7.61, 95% CI 6.62-8.75 for multiple user; HR 3.17, 95% CI 2.77-3.61 for mono user).

Conclusions: This study demonstrated that current use, high dose and polypharmacy of antipsychotics were associated with developing seizure in pediatric patients with psychiatric disease. Therefore, clinicians should carefully consider the risk of seizure when starting treatments with antipsychotics in children and adolescents.

3839 | Safety data collection and risk management in paediatric clinical trials: Literature review of points to consider during protocol development

Beate Aurich
Robert Debré Hospital, Paris, France

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Protocol development for paediatric clinical trials takes the specificities of the study population into account (e.g. pharmacokinetics, reference values). Drug safety and risk management for paediatric trials require an understanding of how these change throughout childhood and how adverse drug reactions (ADRs) present clinically in children.

Objectives: The objectives were to review and summarise the literature providing practical information on how the paediatric drug safety profile informs age group specific safety data collection and risk management in clinical trials.

Methods: Pubmed, Embase, regulatory authority (RA) and learned society (CIOMS, WHO) websites were searched for publications up to 31/12/2019 for children (0-18 years). In addition, the bibliography of included publications was reviewed.

Results: RAs and learned societies provided general and disease specific guidance for paediatric trials with certain sections relating to drug safety. No full text publication was identified describing the practicalities of how the paediatric drug safety profile informs the various sections of a protocol. The existing literature was summarised providing an overview of how the paediatric safety profile supports the development of a paediatric protocol. For example, laboratory values in the exclusion criteria and safety monitoring sections need to be adjusted for age. Vital sign and developmental assessments should be done at least at baseline, trial completion and follow-up.

Conclusions: Safety related protocol sections for paediatric clinical trials are based on the population specific safety profile of the study drug. This review provides an overview of the practical aspects of paediatric drug safety during protocol development.

3873 | Impact of bronchiolitis guidelines publication on primary care prescriptions in Italian children

Elisa Barbieri[1], Carlo Giaquinto[1], Antonio Scamarcia[2], Luigi Cantarutti[2] and Daniele Donà[1]

[1]University of Padova, Padova, Italy; [2]Pedianet Project, Padova, Italy

Background: In the Italian contest two clinical practice guidelines for the diagnosis and treatment of bronchiolitis were published in October 2014 and in December 2015 the first endorsed by numerous scientific societies and the second by Italian NHS. In primary care setting both guidelines recommend supportive care instead of β2-agonists bronchodilators, inhaled corticosteroids and antibiotics.

Objectives: We aimed to determine guidelines impact on prescriptions.

Methods: This retrospective interrupted time series (ITS) analysis assessed the changes in quarterly prescriptions prevalence for bronchiolitis in non-premature (>37 gestational weeks) previously healthy children before and after the two guidelines publication from December 2012 to December 2018 (pre, in-between and post periods). A seasonally adjust quasi-poisson method stratified by age class (0-3, 4-6, 7-12 months; 1-14 years) was used for the ITS. Significance was defined with $p<0.05$. Prescriptions prevalence in the three periods was described as percentages. Data regarding diagnosis, prescriptions and clinical history were retrieved from Pedianet, a pediatric primary healthcare database with more than 261 472 children enrolled through Italy. Diagnosis were retrieved searching ICD9-CM codes (466.1x) and free text fields, manually validated and aggregated to form a bronchiolitis episode (BE) within 30-days gap after the first visit. Antibiotics, β2-agonist bronchodilators and corticosteroids were grouped based on ATC codes (J01x, R03Ax, R03BAx H02x).

Results: In total, 1 528 children (median age (SD) = 5 (0-115) months) received 3 766 prescriptions for 1 661 BE (median = 3.3 prescriptions/BE-treated). In the pre-period 66.9% (658/984) of BE were treated compared to 69.6% (160/239) and 57.5% (257/447) in the in-between- and post-period. Children received antibiotics in more than 30% of BE reaching a peak of 45% (26/58) and 52% (24/46) in the in-between period in children <3 and >12 months. β2-agonists prescriptions varied from 45% (441/658) in the pre-period to 33% (147/257) in the post-period with the highest variation in children <3 months (from 36% (98/270) to 19% (24/126)). Glucocorticoids (inhalants) prescriptions had the highest variation after 2015 guidelines publication especially in older children. ITS did not show any significant variation caused by either of the two guidelines publication in all age groups.

Conclusions: Our results confirmed unnecessary prescribing in primary care setting with no changes after both guidelines publication. The impossibility to validate the clinical diagnosis might represent a limitation.

3887 | Data mining for adverse events of tumor necrosis factor-alpha inhibitors in pediatric patients - A tree-based and tree-temporal scan statistics analysis of Danish nationwide health data

Viktor Wintzell[1], Henrik Svanström[1], Mads Melbye[2], Jonas F. Ludvigsson[1], Björn Pasternak[1] and Martin Kulldorff[3]

[1]Karolinska Institutet, Stockholm, Sweden; [2]Statens Serum Institut, Copenhagen, Denmark; [3]Harvard Medical School and Brigham and Women's Hospital, Boston, MA

Background: Tumor necrosis factor alpha (TNF-α) inhibitors are efficacious and considered generally safe in adults. However, the pediatric-specific safety evidence is scarce.

Objectives: To screen for signals of previously unknown adverse events of TNF-α inhibitors in pediatric patients.

Methods: We conducted a data mining study based on nationwide Danish health care register data, 2004-2016. From a cohort of all pediatric patients (<18 yrs) with confirmed juvenile idiopathic arthritis (n=4,425) or inflammatory bowel disease (n=3,196), we identified 1310 episodes of new TNF-α inhibitor use, which continued as long as the patient was on treatment (maximum 3 yrs). Mean follow-up was 1.0 yr. Two analyses were performed: first, a propensity score matched analysis where TNF-α inhibitor episodes were compared with no-use episodes; second, a self-controlled analysis of a large set of temporal risk windows during follow-up. We screened for signals of adverse events based on incident physician-assigned diagnosis

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

codes (ICD-10) from outpatient and inpatient visits in specialist care. Tree-based and tree-temporal scan statistics were used to identify events with unexpectedly high incidence (significance level: 5%). Diagnoses at all classification levels (cuts) were considered with adjustment for multiple testing and no risk windows were set a priori in the self-controlled analysis. Monte Carlo hypothesis testing was used to estimate p-values.

Results: Among TNF-α inhibitor users, mean age was 13.4 (SD 4.0) yrs, 41% were male, and 51% had JIA, 35% had Crohn's disease and 14% had ulcerative colitis or IBD-unclassified. The propensity score matched cohort was balanced on general potential confounders. We identified two signals of dermatologic complications that have been described previously in adults and children, including dermatitis and eczema (ICD-10 L20-30; risk difference 0.8%; p-value 0.025) and papulosquamous disorders (L40-45; risk difference 0.4%; p-value 0.024). A signal of psychiatric diagnosis adjustment disorders (F43; risk difference 0.9%; p-value 0.003), was likely associated with the underlying disease and its severity, rather than treatment. The self-controlled analysis generated no signals.

Conclusions: We identified no previously unknown adverse events of TNF-α inhibitors in pediatric patients, which is reassuring for patients and clinicians. The newly developed methods for adverse events data mining used in this study can play a particularly important role in pediatrics where safety data are scarce.

3934 | Association between proton pump inhibitor use and risk of fracture in children

Yun-Han Wang[1], Viktor Wintzell[1], Jonas F. Ludvigsson[1,2,3,4], Henrik Svanström[1,5] and Björn Pasternak[1,5]

[1]Karolinska Institutet, Stockholm, Sweden; [2]Örebro University Hospital, Örebro, Sweden; [3]University of Nottingham, Nottingham, United Kingdom; [4]Columbia University College of Physicians and Surgeons, New York, NY; [5]Statens Serum Institut, Copenhagen, Denmark

Background: Proton pump inhibitor (PPI) use has been linked to increased risk of fracture in adults. Despite an increasing trend in prescription of PPIs in children, there is scarce evidence regarding this safety concern in pediatric patients.

Objectives: To evaluate the association between PPI use and risk of fracture in children.

Methods: We conducted a nationwide register-based cohort study of children aged <18 years in Sweden between July, 2006 to December, 2016. The analyzed cohort included 115,933 pairs of PPI initiators and non-initiators matched on propensity score and age. Cox regression was used to estimate hazard ratios (HRs) for a first fracture of any type and 5 subtypes of fracture with follow-up up to 5 years. To address potential residual confounding, high-dimensional propensity score-matching and a direct comparison with histamine-2-receptor antagonists (H2RA) were performed.

Results: During mean 2.2 (standard deviation 1.6) years of follow-up, 5,354 and 4,568 cases of any fracture occurred among PPI initiators and non-initiators, respectively (20.2 versus 18.3 events per 1000 person-years; HR, 1.11; 95%CI, 1.06-1.15). PPI was associated with increased risk of upper limb fracture (HR, 1.08; 95%CI, 1.03-1.13), lower limb fracture (HR, 1.19; 95%CI, 1.10-1.29), other fracture (HR, 1.51; 95%CI, 1.16-1.97) but not head fracture (HR, 0.93; 95%CI, 0.76-1.13) and spine fracture (HR, 1.31; 95%CI, 0.95-1.81). The HRs for fracture according to cumulative duration of PPI use were 1.08 (95%CI, 1.03-1.13) for ≤30 days, 1.14 (95% CI, 1.09-1.20) for 31-364 days and 1.34 (95% CI, 1.13-1.58) ≥365 days. The association was consistent in most sensitivity analyses, including high-dimensional propensity score-matching (HR, 1.10; 95% CI, 1.06-1.15), although the analysis of PPI vs H_2RA did not reach statistical significance (HR, 1.06; 95%CI, 0.97-1.15).

Conclusions: In this large pediatric cohort, PPI use was associated with a small but statistically significant increased risk of any fracture. Risk of fracture should be taken into account when weighing the benefits and risks of PPI treatment in children.

3998 | Predictors of opioid analgesic utilization in children and adolescents with active asthma

Abhishek Nair[1], Harold J Farber[2,3], Mark L. Fleming[4] and Hua Chen[1]

[1]University of Houston College of Pharmacy, Houston, TX; [2]Baylor College of Medicine and Texas Children's Hospital, Houston, TX; [3]Texas Children's Health Plan, Houston, TX; [4]University of North Texas Health Science Center, Fort Worth, TX

Background: CDC guidelines and FDA warnings have reduced the rate of opioid prescriptions in the United States over the years, yet little is known regarding opioid prescribing in the overall pediatric population and those with asthma.

Objectives: The objective of the study was to identify the predictors and risk factors associated with opioid analgesic use in children and adolescents with active asthma.

Methods: The 2013-2018 medical and pharmacy claims data along with provider and practice characteristics obtained from a large pediatric Medicaid Managed Care Plan was analyzed. Eligible children included those who were ≤ 18 years of age; received either incident opioid or non-opioid analgesics after at least one year washout period without receiving these medications and had active asthma defined as having both asthma diagnosis and anti-asthmatic medication during 12 months baseline period. Guided by Andersen Behavioral Model, a multivariable logistic regression was conducted to identify patient, prescriber, and practice setting level predictors associated with opioid utilization in children and adolescents with asthma.

Results: Out of 9,529 children and adolescents with active asthma 2,681 (28.1%) received an opioid and 6,848 (71.9%) received non-opioid analgesic. Children prescribed opioids compared to those prescribed non-opioids were older [10.3±4.8 vs 7.2±4.2 years]. Vast majority 2,582 (96.3%) of patients received their anti-asthmatic prescription and opioid prescription from different prescribers who worked in various care settings. As compared to those who only had

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

encounters at primary care, receiving care from Surgical facilities [AOR: 226.1; 135.0-376.6], Dentists [AOR: 18.01; 14.8-21.9], Emergency Medicine providers [AOR: 10.9; 9.0-13.4] were strong predictors of receipt of an opioid prescription. Receiving analgesics from a prescriber who previously prescribed anti-asthmatic medications to the patient was strongly associated with receipt of non-opioid analgesics [AOR: 0.12; 0.10-0.15]. The likelihood of receiving opioid vs. non opioid analgesics was not associated with asthma severity measured as asthma risk score [AOR: 0.99; 0.94-1.03].

Conclusions: Results indicate that care setting and prescriber specialties were the primary predictors of receipt of an opioid analgesic in children and adolescents with active asthma. Most opioid prescriptions for children with asthma were provided by surgical specialists or Emergency Medicine providers.

4010 | The recording and incidence of thyroiditis in girls' primary care medical Spanish records

Belén Castillo Cano, Mar Martín-Pérez, Dolores Montero Corominas and Elisa Martín Merino

Spanish Agency for Medicines and Medical Devices (AEMPS), Madrid, Spain

Background: The frequency of thyroiditis among girls in Spain is not known.

Objectives: We aimed to estimate the incidence of thyroiditis in the Spanish Primary Care Database For Pharmacoepidemiological Research (BIFAP).

Methods: In this observational study, girls in BIFAP aged 9-18 years between 2002-2016, with primary care (PC) medical records for ≥1 year and free of thyroiditis, were included. Individuals were followed up until there was an ICPC/ICD-9 code indicating thyroiditis, they reached 19 years of age or left, or died, or the study ended. Anonymized PC clinical profiles were reviewed to retrieve diagnosis confirmatory information (endocrinologist discharge letter or free-text comments mentioning it) or discarding information (negative test results, alternative diagnosis or reference to family history) in a random sample. We used the date of first (anti-)thyroid hormones or propranolol prescription or medical comments linked to thyroiditis (the earliest of both) as the thyroiditis onset. The incidence rate of thyroiditis (IR; overall and by year) per 10^5 girls-years, both overall and by calendar periods (2002-2005 and 2007-2016), was estimated after correcting by the proportion of expected discarded cases.

Results: In total, 480,169 girls were identified who met the initial inclusion criteria, of which 641 had a recorded thyroiditis (autoimmune thyroiditis [N=346]; other [N=17] or unspecified aetiology [N=278]. Among the 98 profiles reviewed (15.3%), 60.2% (N=59) were confirmed thyroiditis cases (regardless the aetiology), 32.7% (N=32) were possible and 7.1% (N=7) were discarded. Overall, 64 had treatment or comment before the recording of thyroiditis (range 5 days to 11.49 years). The IR was 20.83 confirmed thyroiditis cases per 10^5 girls-years, increasing up to $32.12/10^5$ when possible thyroiditis were included. The IR was highest among girls aged 13-14 years (30.28 and 46.45 per 10^5 girls-years, respectively). The IR was 16.28 and 20.93 during 2002-2005 and 21.17 and 33.78 during 2007-2016 for confirmed and confirmed plus possible cases respectively.

Conclusions: In primary care clinical profiles, more than half of the recorded thyroiditis among girls included written evidence to confirm the diagnosis, while a third had only the thyroiditis record without additional evidence. That information allowed estimating the incidence of thyroiditis among girls attending public primary care setting in Spain. The incidence of thyroiditis peaked among aged 13-14 years and increased over time.

4012 | Evolution of medication exposure in children, from prenatal life until two years of age, between 2010 and 2015: A study conducted in the POMME cohort

Justine Benevent[1], Caroline Hurault-Delarue[2], Mélanie Araujo[2], Agnès Sommet[3], Isabelle Lacroix[2] and Christine Damase-Michel[1]

[1]INSERM 1027, University Hospital, Toulouse, France; [2]INSERM 1027, Hospital, Toulouse, France; [3]INSERM 1027, University Hospital, CIC INSERM 1436, Toulouse, France

Background: Drug utilization studies in children are sparse and many recommendations were made in pediatrics in the 2010s.

Objectives: To describe the evolution, between 2010 and 2015, of children medication exposure, from prenatal life until the age of two.

Methods: We conducted a descriptive study using the POMME cohort (PrescriptiOn-Médicaments-Mères-Enfants). Children born in Haute-Garonne (south west France), over a 1-year period (from 1 July to 30 June), are registered in POMME in 2010 (POMME-2010) and in 2015 (POMME-2015). Data included i) medications prescribed and reimbursed to children and to their mothers during pregnancy and ii) health certificates at birth, 9 and 24 months.

Results: POMME-2010 and POMME-2015 include respectively 8372 and 10459 children. On average, children in 2015 were exposed to less medications during both prenatal life and childhood than in 2010 (10.2±6.4 versus 8.7±5.5 and 26.7±9.1 versus 20.3 ±8.1 respectively). For each ATC class, percentages of exposed children were lower in 2015 than in 2010. The 3 ATC classes the children were mostly exposed to were: i) anti-infective (99.2% of the children in 2010 and 97.3% in 2015), ii) alimentary tract (98.8% and 91.3%) and iii) respiratory system (92.1% and 83.3%). Vaccination coverage decreased between 2010 and 2015: 97% of the child were prescribed the Diphtheria-Pertussis-Tetanus-Poliomyelitis vaccine in 2010 versus 86% in 2015 and 88% were prescribed the Measles-Mumps-Rubella vaccine in 2010 versus 81% in 2015. Among medications that have been recently contraindicated under 2 years in France, the most significant prescription decreases were observed with codein (6.6% in 2010 versus 0.1% in 2015) and oxomemazin (5.4% and 2.3%).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: This is the first study describing medication exposure in children considering prenatal life and infancy as a continuum. It highlights a decrease in medication prescriptions between 2010 and 2015. The decline in vaccination coverage is of concern.

4467 | Antibiotic consumption in asthmatic and non-asthmatic children: A national cohort study

Florentia Kaguelidou[1], Aya Ajrouche[2], Veronique Houdouin[3], Sylvie Guillo[2], Isabelle Naiim[3], Yann de Rycke[2] and Florence Tubach[2]
[1]*Centre d'Investigations Cliniques, INSERM CIC1425, Hôpital Robert Debré, APHP; Université de Paris, Paris, France;* [2]*Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP. Sorbonne Université, Hôpital Pitié Salpêtrière, Département de Santé Publique, Centre de Pharmacoépidémiologie (Cephepi), CIC-1901, Paris, France;* [3]*Service de Pneumologie Allergologie et CRCM Pédiatrique, Hôpital Robert Debré, APHP; Université de Paris, Paris, France*

Background: Antibiotic therapy is not recommended in the treatment of viral-induced asthma exacerbations involving cough, fever and wheeze, however use of antibiotics is common in children.
Objectives: The objective of this study was to compare the use and type of antibiotics in children with and without asthma.
Methods: This is a retrospective cohort study performed between January 2013 and December 2017 using the EGB (*Echantillon Généraliste de Bénéficiaires*) which is the 1/97th random permanent representative sample of the French national healthcare insurance system database (SNDS). Claims data for all individuals aged from 5 to 18 years' old were retrieved. Children were defined as asthmatic when delivered at least 2 different classes of antiasthmatic drug (R03) over 12 consecutive months and without any delivery in the previous 24 months, and were subsequently matched to 4 non-asthmatic controls on age, sex and area of residence. The rate of antibiotic use during the 2 years following matching was compared between asthmatic and non-asthmatic children using an adjusted Poisson regression model.
Results: Overall, 4,380 asthmatic children were matched to 17,497 non-asthmatic controls. Asthmatic children had a lower socio-economic status and have had more medical consultations and hospitalizations in the year preceeding the matching than the controls. During the 2 years of follow-up, asthmatic children were more likely to receive antibiotics with a relative risk (RR) of 1.66 [95%CI 1.60-1.72] for any antibiotic use, a RR of 1.82 [1.75-1.91] for antibiotics indicated in respiratory tract infections and a RR of 1.83 [1.75-1.91] for wide-spectrum antibiotics. Most frequently prescribed antibiotic was amoxicillin in both asthmatic and non-asthmatic children.
Conclusions: Asthmatic children and adolescents are being prescribed antibiotics more frequently than their non-asthmatic peers. This clinical practice may have a significant public health impact as incidence of the disease is known to be increasing.

4504 | Recent trends in the prevalence of pediatric and neonatal venous thromboembolism in Portugal and the United States

Stephen E. Schachterle[1,2], Sophie Shen[3], Charles Wentworth[1], Prethibha George[1], Jenna Jones[4], Syd Phillips[5], Jill Dreyfus[4], Teresa Davis[4], Anthony Nunes[6], John D. Seeger[6], Sarah MacDonald[5] and James Revkin[1]
[1]*Pfizer, New York, NY;* [2]*City University of New York, New York, NY;* [3]*BMS, Princeton, NJ;* [4]*Premier Inc, Charlotte, NC;* [5]*IQVIA, Durham, NC;* [6]*Optum, Waltham, MA*

Background: Venous thromboembolism (VTE) is rare in pediatric and neonatal populations compared to adults. Information from prior to 2010 had suggested that VTE was increasing in these young patients, but more recent data were not available.
Objectives: We aimed to estimate the annual period prevalence of VTE in pediatric and neonatal patients and to search for trends and potential hospital clusters in the distribution of VTE.
Methods: VTE period prevalence was estimated with annual cross-sectional data. In the US, Optum Insurance Claims (2005-2018), Optum Electronic Health Record (EHR) (2009-2016) and Premier Healthcare Database hospital records (2006-2017) were used. A non US dataset, the Portuguese IASIST Hospital data set (2014-2017) from IQVIA was added to compliment the US based data. The VTE period prevalence in the pediatric populations was estimated as the mean annual period prevalence across multiple years. Patients were stratified by age including those under 28 days (i.e. neonates), 28 days to under 2 years, 2 years to under 12 years, and 12 to under 18 years (i.e. pediatric patients). A prevalent VTE was defined as a record of a VTE diagnosis codes during a hospitalization and denominators were based on the number of patients at midyear for the insurance claims and EMR data or the number of hospitalized patients in the hospital data. The distribution of VTE prevalence was analyzed with chi-square tests and tests for linear trends.
Results: Among all ages, the average annual period prevalence ranged from 1.09 (N_{VTE} = 3,784) to 0.92 (N_{VTE} = 3,317) per 10,000 in the Optum claims and EHR and from 7.66 (N_{VTE} = 366) to 6.68 (N_{VTE} = 8,434) in the Portuguese and US hospital data, respectively. In each of the data source, neonates comprised a lower proportion of prevalent VTE events (4.64% - 14.48%) than any one of the other pediatric age groups (16.12% - 51.72%) but in the US the neonatal population experienced a sustained increase in the prevalence of VTE over time ($p < 0.01$). In the US hospital data, at least one VTE was identified in 147 of 877 total hospitals and half of all VTEs were diagnosed in just 13 hospitals.
Conclusions: Neonatal VTE continues to rise but remains less prevalent than VTE in older pediatric age groups, which was evident in multiple databases. Prevalence estimates from hospital-based data were higher than insurance claims and EHR data which may be attributable to underlying disease in the hospitalized populations. The majority of pediatric VTE appear to be diagnosed in relatively few US hospitals, suggesting future interventions may be focused on the institutions that treat these patients most frequently.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4508 | Epidemiology of heart failure with preserved ejection fraction in pediatric population with obesity

Ayad K. Ali
Eli Lilly and Company, Indianapolis, IN

Background: More than half of adult patients with cardiac dysfunction have heart failure with preserved ejection fraction (HFpEF), i.e., diastolic variant. There is a causal relationship between obesity and HFpEF that is well characterized in adult population.

Objectives: To characterize the epidemiology of HFpEF in obese pediatric patients in the US.

Methods: Between 2004 and 2019, an analysis of the IBM® MarketScan® administrative claims database was conducted to calculate the period prevalence rate (per 100 people) and cumulative incidence rate (per 100,000 person-years) of HFpEF among children (<18 years old) with obesity. Rates were stratified by age, sex, and type 2 diabetes mellitus (T2DM) status. Children with congenital heart disease (CHD) were excluded from the analysis. Obesity, HFpEF, T2DM, and CHD were defined by corresponding ICD-9/10-CM diagnosis codes.

Results: During the analysis period, about 2 million obese children without CHD were identified (representing 11.8% of all obese general population in the database). The prevalence and incidence rates of HFpEF among obese children without CHD were 0.02 and 0.19 (95% CI=0.13-0.27), respectively; compared to corresponding rates in obese adults: 2.5 and 44.8 (95%CI=44.5-45.1). Compared to younger children, those aged >12 had higher HFpEF rates: <5 years old (prevalence, 0.01; incidence, 0.18 [95%CI=0.04-0.53]); 5-12 years old (prevalence, 0.01; incidence, 0.15 [95%CI=0.07-0.24]); and 13-17 years old (prevalence, 0.03; incidence, 0.27 [95%CI=0.13-0.41]). There was no difference in the prevalence of HFpEF between sexes; however, higher incidence rates were observed among boys than girls (prevalence, 0.02 each sex; incidence, 0.25 in boys vs. 0.16 in girls). About 1.4% of obese children without CHD were diagnosed with T2DM during the analysis period, with HFpEF prevalence and incidence rates of 0.14 and 0.43 (95% CI=0.09-1.26), respectively. Among obese children with T2DM, those aged 5-12 years had lower prevalence and higher incidence of HFpEF compared to older age group (prevalence, 0.1 vs. 0.2; incidence, 0.55 vs. 0.35). The condition was more prevalent among boys with obesity and T2DM than girls (0.2 vs. 0.1).

Conclusions: While HFpEF in pediatric population with obesity appears to be rare, children with coexisting obesity and T2DM have higher prevalence and incidence rates compared to general pediatric population with obesity.

4511 | Life-course pharmaceutical phthalate exposure and pediatric cancer incidence: A Danish nationwide cohort study

Thomas P. Ahern[1], Logan G. Spector[2], Per Damkier[3], Sinna P. Ulrichsen[4], Buket Ozturk[4], Katrine Eriksen[4], Henrik Toft Sorensen[4] and Deirdre P. Cronin-Fenton[4]

[1]*University of Vermont, Burlington, VT;* [2]*University of Minnesota, Minneapolis, MN;* [3]*University of Southern Denmark, Odense, Denmark;* [4]*Aarhus University, Aarhus, Denmark*

Background: Phthalates are plasticizing agents added to pharmaceutical formulations when a delayed release of the active ingredient is required. Some phthalates are endocrine disruptors and may interfere with fetal development and promote cancer. Their association with pediatric cancer risk is unknown.

Objectives: To estimate associations between *in utero* and childhood phthalate exposure through medication ingestion and the incidence of overall and site-specific pediatric cancer.

Methods: We queried a Danish Medicines Agency database to characterize the phthalate content of drugs marketed in Denmark since 1995. We merged this with the Danish National Prescription Registry to measure phthalate exposure in a cohort of all live births between 1997-2017. Exposure was positive if a prescription was filled for a phthalate-containing pharmaceutical product; *in utero* exposures considered prescriptions filled for birth mothers and childhood exposures considered prescriptions filled for the children. Children were followed from birth until age 18 for incidence of any cancer, ascertained with the Danish Cancer Registry through January 1, 2018. *In utero* and childhood exposures were modeled as separate terms in Cox models of time to first cancer diagnosis; patients were censored upon death or emigration.

Results: Our cohort included 1.28 million children, among whom 100,677 (7.9%) were exposed to a phthalate. Most exposures were to hydroxypropyl methylcellulose phthalate (HPMCP; n=92,429) and diethyl phthalate (DEP; n=30,356). Exposure was more common earlier in the study; otherwise exposed and unexposed were similar on birth factors (singleton/multiple, natal sex, gestational age, and birth weight) and maternal factors (age at delivery, mode of delivery, pre-pregnancy BMI, parity, and smoking status). Children exposed to phthalates had approximately the same rate of any cancer diagnosis as unexposed children ($HR_{gestational}$=0.80, 95% CI: 0.60, 1.2; $HR_{childhood}$=1.2, 95% CI: 1.0, 1.4). Associations between *in utero* exposure to any phthalate and specific cancers were near-null. Most associations between childhood exposure to any phthalate and specific cancers were near-null, with the exception of lymphoma ($HR_{childhood}$=1.5, 95% CI: 1.0, 2.3) and osteosarcoma ($HR_{childhood}$=2.2, 95% CI: 1.3, 3.9).

Conclusions: While our overall results indicate no positive association between phthalate exposure during pregnancy or childhood and combined childhood cancer incidence, positive associations with lymphoma and osteosarcoma warrant follow-up.

4570 | Signal detection of suspected drug-induced liver injury in children using the FDA adverse event reporting system (FAERS) database

Hailong Li and Lingli Zhang
Department of Pharmacy/Evidence-Based Pharmacy Center, West China Second Hospital, Sichuan University, Chengdu, China

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Drug-induced liver injury is one of the main reasons for drug withdrawal, but very little is known about drug-induced liver injury in children.

Objectives: To identify drugs are potentially associated with reports of suspected liver injury in pediatric population using FDA Adverse Event Reporting System (FAERS) Database.

Methods: We conducted case by non-case disproportionality analysis to detect the suspected liver injury related adverse drug reactions in the population <18 years old. Using FAERS database, we identified the reports of suspected liver injury as cases from January 2004 to December 2019. Proportional reporting ratio (PRR) was calculated to assess the association between drug and suspected hepatic ADRs. A positive signal was defined as PRR at least two, chi-squared of at least four, and three or more cases. Subgroup analyses were performed in the following age categories: 0-1 month, 0-2, 3-11 and 12-17 years.

Results: Overall, 1,423 (0.01%) out of 7,582,465 ADR records pediatric population concerned hepatic injury. Most of the reported liver injuries concerned children aged 12-17 years. 645 Drugs with reports of suspected liver injury were identified. 23 positive drug-liver injury associations were detected, including antituberculosis drugs (pyrazinamide, ethambutol, isoniazid, amikacin, and rifampin), which are already known.

Conclusions: Drug-induced liver injury is infrequently reported (only 0.01% of total) as a suspected ADR in children and adolescents. The drugs associated with reported hepatotoxicity (paracetamol, antiepileptic and anti-tuberculosis agents) are known to be hepatotoxic in adults as well, but age related changes in associations were observed. FAERS is useful as a start to plan further drug safety studies in children.

4714 | The relationship between psychotropic use and community-based measures among children in foster care

Laura M. Bozzi, Pinky Shah, O'Mareen Spence and Susan dosReis
University of Maryland School of Pharmacy, Baltimore, MD

Background: Community-level factors account for variation in psychotropic treatment. However, among youth in foster care, with relatively high prevalence of psychotropic medication use, limited evidence exists to determine if community-based performance measures impact psychotropic medication use.

Objectives: To evaluate the association between psychotropic medication use and community-based performance measures among children in foster care in one US state.

Methods: This study integrated data from child welfare records, Medicaid medical and pharmacy, and community-based measures from Kids Count and the US Census. The population included children age 5-18 years in foster care in 2014 from one US state. Community-based performance measures included education (4-year high school graduation and drop-out rates; eighth-grade reading and math proficiency), juvenile justice arrest rate, and socioeconomic status (supplemental nutrition assistance program [SNAP] participation), which were assessed at the local county jurisdiction. K-means cluster analysis was used to address multicollinearity among the community measures and cluster jurisdictions with similar community-based performance measures. We defined any psychotropic medication use, the dependent variable, as ≥1 antipsychotic, antidepressant, stimulant, mood stabilizer, sedative/hypnotic, or anxiolytic. A logistic regression model examined the association between any psychotropic medication use and community performance cluster, adjusting for age, gender, race, any psychiatric diagnosis, psychotherapy use, number of days in foster care, and number of foster care placements.

Results: The 4,334 children in foster care were predominantly female (51%), black (63%), with 264 mean days in foster care (SD: 127 days) and had on average 2 different foster placements in the year. Three clusters were identified as high, medium and low performance. The cluster with high performance had a 92% graduation rate, 4% juvenile justice involvement, and 13% SNAP use. The cluster with low performance measures had a 70% graduation rate, 7% juvenile justice involvement, and 43% SNAP use. Psychotropic prevalence was 48%, 53%, and 33% in high, medium, and low performance clusters, respectively. Relative to low, high (OR: 1.82, 95% CI: 1.51-2.20) and medium (OR: 1.97, 95% CI: 1.65-2.35) performance clusters were more likely to use psychotropic medication.

Conclusions: Low performance areas had lower psychotropic prevalence among children in foster care. It is possible that low education and socioeconomic status contribute to treatment access barriers.

4760 | Real world use of posaconazole in pediatric populations: A review of published literature

Nicole Cossrow[1], Alexandria Kachurak[1], Yun-Ping Zhou[2], Havilland Campbell[3], Deborah D. Brown[2] and Hetty Waskin[3]
[1]*Merck Sharp & Dohme Corp., West Point, PA;* [2]*Merck Sharp & Dohme Corp., North Wales, PA;* [3]*Merck Sharp & Dohme Corp., Rahway, NJ*

Background: Posaconazole (POS), approved in 2005, is indicated for treatment and prevention of invasive fungal infections (IFIs) in patients ≥13y. Pediatric patients are susceptible to IFI and evidence from literature indicates POS is used to treat or prevent IFIs in pediatric patients.

Objectives: The purpose of this systematic literature review (SLR) was to determine the use, safety and effectiveness of POS in patients <18y, in real-world settings.

Methods: A SLR of English language publications from 2005 to 2019 was conducted, for approved formulations of POS. An Embase search strategy identified 580 articles with key words 'posaconazole' and 'pediatric' (including 'pediatric', 'child', 'adolescent', 'infant' OR 'newborn'). Per Populations, Interventions, Comparators, Outcomes, Study design (PICOS) criteria, publications were selected if they included pediatric patients (0-18 y), POS use, and were observational. Comparators were not required; outcomes included safety, mortality and IFI. Case reports were excluded. Using these criteria, 115 publications were flagged for full review and extraction. After extractions, 23 unique publications were selected for inclusion.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Studies ranged from n=4 to 878 patients, with a majority having fewer than 100. Most patients were male. All studies included adolescents (13-18y) and children (2-12y). Eleven studies included patients younger than 2y. Eleven studies reported use of oral suspension, six reported use of delayed release tablet and four reported use of IV formulation. POS was commonly used in the refractory disease or secondary prophylaxis setting (n= 13 studies), rarely as first line therapy (especially in the years soon after approval of POS) and often in combination with other antifungals. While commonly used in pediatric patients receiving chemotherapy or stem cell transplant, interestingly, POS was used as treatment in CF patients and demonstrated improved lung function (n=3 studies). Duration of POS use ranged from 2 to 1117 days. Reported AEs were minor or moderate and included nausea, vomiting and abdominal pain. POS was well tolerated and there were few discontinuations. Death attributed to IFI while on POS was reported in one study. Most studies reported no breakthrough or progression of IFI while on POS treatment or prophylaxis.

Conclusions: This SLR, which included a heterogeneous group of small observational studies published in the last 10 years, demonstrates that POS is used off label in pediatric patients. Per this SLR, use of POS appears to be safe and effective for the treatment or prevention of IFI in patients 0 to 18y, regardless of formulation.

4766 | Comparative effectiveness of diuretics and inhaled corticosteroids for evolving bronchopulmonary dysplasia in preterm infants

Jonathan L. Slaughter[1,2], Mark A. Klebanoff[1,2] and Erinn M. Hade[2]
[1]*Nationwide Children's Hospital, Columbus, OH;* [2]*The Ohio State University, Columbus, OH*

Background: Treating preterm infants with diuretics and inhaled corticosteroids (ICS) is common for both evolving and established bronchopulmonary dysplasia (BPD). However, the effectiveness of these medications in reducing mortality or improving BPD-related outcomes is unclear.

Objectives: Our objective in this investigation was to utilize "real-world" patient data to determine whether diuretic and ICS treatments for evolving BPD in preterm infants, from 10-27 days postnatal, reduce the risk of mortality or severity of BPD at 36-weeks postmenstrual age (PMA), as compared to no treatment.

Methods: Our retrospective cohort included <28-weeks birth gestation preterm infants within the 2006-2016 Pediatric Health Information System (PHIS) (administrative database; freestanding US Children's Hospitals), who were admitted by postnatal day 1, survived at least 10-days, and were determined to have evolving BPD, as defined by an oxygen requirement or positive pressure dependence at postnatal day 10. Our composite primary outcome was mortality or persistent oxygen or positive pressure dependence [i.e. moderate or severe BPD] at 36-weeks PMA (primary BPD-related outcome in most randomized trials due to competing risks between mortality and BPD). We fit two separate models, one for diuretics and another for ICS exposure. Only infants without prior diuretic or inhaled steroid exposure at day 10 were included (new-users). We adjusted for fixed demographics (sex, insurance, race/ethnicity, gestation, hospital volume, birth year and time varying confounders (previous diuretic or ICS treatment, ventilation status and type) via marginal structural models. PHIS billing data allowed determination of medication administration and respiratory support by each hospital day between postnatal days 10-27 and at 36-weeks PMA (BPD outcome).

Results: Of 11,949 included patients with evolving BPD at 10 days postnatal, 4220 (35.3%) were ever treated with diuretics and 4240 (35.5%) were ever treated with ICS between postnatal days 10-27. 5925 (49.6%) died (806 deaths) or developed moderate or severe BPD by 36-weeks PMA. After adjusting for fixed demographics and time varying confounders, the associated risk of mortality or BPD at 36-weeks PMA was 0.81 (adjusted risk ratio [aRR]) (95% CI: 0.66-1.00) following diuretic exposure and 0.82 (aRR) (95% CI: 0.66-1.01) following ICS.

Conclusions: Diuretic and ICS exposure between days 10-27 were associated with a 19% and 18% reduction, respectively, in the risk of death or BPD at 36-weeks PMA among infants with evolving BPD at postnatal day 10.

4790 | Antipsychotic medication use among hospitalized infants using inpatient data in FDA's sentinel system

Mayura Shinde[1], Candace Fuller[1], Rong Tilney[1], Austin Cosgrove[1], Jason Hickok[2], Russell Poland[3], Karla Miller[3], Crystal Garcia[1], Corinne Woods[4] and Andrew Mosholder[4]
[1]*Harvard Medical School and Harvard Pilgrim HealthCare, Boston, MA;* [2]*Ondine Biomedical Inc., Bothell, WA;* [3]*HCA Healthcare, Nashville, TN;* [4]*United States Food and Drug Administration, Silver Spring, MD*

Background: The extent of antipsychotic (AP) use among infants admitted to neonatal intensive care units (NICUs) is unknown. A recent case report described use of APs to treat delirium in infants admitted to NICUs, but no observational studies have examined AP utilization among hospitalized infants.

Objectives: To quantify the frequency of typical and atypical AP administrations among hospitalized infants.

Methods: We identified typical and atypical AP administrations in hospitalized infants using inpatient data from one Sentinel Data Partner (DP) from 7/1/2011 - 9/30/2017. Inpatient electronic pharmacy data from 175 facilities during the study period was available. We included infants <6 months of age on admission with a length of stay (LOS) of >3 days. We identified typical and atypical APs through mapping hospital-specific drug mnemonics at each facility and using National Drug Codes (NDC). We examined demographics (e.g., age, sex), hospitalization characteristics (e.g., admission year, LOS) and NICU level of facilities in which infants were hospitalized. We also examined duration of AP use and frequency of administration during inpatient stays.

Results: We identified 29 hospitalized infants with AP administrations among the 482,053 infant hospitalizations during the study period,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

representing a rate of 6.02 per 100,000 inpatient stays. All 29 infants received typical AP, but 3 also received atypical AP. Only four out of 120 facilities reported AP administration to hospitalized infants, of which two facilities were level III and two were level IV NICUs. We observed a longer median LOS among infants with AP than among all hospitalized infants (114 days vs 4 days). Infants were administered typical AP for a median duration of 4 days (range 1, 63 days) and atypical AP for median duration of 18 days (range 2, 43 days) during the inpatient stay. Haloperidol was the most commonly administered AP (n=23, 79%). The median frequency of AP administration was 5 (range 1, 160).

Conclusions: Overall, AP administration among hospitalized infants was rare. This is one of the first assessments for AP use among infants using inpatient electronic data from the Sentinel System. Our findings are limited to only four facilities that noted AP use in infants. Future work may include assessment of indications for use and adverse effects and explore the extent of AP administrations in infants across other hospital networks in the US. This abstract reflects the views of the authors and should not be construed to represent the views or policies of the FDA or any affiliated entity.

4796 | Antipsychotics use and weight gain in children compared to adults: Analysis of spontaneous adverse drug reaction reports

Florentia Kaguelidou[1], Zaba Lieber[1], Francois Montastruc[2], Genevieve Durrieu[2], Jean-Marc Treluyer[3] and Laurent Chouchana[3]

[1]Centre d'Investigations Cliniques, INSERM CIC1426, Hôpital Robert Debré, APHP; Université de Paris, Paris, France; [2]Service de Pharmacologie Médicale et Clinique, Centre Midi-Pyrénées de PharmacoVigilance, de Pharmacoépidémiologie et d'Informations sur les Médicaments, INSERM UMR 1027, CIC 1436, Centre Hospitalier Universitaire et Faculté de Médecine, Toulouse, France; [3]Centre Régional de Pharmacovigilance, Hôpital Cochin, AP-HP, EA7323 « Evaluation Thérapeutique et Pharmacologie Périnatale et Pédiatrique », Université de Paris, Paris, France

Background: Weight gain and obesity are common adverse effects of antipsychotics (APs). Besides a well-known morbidity, obesity has also negative social effects particularly in children.

Objectives: We aimed to assess AP-induced weight gain in pediatrics compared to adults.

Methods: In a case-non case study using the WHO global database of individual case safety reports (ICSRs), VigiBase®, we evaluated the existence of disproportionality in weight gain reporting under antipsychotic treatment in pediatric compared to adult patients. All ICSRs with an AP (ATC N05A) reported as 'suspect' or 'interacting' drug, were retrieved for children (2-11 years), adolescents (12-17 years) and adults (18-64 years). Disproportionality of weight gain reporting was evaluated using the reporting odds ratio (ROR) with corresponding 95% confidence intervals (95%CI). Analysis was adjusted for sex, reporting country, year of notification, reporter qualification and concomitant use of antidepressants (ADs).

Results: A total of 306,807 ICSRs reported with an AP were retrieved: 7,679 (2.5%) in children, 15,272 (5%) in adolescents and 283,856 (92.5%) in adults. Most ICSRs concerned male patients (54%) and were reported by health professionals (56%) in North America (40%) or Europe (35%). Concomitant use of ADs was reported in 19% of ICSRs. In children, 1,570 (20%) of ICSRs reported weight gain, 1,862 (12%) in adolescents and 14,707 (5.2%) in adults. Disproportionality of weight gain reporting associated with APs was found in children (ROR: 4.7 [95%CI 4.44-4.98]; aROR 3.2 [95%CI 2.99-3.41]) and in adolescents (crude ROR: 2.54 [95%CI 2.41-2.67]; adjusted ROR: 2.23 [95%CI 2.1-2.35]) and compared to adults.

Conclusions: Children and adolescents are at higher risk of reported weight gain under APs than adults. Since use of APs in the pediatric population is increasing, weight gain under treatment should be closely monitored and prevented in order to limit any adverse impact in adulthood, mainly cardiovascular morbidity and mortality.

4890 | Stopping medicines for inactive juvenile idiopathic arthritis: What do patients and families consider?

Daniel B. Horton[1], Jomaira Salas[1], Aleksandra Wec[2], Pooja Kapadia[1], Timothy Beukelman[3], Alexis D. Boneparth[4], Jaime Guzman[5], Ky Haverkamp[6], Melanie Kohlheim[7], Melissa L. Mannion[3], Lakshmi N. Moorthy[1], Elizabeth Stringer[8], Lori Tucker[5], Sarah Ringold[9] and Marsha Rosenthal[1]

[1]Rutgers University, New Brunswick, NJ; [2]Mathematica Policy Research, Princeton, NJ; [3]University of Alabama at Birmingham, Birmingham, AL; [4]Columbia University Medical Center, New York, NY; [5]British Columbia Children's Hospital, University of British Columbia, Vancouver, BC, Canada; [6]University of Washington School of Medicine, Seattle, WA; [7]Pediatric Rheumatology Care and Outcomes Improvement Network, Cincinnati, OH; [8]IWK Health Centre, Dalhousie University, Halifax, NS, Canada; [9]Seattle Children's Hospital, Seattle, WA

Background: Limited evidence guides clinical decision-making around stopping drugs for well-controlled JIA. These decisions are, thus, heavily influenced by the preferences of clinicians, patients, and caregivers.

Objectives: To study the trade-offs that patients and caregivers consider when deciding to stop JIA treatments.

Methods: From June 2017 to February 2018, we conducted an anonymous online survey of patients with JIA ages 13 and older and caregivers recruited via clinics, social media, and email. Survey questions focused on factors that might influence decisions about stopping JIA treatment. We used factor analysis to identify key themes and logistic regression to identify factors associated with respondents' agreement with doctors' hypothetical recommendations to withdraw or continue treatment.

Results: 1456 individuals opened the survey and 839 (58%) completed it, including 782 eligible participants (40 patients age 13-17, 120 patients age 18+, and 622 caregivers). Most participants were from the US (94%) and had used systemic anti-rheumatic medicines

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(92%). We identified 7 key factors important in making decisions about stopping treatment. Among patients and caregivers, damage from JIA was the most highly ranked factor in deciding whether to stop treatment; groups differed in how they prioritized other factors, such as drug-related harms, trust in physicians, and drug cost and access. High levels of trust in physicians corresponded with greater agreement with physicians' recommendations to withdraw or continue treatment (adjusted odds ratio [aOR] 2.3-5.4). Those most concerned about disease flare or treatment-related harms were less likely to agree with recommendations to withdraw treatment (aOR 0.4, 95% CI 0.2, 0.5) or continue treatment (aOR 0.7, 95% CI 0.5, 0.9), respectively. After adjustment for other factors, patients and caregivers did not appreciably differ in their likelihood to agree with recommendations. Limitations included a low response rate, self-reported data, and generalizability of study participants to other populations.

Conclusions: Among survey respondents, JIA-related damage was the top consideration in deciding whether to stop treatments for well-controlled JIA, but patients and caregivers prioritized other factors differently. Those expressing greater trust in physicians were more likely to agree with treatment recommendations, whereas strong concerns about disease flare or treatment corresponded with risk-averse decision-making. These findings can help inform shared decision-making around describing medicines for well-controlled JIA.

5006 | Irrational treatment of childhood diarrhoea among internally displaced persons in Maiduguri, Northeast Nigeria

Sulayman Tunde Balogun[1], Aisha Grema Mustapha[1], Kenneth O. Okon[2], Ayodele O. Akanmu[1], Leonard M. Paul[1] and Olufunke A. Sodipo[1]

[1]*University of Maiduguri, Maiduguri, Nigeria;* [2]*Federal Medical Centre, Makurdi, Nigeria*

Background: Protracted armed conflict in Northeast Nigeria has displaced millions of people who found shelters in internally displaced persons (IDPs) camps. Poor resources coupled with over population at the camps promote childhood diarrhoea (CD). Prompt and effective treatments are essential to the survival of the children.

Objectives: The study assessed the incidence, causes and treatment of CD among IDPs in Maiduguri, Northeast Nigeria.

Methods: Between 2018 and 2019, 173 symptomatic IDPs were screened in the health facilities at three IDPs camps in Maiduguri and 51 with diarrhoea or history of diarrhoea were enrolled into the study following an informed consent. Demographic data and faecal samples were collected and analyzed by microscopy and culture to determine the aetiology of the CD. Medication data were extracted from the prescription given to the subjects at the facilities.

Results: CD incidence among the screened subjects was 29.5% (51/173). Mean age (± standard deviation) of the 51 subjects with CD was 2.7 (±2.2) years; 39.2% (20/51) and 60.8% (31/51) were females and males, respectively. Diarrhoea (100.0%), abdominal ache (47.0%), fever (35.9%), vomiting (21.5%), weight loss (13.4%), malnutrition (11.8%), headache (8.1%) and conjunctivitis (3.9%) were the symptoms presented by the subjects. *E. coli* (68.6%; 35/51), *Shigella spp*. (11.8%; 6/51), *A. lumbricoides* (17.6%; 9/51), *H. nana* (5.9%; 3/51), *G. lamblia* (3.9%; 2/51) and *S. strongyloides* (9.8%; 5/51) were diagnosed as the CD causative agents. The subjects were given supportive therapies with oral rehydration solution (60.8%; 31/51), zinc sulphate (11.8%; 6/51) and macronutrient (13.7%; 7/51). In addition, they received albendazole (21.6%; 11/51), amoxycillin (9.8%; 5/51), gentamicin (5.9%; 3/51), metronidazole (43.1%; 22/51) and paracetamol (23.5%; 12/51). Meanwhile, only 29.3% (12/41) of subjects with bacterial CD and 47.1% (8/17) of subjects with helminthic CD received antibacterial and anthelmintic therapies, respectively. Similarly, 11 subjects who did not require antibacterial therapy were given antibacterials.

Conclusions: CD of microbial aetiology is common among IDPs in Maiduguri and supportive therapies are given in line with WHO recommendation. However, irrational antimicrobial medications are common largely due to lack of pre-treatment laboratory investigations. This is of public health concern in region devastated by poor resources and armed conflict among other challenges.

Pharmacovigilance -> Cancer

28 | Drug related problems & its associated factors among breast cancer patients at University of Gondar comprehensive specialized hospital, Ethiopia

Amsalu Defersha[1] and Kassu Kebede[2]

[1]*United States International University-Africa, School of Pharmacy and Health Sciences, Nairobi, Kenya;* [2]*University of Gondar, College of Medicine and Health Sciences, School of Pharmacy, Department of Clinical Pharmacy, Gondar, Ethiopia*

Background: Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women worldwide. If untreated and undetected at the early stage, it causes death by spreading to distant organs. Despite various studies suggesting the high prevalence of drug related problems (DRPs) among cancer patients, there was a paucity of data regarding the problems among breast cancer patients in our setting.

Objectives: Hence, this study was aimed to assess DRPs among patients with breast cancer at the Oncology Unit of University of Gondar Comprehensive Specialized Hospital.

Methods: A retrospective cross-sectional study was conducted at the Oncology Unit of University of Gondar Comprehensive Specialized Hospital. The data were collected by retrospective reviewing of medical records of 107 breast cancer patients. The data entry and analysis were done using SPSS version 20.0 statistical software. Descriptive statistics such as percent and frequency were used to summarize categorical variables of patients' characteristics. Univariable and multivariable binary logistic regression analyses were used to investigate the potential predictors of DRPs. A p-value of ≤0.05 was considered statistically significant.

Results: A total of 203 DRPs were identified from 76 breast cancer patients, translating to a prevalence of 71.03%. Among the DRPs

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

identified, adverse drug reaction (48.6%), need for additional drug therapy (45.8%) and non-adherence (32.7) were the most prevalent. In the multivariable analysis, breast cancer patients who had concurrent co-morbidities were almost three times (AOR=2.97, p=0.05) more likely to experience DRPs as compared to those patients without co-morbidity. Moreover, those patients who had been treated with neoadjuvant chemotherapeutic regimens were 0.35 times less likely (COR= 0.35, p=0.05) to have DRPs as compared to patients treated with adjuvant chemotherapy regimens.

Conclusions: The prevalence of DRPs was high in our setting. Adverse drug reactions, non-adherence and the need for additional drug therapy were the most frequently occurred DRPs in the study setting. Neoadjuvant chemotherapy and the presence of co-morbidities were significant predictors of DRPs among breast cancer patients.

2328 | Time to onset analysis of letrozole associated osteonecrosis of jaw in FDA adverse event reporting system (FAERS) database

Subeesh Kulangara Viswam[1], Neha Reddy[1], Nair Gouri[1], Minnikanti Satya Sai[1], Radhika Kunnavil[2] and Eswaran Maheswari[1]
[1]*M.S. Ramaiah University of Applied Science, Bangalore, India;* [2]*Ramaiah Medical College, Bangalore, India*

Background: Our study aimed to refine the potential signal of letrozole associated osteonecrosis of jaw which we identified in a previous study using disproportionality analysis (proportional reporting ratio of 13.1). As the signal identified from spontaneous reporting database known to have confounding factors, it is important to refine and reconfirm the signal using an alternate analytical method.

Objectives: To analyze the association between letrozole and osteonecrosis of jaw using time to onset analysis

Methods: A systematic data mining was performed in FAERS Database (Q4/2003-Q3/2019) using OpenVigil 2.1, a pharmacovigilance analytical tool. Cumulative incidences of osteonecrosis of jaw was assessed using the Kaplan-Meier method and Log-rank test was used to compare the cumulative incidences of osteonecrosis of jaw between patients treated with letrozole and those treated with all the other drugs. Time-to-onset profiles were analyzed using the Weibull shape parameter test. A larger value of scale parameter stretches the distribution, whereas a smaller value shrinks the distribution. If the drug and event are not associated, the distribution tend to have a larger value of scale parameter. shape parameter <1, ~1 and >1, the hazard was considered to have early failure-type profile, random failure type profile and wear-out failure-type profile respectively. Shape and scale parameter of letrozole were also compared with all the other drugs reported for osteonecrosis of jaw.

Results: We identified 15,178 reports for osteonecrosis of jaw, of which 448 (3%) were attributed to letrozole. The median time-to-onset of osteonecrosis of jaw associated with letrozole was 266(range: 88-850) days. Reports of patients treated with other drugs showed a shorter time-to-onset, 122.5 days (range: 28.25-470.5). Letrozole associated osteonecrosis of jaw indicated a wear-out failure-type profile and the time to onset data are more widely distributed which is unlikely for an onset time data (shape:1.2, scale:50.2). In contrast, all other drugs associated osteonecrosis of jaw reports indicated an early failure-type profile (shape: 0.4, scale: 5.5). The cumulative incidence of osteonecrosis of jaw did not significantly differ between patients treated with letrozole vs other drugs (log-rank test, $P < 0.08$).

Conclusions: Our study suggests that the initial signal generated for letrozole associated osteonecrosis of jaw in FAERS database was a false positive. Time to onset analysis can be used as a measure to identify false signals.

2401 | Evaluation of spontaneous adverse event reports for kidney injury attributed to atezolizumab within the FDA adverse events reporting system

Ola Zaafan
Alexandria University, Alexandria, Egypt

Background: Atezolizumab is the first approved member of the immune checkpoint inhibitors in the treatment of several cancer types, kidney injury is listed in the side effects however less is known about its incidence in post marketing use.

Objectives: To describe and evaluate spontaneous adverse event reports of kidney injury attributed to atezolizumab.

Methods: The published database quarterly files starting from the first quarter of 2017 till the third quarter of 2019 were queried for reports listing kidney injury attributed to atezolizumab administration as the primary suspected drug. We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR).

Results: We identified 1,587,133 FAERS reports in the period between January 2017 and September 2019: 3,974 (0.25%) reports mentioned atezolizumab. There were 46,153 (2.91%) kidney injury reports during the same period of which 232 (0.5%) were attributed to atezolizumab administration. The PRR and ROR were as following: PRR: 2.01, 95% CI: 1.78 - 2.28, ROR: 2.08, 95% CI: 1.82-2.37.

Conclusions: Although FAERS is subject to many limitations such as under reporting, the results suggest that atezolizumab is associated with higher risk of kidney injury which needs further studies to confirm or deny this claim.

2403 | Evaluation of spontaneous adverse event reports for anaemia attributed to atezolizumab within the FDA adverse events reporting system

Ola Zaafan
Alexandria University, Alexandria, Egypt

Background: Atezolizumab is the first approved member of the immune checkpoint inhibitors in the treatment of several cancer types, anaemia is listed in the side effects however less is known about its incidence in post marketing use.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To describe and evaluate spontaneous adverse event reports of anaemia attributed to atezolizumab.

Methods: The published database quarterly files starting from the first quarter of 2017 till the third quarter of 2019 were queried for reports listing anaemia attributed to atezolizumab administration as the primary suspected drug. We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR).

Results: We identified 1,587,133 FAERS reports in the period between January 2017 and September 2019: 3,974 (0.25%) reports mentioned atezolizumab. There were 22,480 (1.42%) anaemia reports during the same period of which 115 (0.51%) were attributed to atezolizumab administration. The PRR and ROR were as following: PRR: 2.05, 95% CI: 1.71 - 2.45, ROR: 2.08, 95% CI: 1.73-2.50.

Conclusions: Although FAERS is subject to many limitations such as under reporting, the results suggest that atezolizumab is associated with higher risk of anaemia which needs further studies to confirm or deny this claim.

2436 | Pharmacovigilance cohort study of osteonecrosis of the jaw and serious infection among cancer patients treated with denosumab or zoledronic acid in Denmark, Norway, and Sweden

Vera Ehrenstein[1], Uffe Heide-Jørgensen[1], Morten Schiødt[2], Olof Akre[3], Bente B. Herlofson[4], Svein Hansen[5], Cecilia Larsson Wexell[6], Sven Erik Nørholt[1], Steinar Tretli[5], Anders Kjellman[3], Henrik T. Sørensen[1], Anthony Glennane[7] and Kimberly Lowe[7]

[1]Aarhus University Hospital, Aarhus, Denmark; [2]Rigshospitalet, Copenhagen, Denmark; [3]Karolinska University Hospital, Stockholm, Sweden; [4]University of Oslo, Oslo, Norway; [5]Cancer Registry of Norway, Oslo, Norway; [6]Skane University Hospital, Lund, Sweden; [7]Center for Observational Research, Amgen Inc, Thousand Oaks, CA

Background: Denosumab 120 mg subcutaneously every 4 weeks has been approved since 2011 and is currentlyindicated for prevention of skeletal-related events (SRE) in adults with malignancies involving bone. Osteonecrosis of the jaw (ONJ) is a known adverse event of antiresorptive treatment. Serious infection is an essential concern in patients with advanced cancer.

Objectives: The objective was to estimate, in routine clinical practice, 5-year incidence proportions (IPs) of ONJ and 3-year IPs of serious infection in cancer patients initiating denosumabor zoledronic acid (ZA) for SRE prevention. Incidence rates (IRs)/100 person-years of the two events were estimated to account for differential follow-up.

Methods: This Scandinavian cohort study was conducted among cancer patients initiating denosumab or ZA for SRE prevention, from 1-Oct-2011 through 2013 in Sweden and Norway, and through2014 in Denmark. We defined denosumab and ZA inception cohorts as treatment-naïve patients, and a denosumab-switch cohort as patients switching to denosumab after a maximum of 24 monthly cancer doses of bisphosphonates. Follow up was for up to 5 years until death, event of interest, switch, emigration or 31-Dec-2018. All ONJ cases were confirmed by an adjudication committee. Serious infection was defined, using routinely collected data, by primary discharge diagnoses during an inpatient stay.

Results: 2,877 patients were included in the analysis: 1,340 in the denosumab inception cohort (73%men, median age 70 years, median follow-up 19.8 months); 1,352 in the ZA inception cohort (54% men, median age 69 years, median follow-up 12.9 months);and 408 in the denosumab-switch cohort (48% men, median age 70 years, median follow-up 13.3 months). Crude 5-year IPs(95% confidence interval [CI]) of ONJ were 5.7% (4.4, 7.3) in the denosumab inception cohort, 1.4% (0.8, 2.3) in the ZA inception cohort, and 6.6% (4.2,10.0) in the denosumab-switch cohort. The corresponding IRs were 3.0 (2.3, 3.7), 1.0 (0.6, 1.5), and 4.3(2.8, 6.3). Crude 3-year IPs(95% CI) of serious infection were 28.9% (26.5, 31.4) in the denosumab inception cohort, 22.5% (20.3, 24.8) in the ZA inception cohort, and 22.8%(18.8, 27.2) in the denosumab-switch cohort. The corresponding IRs were 17.3 (15.7,19.1), 16.8 (15.0, 18.8), and 16.7 (13.6, 20.4).

Conclusions: 5-year IPs ONJ were 5.7%, 1.4% and 6.6% in the denosumab inception, ZA inception, and denosumab-switch cohort. The respective 3-year IPs of serious infection were 28.9%, 22.5%, and 22.8%. patients' characteristics varied by treatment cohort.

2560 | Assessing the risk of non-melanoma skin cancer associated with hydrochlorothiazide use in hypertensive patients: A nested case-control study in Korea

Bora Yeon, Ahyoung Suh, Eunmi Choi, Bonggi Kim, Soon Young Han and Soo Yeon Chung

Korea Institute of Drug Safety and Risk Management, Anyang-si, Gyeonggi-do, Republic of Korea

Background: Hydrochlorothiazide (HCTZ) is one of the most frequently prescribed antihypertensive drugs. There have recently been safety issues associated with the use of HCTZ and skin cancer.

Objectives: To evaluate the association between HCTZ use and the risk of non-melanoma skin cancer (NMSC) in patients with hypertension.

Methods: We performed a nested case-control study using the National Health Insurance claim data from 2002 to 2017. As an initial cohort, we included the patients with hypertensive disorder (defined by ICD-10: I10-I15) older than 30 years, and excluded the patients with diagnosed NMSC (ICD-10: C44) or prescribed HCTZ for one year prior to first diagnosis of hypertension (entry date). We identified patients (case) who diagnosed with NMSC during 2008-2017 in the cohort. For each case, we used risk-set sampling and randomly matched 4 population controls by same sex, age and entry date. We excluded those who were diagnosed with cancer or HIV and those prescribed immunosuppressants before first diagnosis of NMSC (index date). HCTZ use considered from entry date to 2 years prior to the index date. Using conditional logistic regression models, we computed the odds ratio (OR) for the association of NMSC with HCTZ use adjusted for the potential confounders. In addition, we conducted the subgroup analysis on the risk of developing NMSC based on HCTZ cumulative dose and long-term use.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: We identified 10,565 NMSC patients with matched 42,260 controls and among them, HCTZ users were 4,098(38.8%) and 15,984 (37.8%), respectively. There was no statistically significant associated with the use of HCTZ and the risk of NMSC (OR: 1.02, 95% CI: 0.98-1.07). As a result of analyzing the cumulative dose and long-term use of HCTZ, we found no statistically differences.

Conclusions: HCTZ use is not associated with an increased risk of non-melanoma skin cancer in Korean people. However, additional studies are needed to confirm the association between HCTZ and non-melanoma skin cancer, as previous studies in Asian populations are limited. Also, healthcare professionals should be aware of NMSC risk associated with HCTZ among Caucasian population and regularly monitor if suspicious skin lesion occurs.

3801 | Vascular endothelial growth factor tyrosine kinase inhibitors and the risk of aortic dissection: A pharmacovigilance analysis

Michael Dörks[1], Kathrin Jobski[1], Falk Hoffmann[1] and Antonios Douros[2,3,4]

[1]*Carl von Ossietzky University Oldenburg, Oldenburg, Germany;*
[2]*Department of Medicine, McGill University, Montreal, QC, Canada;*
[3]*Department of Epidemiology, McGill University, Montreal, QC, Canada;*
[4]*Charité – Universitätsmedizin Berlin, Berlin, Germany*

Background: Vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) target angiogenesis in several tumors and have shown good efficacy in randomized controlled trials. However, there are ongoing concerns about their risk of aortic dissection, an often fatal adverse effect, with the underlying mechanism possibly involving a subacute elevation of blood pressure (BP). To date, data on this potential association are scarce.

Objectives: To assess whether there is an association between use of VEGF TKIs and risk of aortic dissection, thereby examining the potential role of BP.

Methods: We queried the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database from the third quarter of 2004 (first report including a VEGF TKI) to the third quarter of 2019 for reports including VEGF TKIs as 'primary suspect' drug. The study outcome was defined using the Medical Dictionary for Regulatory Activities terms 'aortic dissection', and 'aortic dissection rupture'. The primary analysis estimated age- and sex-adjusted reporting odds ratios (ROR) and 95% confidence intervals (CIs) of aortic dissection associated with overall VEGF TKI use. In secondary analyses we assessed the risk of aortic dissection reporting separately for VEGF TKIs strongly increasing BP (>10 mmHg in systolic or diastolic BP; axitinib, sunitinib) and VEGF TKIs moderately increasing BP (<10 mmHg in systolic and diastolic BP; cabozantinib, pazopanib, sorafenib), as well as in patients with and without hypertension.

Results: Overall, 11,014,781 cases (6,395,662 with valid information on age and sex) were submitted to FAERS during the study period, with 3049 of those referring to aortic dissection. There were 102 reports of aortic dissection involving VEGF TKIs, mostly sunitinib (43; 42%) and sorafenib (21; 21%). VEGF TKIs were associated with an increased risk of aortic dissection (ROR, 4.31; 95% CI, 3.43 to 5.42), with the median time-to-onset being 89.5 days (interquartile range: 15 to 393 days). The increase in the risk was higher for VEGF TKIs strongly increasing BP (ROR, 5.33; 95% CI, 3.88 to 7.32) than with VEGF TKIs moderately increasing BP (ROR, 2.79; 95% CI, 1.83 to 4.27). The risk was similar between patients with hypertension (ROR, 5.21; 95% CI, 2.88 to 9.41) and those without (ROR, 4.27; 95% CI, 3.34 to 5.47).

Conclusions: Our pharmacovigilance analysis showed an increased risk of aortic dissection reporting associated with VEGF TKIs. The strength of BP elevation rather than underlying hypertension seems to be involved in the pathophysiology of this adverse effect.

3899 | Prevalence of cancer chemotherapy related problems among breast cancer patients at a specialty hospital in Ethiopia

Amsalu Defersha[1] and Kassu Kebede[2]

[1]*United States International University-Africa, Nairobi, Kenya;*
[2]*University of Gondar, Gondar, Ethiopia*

Background: A drug-related problem is defined as an event involving drug therapy that has the potential to interfere with the desired health outcomes. Despite various studies suggesting the high prevalence of drug-related problems among cancer patients, there was a paucity of data regarding the problems among breast cancer patients.

Objectives: To assess the prevalence and types of drug-related problems and associated factors among patients with breast cancer at the speciality Hospital.

Methods: A cross-sectional study was conducted at the speciality Hospital. The data were collected by review of medical records of 107 breast cancer patients from January- June 2018. Relevant information about each patient such as socio-demographic characteristics, types of co-morbidity, treatment regimen, hormone receptor status, adverse drug reactions and rate of adherence were recorded. Three oncology pharmacists were involved in the data collection after proper training of the data collection tools. The data collection tool was designed after reviewing different studies. The adequacy of the was defined using the European Society for Medical Oncology practice guideline of breast cancer. Univariable and multivariable binary logistic regression analyses were used to investigate the potential predictors of DRPs. Data were analysed using SPSS.

Results: A total of 203 drug related problems were identified in 76 breast cancer patients, translating to a prevalence of 71.03%. Among the drug related problems identified, adverse drug reaction (48.6%), need for additional drug therapy (45.8%) and patients' non-adherence (32.7) were the most prevalent. Of these, nine co-morbidities diagnosed, anemia was the most frequently occurring co-morbidity among the study participants. The least frequently occurred comorbidities were tuberculosis and retroviral infection each appearing only in two patients. In the multivariable analysis, breast

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

cancer patients who had anemia as a concurrent co-morbidity were almost three times (AOR=2.97, p=0.05) more likely to experience drug related problems as compared to those patients without anemia after adjusting for age. Moreover, those patients who had been treated with neoadjuvant chemotherapeutic regimens were 0.35 times less likely (COR= 0.35, p=0.05) to have drug related problems as compared to patients treated with adjuvant chemotherapy regimens.

Conclusions: The prevalence of drug-related problems was high in our setting. Therefore, appropriate pharmacist's intervention was required among breast cancer patients in the study setting.

3965 | Use of methotrexate and risk of skin cancer: A nationwide case-control study

Sam Polesie[1,2], Martin Gillstedt[1,2], Sigrún Alba Jóhannesdóttir Schmidt[3], Alexander Egeberg[4,5], Anton Pottegård[6] and Kasper Bruun Kristensen[6]

[1]University of Gothenburg, Gothenburg, Sweden; [2]Sahlgrenska University Hospital, Gothenburg, Sweden; [3]Aarhus University Hospital, Aarhus, Denmark; [4]Herlev and Gentofte Hospital, Copenhagen, Denmark; [5]University of Copenhagen, Copenhagen, Denmark; [6]University of Southern Denmark, Odense, Denmark

Background: Despite being introduced over seventy years ago, methotrexate (MTX) remains an important anti-inflammatory and immunosuppressive drug in the treatment of immune-mediated inflammatory diseases. MTX use has been suspected of increasing the risk of skin cancer, including cutaneous malignant melanoma (CMM), cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC).

Objectives: To examine the association between MTX use and risk of BCC, cSCC and CMM.

Methods: We conducted a nationwide Danish case-control study. As cases, we identified incident, histologically-verified BCC, cSCC, or CMM from 2004 through 2015. Population controls were sex- and age-matched to cases (20:1) using risk-set sampling. We computed crude and adjusted odds ratios (ORs) for BCC, cSCC, and CMM associated with MTX use using conditional logistic regression, adjusting for comorbidity, use of photosensitizing and immunosuppressive agents, and educational level. We defined the main exposure as a cumulative MTX dose of ≥ 2.5 g with never-users as reference in all analyses. We evaluated dose-response patterns modeling dose as an ordinal variable and as a continuous variable using restricted cubic splines.

Results: We identified 70,093 cases of BCC, 9499 cases of cSCC, and 18,799 cases of CMM. Use of MTX (≥ 2.5 g) was associated with increased risks of BCC and cSCC: ORs (95% confidence interval) 1.3 (1.2-1.5) and 1.9 (1.5-2.3), respectively. ORs increased with higher cumulative doses, e.g. use of < 1.25 g MTX showed an OR of 1.1 (1.0-1.2) for BCC and 0.9 (0.7-1.2) for cSCC compared with > 7.5 g MTX with ORs of 1.3 (1.1 - 1.6) for BCC and 1.9 (1.3-3.0) for cSCC. There was no effect measure modification by the presumed indication for MTX (psoriasis or rheumatoid arthritis). A weak association was observed between MTX and CMM with an OR of 1.2 (0.9-1.5) and no evidence of a dose-response pattern. The findings were robust in sensitivity analyses, including restriction to new users of MTX, applying different lag-periods, and with inclusion of patients with a history of other cancers.

Conclusions: We observed an increased risk of BCC and cSCC associated with use of MTX with evidence of a dose-response pattern. The association was most striking for cSCC, which could suggest that the photosensitizing properties of MTX is involved in carcinogenesis. There was limited evidence of an association with CMM.

4168 | Use of ranitidine and risk of bladder cancer

Mette Nørgaard[1], Uffe Heide-Jørgensen[1], Rune Erichsen[1], Lars Pedersen[1], Judy Rees[2], Margaret R. Karagas[2] and Henrik T. Sørensen[1]

[1]Aarhus University Hospital, Aarhus N, Denmark; [2]Geisel School of Medicine at Dartmouth, Lebanon, NH

Background: Almost half of all bladder cancers are attributed to smoking. Other risk factors include environmental or occupational exposure to carcinogens including N-nitrosamines. The H2-receptor antagonist, ranitidine, has been among the most widely used pharmaceuticals to treat gastroesophageal reflux disease and peptic ulcers. Ranitidine is an amine-based agent and production of nitrosodimethylamine through nitrosation of ranitidine can occur under stomach-relevant pH conditions. Use of ranitidine may thus lead to an increased risk of bladder cancer.

Objectives: To examine the risk of bladder cancer in new users of ranitidine compared with new users of other H2-receptor antagonists

Methods: We conducted a nationwide population-based cohort study using Danish medical databases. We identified all persons who filled their first prescription for an H2-receptor antagonist in the period 1996-2009 and had filled no prescription for proton pump inhibitors previously. We categorized first-time H2-receptor antagonists use as use of ranitidine or use of other H2-blockers. We followed these persons to end of 2017 for occurrence of non-invasive or invasive bladder cancer. Users of other H2-blockers who later filled a ranitidine prescription were censored with one year lag time. We computed cumulative incidence of bladder cancer by exposure status and compared ranitidine initiators with initiators of other H2-blockers using Cox proportional hazard analysis. We computed hazard ratios of bladder cancer overall and invasive and non-invasive tumors separately. We adjusted for age, sex, marital status, calendar time, presence of selected comorbidities at baseline, use of the following drugs at baseline: NSAIDS, thiazolidinediones, aspirin or other platelet inhibitors, and oral anticoagulants.

Results: We identified 66,940 new users of ranitidine and 223,094 new users of other H2-blockers. Baseline characteristics were similar between the two exposure groups. During a median follow-up of 15 years (IQR, 11-19) and 16 years (IQR, 11-20), respectively, we identified 450 bladder tumors in ranitidine users and 1,364 in users of other H2-receptor antagonists. The 10-year cumulative incidence of bladder cancer was 0.22% (95% CI, 0.18-0.25) in ranitidine users and 0.20% (95% CI, 0.18-0.21) in users of other H2-blockers. Adjusted

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

HRs were 1.01 (95% CI, 0.90-1.13) for any bladder tumor and 1.06 (95% CI, 0.91-1.22) for invasive cancers.

Conclusions: Compared with use of other H2-blockers, ranitidine use was unrelated to risk of bladder cancer. Thus in our study a routine clinical care setting, nitrosation of ranitidine did not appear to affect the occurrence of bladder cancer.

4284 | Checkpoint inhibitors and potential risks of acute vascular event: A case series

Hadir Aljohani, Eman Alghamdi, Waad Alghamdi and Fawaz Al-Harbi
Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: The immune-related toxicities of programmed cell death-1 (PD-1) checkpoint inhibitors including pembrolizumab, nivolumab, and Atezolizumab require immediate diagnosis and treatment, atherosclerotic lesions could be provoked by the immune system and may induce vascular complications such as ischemic heart disease (IHD), Deep vein thrombosis (DVT) and pulmonary embolism (PE).

Objectives: To examine the potential association between acute vascular events (AVEs) with the use of PD-1 inhibitors.

Methods: This is a descriptive case series assessment of AVEs associated with the use of PD-1 inhibitors. The search has been done in VigiBase (the WHO global individual case safety reports database) in December 2019, to retrieve reported cases between 1971 and 2018 using the terms 'pembrolizumab' OR 'nivolumab' OR 'atezolizumab' (substance (WHO Drug)) [AND] 'ischemic heart disease' OR 'pulmonary embolism' OR 'deep vein thrombosis'(reaction preferred term (PT) (MedDRA). All serious cases with a completeness score of 0.85 and above were included. The primary outcome is the development of AVEs following the use of PD-1 inhibitors, while the secondary outcome includes the occurrence of AVE during receiving anticoagulant prophylaxis. The causality assessment was done using the WHO-Uppsala Monitoring Center causality system. Microsoft Excel 2019 was used for performing the descriptive analysis.

Results: A total of 50 AVEs cases were included, all of them were serious, the most frequent reported AVEs was a pulmonary embolism (65%). Nivolumab was reported in 64% of cases, pembrolizumab in 30%, while atezolizumab reported in 6 % of all cases. Anticoagulation prophylaxis was used in 6 reported cases (20%). PE events were developed in 12% of patients with anticoagulant prophylaxis in comparison to 48% with no anticoagulation. Among all cases, DVT was reported with six patients while acute coronary syndrome was reported in only one patient. The majority of PE cases were found among lung cancer patients. The causality assessment of included cases showed that 42% of reported AVE events were possibly related to the suspected reported medication, while 14 % were unlikely related. Positive de-challenge was found in 14% of the reported cases, which has been assessed as probably related.

Conclusions: The results of this study show that a reasonable number of patients developed PE while using anticoagulation prophylaxis. The relation between AVEs and the use of PD-1 inhibitors were found to be possibly related in more than 40% of the cases. This may trigger the need for further investigations to confirm these results.

4307 | Vedolizumab associated haematochezia: A disproportionality analysis in USFDA adverse event reporting system database

Anusha Bellapu, Subeesh K. Viswam, Vasista Sharma and Stephy T. Chacko
M.S.Ramaiah University Of Applied Sciences, Bangalore, India

Background: Signal detection is one of the most advanced and emerging field in pharmacovigilance. It helps in early detection of adverse drug reactions. Vedolizumab is a humanized monoclonal antibody that binds to the $\alpha 4\beta 7$ integrin, which is a mediator of gastrointestinal inflammation approved by USFDA in 2014 for ulcerative colitis and crohn's disease. This study aims in the identification of events associated with vedolizumab using disproportionality analysis of the FDA Adverse Event Reporting System (FAERS).

Objectives: To identify the number of events of Haematochezia associated with vedolizumab using disproportionality analysis of the FDA Adverse Event Reporting System (FAERS).

Methods: Data were obtained from the public release of data in FAERS. Case/non-case method was adopted for the analysis of association between Vedolizumab use and Haematochezia. The data-mining algorithm used for the analysis were Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR). A value of ROR-1.96SE>, PRR≥2 were considered as positive signal.

Results: A total of 317 DEC's associated with vedolizumab use and haematochezia were reported. The mean age of the patients of vedolizumab associated events was found to be 54 years [95% CI: 36-59], nevertheless age was not mentioned in all the reports. The reports by gender were distributed with a male to female ratio of 1.25:1, though gender was not revealed in 40 reports. The data mining algorithms exhibited positive signal for haematochezia (PRR: 7.13, ROR: 7.15) upon analysis as those were well above the pre-set threshold.

Conclusions: Vedolizumab associated potential signal was generated by data mining in the FDA AERS database. The result requires an integration of further clinical surveillance for the quantification and validation of possible risks for the AEs reported of vedolizumab

4330 | The mirabegron post-marketing requirements (PMRs)/ non-interventional post-authorization safety study (NI-PASS) program

Stefan de Vogel[1], Veena Hoffman[2], Kelesitse Phiri[2], John Seeger[2], Alejandro Arana[3], Andrea Margulis[3], Lisa McQuay[4], Susana Perez-Gutthann[3], Jesper Hallas[5], Nina Sahlertz Kristiansen[5], Brandon Suehs[6], Claudia Uribe[6], Kwame Appenteng[7] and Noah Jamie Robinson[1]
[1]Astellas Pharma BV, Leiden, Netherlands; [2]Optum, Boston, MA; [3]RTI Health Solutions, Barcelona, Spain; [4]RTI Health Solutions, Research Triangle Park,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

NC; [5]University of Southern Denmark, Odense, Denmark; [6]Humana Healthcare Research, Louisville, KY; [7]Astellas Pharma US, Northbrook, IL

Background: Mirabegron was approved by the US FDA and EMA in 2012 for the treatment of overactive bladder (OAB). Based on safety observations in the clinical development program, FDA requested PMRs to evaluate the risk of cardiovascular (CV) and cancer events in mirabegron users. EMA requested an NI-PASS to assess CV safety.

Objectives: To generate rigorous, long-term safety assessments of CV and cancer outcomes among mirabegron users and to submit the results to FDA and, for the CV study, to EMA by June 2019.

Methods: A PMR/NI-PASS program using electronic health care databases from the US (Humana, Optum) and Europe (UK CPRD, Danish Registries, Swedish Registries). Analyses in each database followed a common core protocol.

Results: Five academic and contract research organizations conducted the studies, analyzing these respective data sources. An independent scientific advisory board (SAB) provided input to the study design and interpretation of study results. Five initial database-specific validation studies were undertaken to assess the performance of algorithms to identify CV and cancer events, and to inform choice of comparator groups for the subsequent two core NI-PASS (CV and cancer). These seven studies (5 validation, 2 core) were registered on the EU electronic Register of Post-Authorization Studies (EU PAS Register). Five site-specific validation study protocols (combining CV and cancer outcomes) and respective interim and final reports were prepared. For the two core studies, the team developed two core protocols, 10 site-specific protocols (separate for CV and cancer outcomes in each site), two statistical analysis plans, two interim reports, two final reports, and 10 site-specific final reports. All these study documents were required for submission to FDA and/or EMA. After 7 years of follow up, the core studies included data from approximately 250,000 OAB medication users (mirabegron and comparators combined), and approximately 3,200 CV cases and 5,800 cancer cases. The target date of June 2019 was met for the cancer study; a 6-month extension was required for the CV study.

Conclusions: This PMR/NI-PASS program has been a large undertaking requiring long-term commitment from all parties, an effective coordinating center, and extensive scientific interactions across research partners, SAB, Marketing Authorization Holder and regulators. The results (presented elsewhere) have strengthened understanding of the safety profile of mirabegron, and the endeavor has delivered useful learnings related to the design and organization of multi-database NI-PASS.

4352 | A study of cancer occurrence in users of mirabegron and antimuscarinic treatments for overactive bladder

Kelesitse Phiri[1], Jesper Hallas[2], Marie Linder[3], Andrea Margulis[4], Brandon Suehs[5], Alejandro Arana[4], Shahram Bahmanyar[3], Cheryl Enger[1], Libby Horter[5], Ingvild Odsbu[3], Morten Olesen[2], Susana Perez-Gutthann[4], Nina Sahlertz Kristiansen[2], Kwame Appenteng[6], Stefan de Vogel[7] and John Seeger[1]

[1]Optum, Boston, MA; [2]University of Southern Denmark, Odense, Denmark; [3]Karolinska Institutet, Stockholm, Sweden; [4]RTI Health Solutions, Barcelona, Spain; [5]Humana Healthcare Research, Louisville, KY; [6]Astellas Pharma US, Northbrook, IL; [7]Astellas Pharma BV, Leiden, Netherlands

Background: The β3-adrenergic agonist mirabegron is an alternative to antimuscarinics (AMs) for treatment of overactive bladder. During mirabegron development, a greater number of cancers were observed in mirabegron than tolterodine/placebo patients.

Objectives: This post-authorization safety study was designed to generate additional evidence related to this observation and compared incidence of sex-specific composite cancer outcomes (first occurrence of cancer of the lung/bronchus, colon/rectum, melanoma of skin, urinary bladder, non-Hodgkin's lymphoma, kidney/renal pelvis, pancreas [prostate in men and breast/corpus uteri in women]) in patients prescribed/dispensed mirabegron vs AMs. Comparisons were made overall and for person-time in the 1 year and >1 year following start of treatment, for all ages and for a subgroup ≥65 years.

Methods: Cohorts of mirabegron initiators were matched using propensity scores to AM initiators within real-world data sources (Danish National, Swedish National, Clinical Practice Research Datalink [UK], Optum Research [US], Humana [US]). Between 2012 and 2018, cancer cases occurring during cohort follow-up were identified from direct linkage to cancer registries or validated through medical record review or physician questionnaires.

Results: Among the 80,637 mirabegron initiators matched to 169,885 AM initiators, 68% were ≥65 years of age and 66% were women. Follow-up of these cohorts identified 5,835 cancer cases. Incidence rates (IRs) were higher for men than women for composite and individual cancer outcomes; there was no appreciable heterogeneity of cancer incidence across specific AM medications. The pooled fixed effects HR for composite cancer outcomes (all ages) was 1.05 (95% CI: 0.98, 1.14) for women and 1.06 (95% CI: 0.98, 1.14) for men. Results were similar in persons ≥65 years. IRs for bladder and prostate cancers were higher in both mirabegron and AM cohorts in the first 6 months after treatment initiation, suggesting protopathic bias.

Conclusions: This large multi-country real-world study, with up to 6 years of follow up, found no evidence of an association between mirabegron use and risk of the studied cancers, compared to AMs, in either men or women.

4379 | Immune-mediated necrotizing myopathy and pembrolizumab

Thierry Trenque, Elise Lepoix, Agathe Trenque, Aurore Morel and Brahim Azzouz

CHU, Reims, France

Background: Immune checkpoint inhibitor therapy has revolutionized the management of several cancers with a poor prognosis. Pembrolizumab is a monoclonal antibody with a high affinity and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

selectivity against, the immune checkpoint Programme cell Death 1 (PD-1). This therapy is associated with a wide spectrum of immune-related adverse events.

Objectives: To investigate the association between pembrolizumab and immune-mediated necrotizing myopathy.

Methods: Data from Vigibase, the WHO pharmacovigilance database including more than 21 million reports of Individual Case Safety Reports (ICSRs) sent by national pharmacovigilance systems, up to 31st January 2020, were used for this disproportionality analysis. We analyzed reports in the database that were coded with the MedDRA Lower Level Terms (LLT) "Immune-mediated necrotizing myopathy" and "immune-mediated necrotising myopathy". For this analyze, the Proportional Reporting Ratio (PPR) and the Reporting Odds Ratio (ROR) were calculated. The 95% Confidence Intervals (CI) were calculated using the Woolf Method.

Results: Among the 21 836 888 ICSRs registered in Vigibase, 14 cases with the LLT selected were reported with pembrolizumab treatment. We identified 14 cases with pembrolizumab with the mean age of 68.3 (age-range, 60-86 years) and 86% male. Pembrolizumab was used, essentially, for melanoma (n=6) and lung cancer (n=3). A biopsy was realized in three patients and confirmed the diagnosis. The presence of antisignal recognition particle (SRP) antibodies is positive in five patients. The PRR and ROR was respectively 24.61 (95% CI: 14.5-41.8) and 24.62 (95% CI: 14.5-41.9).

Conclusions: The occurrence of auto-immune adverse events due to immune check point blockade is described. Myasthenia gravis is the most common PD-1 inhibitor-associated neuromuscular complication. Muscle biopsy is a diagnostic tool to differentiate patients with myasthenia gravis from patients with necrotizing myopathy. Immune-mediated necrotizing myopathy is an important risk associated with pembrolizumab treatment. A interdisciplinary management (oncologist, neurologist) is needed.

4393 | Safety of abiraterone and enzalutamidein French real-world experience

Lucie-Marie Scailteux[1], Fabien Despas[2], Sandrine Kerbrat[3], Boris Campillo-Gimenez[4], Romain Mathieu[5], Sébastien Vincendeau[6], Frédéric Balusson[7], André Balusson[8], Emmanuel Nowak[9] and Emmanuel Oger[1]

[1]Rennes University Hospital - Univ Rennes, EA 7449 REPERES - PEPS Research Consortium, Rennes, France; [2]Toulouse University Hospital - Inserm 1027, Université Paul Sabatier, Toulouse, France; [3]PEPS Research Consortium - Univ Rennes, EA 7449 REPERES, Rennes, France; [4]Eugène Marquis Comprehensive Cancer Regional Center - Univ Rennes, INSERM 1099 'LTSI', Rennes, France; [5]Rennes University Hospital - Univ Rennes, Irset UMR_S 1085, Rennes, France; [6]Rennes University Hospital - CIC 1414, Rennes, France; [7]Univ Rennes, EA 7449 REPERES, Rennes, France; [8]Univ Rennes, EA 7449 REPERES - PEPS Research Consortium, Rennes, France; [9]Université de Bretagne Loire, Université de Brest, INSERM CIC 1412, CHRU de Brest - PEPS Research Consortium, Brest, France

Background: Abiraterone acetate (ABI) and enzalutamide (ENZ) are two novel hormonal therapies (NHT) used since 2012 in the treatment of castration-resistant prostate cancer (CRPC). The knowledge about their respective safety profile is mostly based on phase III clinical trials.

Objectives: To estimate the incidence of some potential adverse effects (AEs) related to the ABI or ENZ intake in a nationwide real-world experience.

Methods: Through a 6-year French descriptive population-based study using the National Health Data System "SNDS", we identified adult men with a first reimbursement of ABI or ENZ between 2013 and 2017, and followed them until December 31st, 2018. Two CPRC target populations were considered: patients whose disease has progressed after chemotherapy sessions (cohort 1) and chemotherapy-naïve patients (cohort 2). Outcomes concerned potential AEs leading to hospitalization, medical acts or biological test for cardiac failure or decompensation, cardiovascular ischemic events, atrial fibrillation, seizure, acute renal failure, hepatitis and increased use of liver testing (more than double than recommending schedule). Proportions and incidence (for 1000 person-year, 95 % confidence interval) were estimated for each potential AE in all patients exposed, in patients with or without history of diseases or specific treatments (e.g. cardiac failure, chronic renal or liver disease, benzodiazepine use, anticoagulant use), as well as in patients without any ABI and ENZ precautions for use. Statistical analyses are ongoing and definitive results expected in March 2020.

Results: Overall, 15,354 patients were reimbursed for the first time for NHT: in cohort 1 and cohort 2, 75% and 25%, and 69% and 31% were treated with ABI and ENZ, respectively. Baseline characteristics were broadly similar in each cohort. Among patients without history of specific diseases or specific treatments, hospitalization for acute heart failure/ decompensation, cardiovascular ischemic events, seizure, and acute renal failure concerned less than 2% of ABI or ENZ patients; incidence seemed similar between ABI and ENZ. An increased use of liver testing was observed in 19.6% and 8.7% of ABI and ENZ patients. We identified 7 and 1 hospitalizations for hepatitis in ABI and ENZ exposed patients, respectively.

Conclusions: Hospitalization for potential AEs such as acute heart failure/ decompensation, cardiovascular ischemic events, seizure, and acute renal failure were rarely observed in our study. Although we observed a substantial proportion of patients with more tests than recommended, more accurate identification of symptomatic hepatitis is required.

4491 | Risk of posterior reversible encephalopathy syndrome with tyrosine kinase inhibitors: A disproportionality analysis from Vigibase and AERS databases

Luis Velez-Nandayapa[1,2], Gopal Sharma[3], Senthilkumaran Janagyraman[4], Paul W. Manley[1], Paola Aimone[1], Maria Nicolaides[1], Pierre de Zeeuw[1], Christiane Michel[1], Johannes Eisinger[1] and Andreas Brueckner[1]

[1]Novartis AG, Basel, Switzerland; [2]University of Basel, Basel, Switzerland; [3]Novartis, Hyderabad, India; [4]Novartis AG, Hyderabad, India

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical radiologic syndrome characterized by symptoms such as headache, seizure, altered consciousness and visual disturbances. PRES has been associated with sepsis, malignant hypertension, transplants, and the use of chemotherapeutic agents, immunosuppressants, or cytotoxic treatments for malignant neoplasms, but its pathogenesis remains poorly understood.

Objectives: To quantify disproportionate reporting (Disp-Rep) for the risk of PRES for 29 different tyrosine kinase inhibitors (TKIs) in 2 groups: 1) Anti-angiogenic (AA) TKIs; 2) Non-anti-angiogenic (NAA) TKIs.

Methods: We used the Vigibase and AERS databases, with data up to September 2019 for analysis. Cases were identified using MedDRA (v22.0) Preferred Term "Posterior reversible encephalopathy syndrome". Empirical Bayes Geometric Means (EBGM) were calculated to quantify Disp-Rep. We considered Dis-Rep as confirmed if the lower bound, EB05, > 2. We studied 3 groups of drugs: 1) a positive control group (non-TKIs associated with PRES: cyclosporine, tacrolimus and bevacizumab) and groups of TKIs: 2) AA TKIs & 3) NAA TKIs. Drugs were identified by non-proprietary name.

Results: We retrieved 1,661 cases of PRES in Vigibase and 2,116 in AERS. In Vigibase; Disp-Rep with EBGM [90%CI, EB05-EB95] was confirmed for the positive control group: cyclosporine 32.5 [30.1-35.1], tacrolimus 31.5 [29.3-33.8] and bevacizumab 23.0 [20.9-25.2]. Disp-Rep for 9 of 14 AA TKIs: axitinib, lenvatinib, pazopanib, sunitinib, cabozantinib, regorafenib, sorafenib, vandetanib, & ponatinib was confirmed with the Dis-Rep ranging from 44.5 [35.7-55] for axitinib to 4.0 [2.3-6.8] for ponatinib. Few AA with no Disp-Rep (EB05 <2) were found: tivozanib 1.5; nintedanib 0.2; acalabrutinib with no reports in database (NR); dacomitinib NR and neratinib NR. No Dis-Rep (EB05< 2) was found for any of the NAA compounds: dasatinib 1.3; crizotinib 1.1; imatinib 1.1; vemurafenib 1.0; erlotinib 0.9; ibrutinib 0.8; cobimetinib 0.7; gefitinib 0.7; bosutinib 0.5; dabrafenib 0.3; nilotinib 0.2; afatinib NR; ceritinib NR; lapatinib NR and osimertinib NR. The analysis in AERS yielded similar results.

Conclusions: All TKIs with confirmed Disp-Rep were from the AA group. This finding suggests a potential class effect for the event of PRES for AA TKIs. Our results however, should be interpreted with caution as disproportionality analyses are hypothesis generating rather than hypothesis testing. Further analysis are planned to better understand this potential class effect.

4797 | Ramucirumab use and potential risks of interstitial lung disease and pneumonitis: Analysis of individual case safety reports in VigiBase

Nouf Alfadel and Fawaz Alharbi
Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: Ramucirumab, a recombinant monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR2), is indicated for lung, gastric and colorectal cancer. Interstitial lung disease (ILD) and pneumonitis have been reported in patients who received ramucirumab in several clinical studies.

Objectives: To assess the causality of ILD and pneumonitis reported cases with ramucirumab use.

Methods: A search in the VigiBase (the WHO global database of individual case safety reports) was conducted on January 2020 to retrieve all reported cases between 1971 and 2019 using the term 'ramucirumab' (substance (WHODrug)) [AND] "Interstitial lung disease " (reaction preferred term (PT) (MedDRA), "Interstitial pneumonia " (PT), and "pneumonitis" (PT). The causality was assessed using the WHO-Uppsala Monitoring Center causality system. A descriptive analysis was conducted.

Results: The search of the WHO database resulted in 137 cases of ILD and 26 cases of pneumonitis. Most of the cases were from Japan (n=158,97%) and involved male patients (n=138, 84.7%). The age group range in most cases was ≥ 65 years old (n=108, 66.3%). The main indication of ramucirumab was lung cancer (n=73 cases) and gastric cancer (n=76 cases). Of these cases, 32 cases (19.6%) reported fatal outcome which is likely to be related to the progression of underlying malignancy. Upon review, 62 cases (38%) were poorly documented and considered un-assessable. The remaining cases (n=101, 62%) suggested a possible causality. However, all these cases had at least one possible confounder that could reduce the strength of the causality between the adverse event and ramucirumab include concurrent condition of lung cancer and lung infection, concomitant medications which are known to cause pulmonary toxicity such as paclitaxel, docetaxel, pegfilgrastim, irinotecan, statins, filgrastim, and nivolumab and potentially ethnicity.

Conclusions: We think that there is a potential association between ramucimurab and ILD and pneumonitis especially in Japanese population. Further studies are needed to assess the potential risks of these adverse events with the use ramucirumab.

4818 | Safety and risk minimization of CAR T cell therapies: US and EU perspectives

Harshil Patel
APCER Life Sciences, Ahmedabad, India

Background: Two chimeric antigen receptor (CAR) T cell therapies for hematological malignancies are approved in US (axicabtagene ciloleucel approved in 2017, tisagenlecleucel in 2018) and EU (both therapies in 2018). Main safety concerns related to these therapies are cytokine release syndrome (CRS) and neurotoxicity, which necessitates risk minimization measures. Considering these two therapies are the only marketed therapies and literature revealed long-term follow-up challenges, leading the study to analyze only these drugs.

Objectives: 1) To analyze the occurrence and nature (with respect to population, fatalities) of CRS and neurotoxicity with CAR T cell therapies in US and EU. 2) To evaluate associated risk minimization strategies in US and EU with focus on long-term safety monitoring challenges

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: FAERS (US) and Eudravigilance (EU) database line listings of these therapies were evaluated (until the available date in both databases) focusing on occurrence of CRS and neurotoxicity. To calculate the incidences of CRS and neurotoxicity, descriptive analysis was carried out. Further, to comprehend the risk mitigation strategies and challenges, US Risk Evaluation and Mitigation Strategies (REMS) and EU Risk Management Plan (RMP) were analyzed.

Results: Safety data revealed that compared to US (1141 cases), there were only 106 cases with these therapies. Unlike US, these therapies were used more in adult lymphoma (55%) possibly attributed to priority medicine and orphan status in EU. Incidences of CRS and neurotoxicity was 57% (US) and 61% (EU), and 33% (US) and 20% (EU), respectively. Fourteen percent of cases from US had fatal outcome compared to 10% in EU. Evaluation of US REMS and EU RMP revealed similarities in risk minimization strategies for these risks, which include education programs, controlled distribution and treating CRS with tocilizumab. Amidst similar risk minimization strategies, differences in safety reports between US and EU prevails. These differences prevails due to differences in health system governance, approval timelines, accessibility, exposure in target population and tocilizumab product information. Further, long-term safety monitoring remains a challenge due to overlapping disease or CRS presentation.

Conclusions: Given the responses seen in haematological malignancy patients and irrespective of the disparities and challenges, access and utilization of CAR T cell therapies along with risk mitigation strategies are critical for both the geographies.

5033 | Serious chemotherapy-induced neurotoxicity in multiple myeloma patients

Paula Lana de Miranda Drummond[1], Jéssica Malta Soares[2], Lívia Pena Silveira[2], Naiane Lima Costa[2], Taisa Roberta Lopes Machado[2], Roberta Márcia Marques dos Santos[1], Adriano Max Moreira Reis[2] and Cristiane Aparecida Menezes de Pádua[2]

[1]Fundação Ezequiel Dias, Belo Horizonte, Brazil; [2]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Background: Neurotoxicity is one of the most common adverse effects to the treatment of multiple myeloma (MM) and can become permanent, compromising patients activities of daily living (ADL).

Objectives: To assess serious neurotocicity in MM patients exposed to chemotherapy and their impact on ADL.

Methods: Cross-sectional study with MM patients (≥18 years old), who consulted outpatient services in Belo Horizonte, Brazil (April-November 2019), in treatment or previously treated with chemotherapy were invited to participate in the study. Socio-demographic and clinical variables were collected through interview and review of medical records. Neurotoxicity was measured using Chemotherapy-Induced Neurotoxicity Questionnaire (CINQ) with 29 questions regarding symptoms in lower and upper limbs and orofacial region. Patients scored (1 to 5) each symptom for frequency and rated if it had impaired their ADL. Serious neurotoxicity was considered as score 4 or 5. Absolute and relative frequencies, mean and standard deviation (SD) were estimated. Binary logistic regression was used to assess the association between serious neurotoxicity (at least one symptom) and exposure variables estimated through odds ratios (OR) with 95% confidence intervals (CI).

Results: Altogether 182 patients enrolled the study, about half of them was female, mean aged 66.2 years old (SD 11.2) and attended private health services; 56.6% had family income ≥ 3 minimum wages and 43.4% studied until elementary school. Patients were in induction chemotherapy (48.4%), maintenance treatment (10.4%), or in remission (40.3%). Cyclophosphamide, thalidomide, and dexamethasone (CTD) regimen was mostly used in public services whereas in the private sector the most common were the combinations of bortezomib, cyclophosphamide and dexamethasone (VCD) and bortezomib, thalidomide and dexamethasone (VTD). 128 participants reported at least one serious symptom of numbness or tingling impairing the ADL. Numbness in the lower limbs was the symptom most reported. Serious neurotoxicity was present in lower limbs (86.8%), in upper limbs (36.8%), and in orofacial region (91.2%). A total of 391 answers were given as scores 4 and 5. Serious symptoms of neurotoxicity were associated with maintenance treatment with thalidomide (OR=4.8; CI95%: 1.2-19.0).

Conclusions: Serious neurotoxicity might result from the exposure to thalidomide (maintenance treatment) but also to the long-term exposure to chemotherapeutic agents during the MM treatment. Considering that MM has no cure, neurotoxicity should be monitored to prevent disabilities, aiming at better quality of life of patients.

Pharmacovigilance -> Cardiovascular

2381 | Continuous versus traditional, 28-day cycle combined oral contraceptives and risk of venous thromboembolism

Sigalit Kaplan[1], Monica L. Bertoia[2], Li Zhou[2], Amir Lass[3], Florence T. Wang[2] and John D. Seeger[2]

[1]Teva Pharmaceutical Industries Ltd., Netanya, Israel; [2]Optum Epidemiology, Boston, MA; [3]Theramex, London, United Kingdom

Background: The risk of VTE associated with continuous as compared to traditional, 28-day cycle combined oral contraceptives (COCs) is uncertain. This study examined exposure to Seasonique, an extended, 91-day COC containing levonorgestrel (LNG).

Objectives: To estimate the relative risk of venous thromboembolism (VTE) in women exposed to Seasonique compared with those exposed to 28-day cycle LNG-containing COCs (COC_{LNG}).

Methods: This cohort study was conducted within the Optum Research Database (ORD), a US health insurance claims database. Women exposed to Seasonique or 28-day COC_{LNG} (comparator cohort) were identified between 2006 and 2017. Episodes of COC use were constructed and categorized as naïve, new, re-starter, or switcher based on any prior COC use to account for time-varying VTE risk in relation to COC use. Naïve and new users represented the primary analysis. Naïve users had no combined hormonal contraceptive

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

in the 12 months preceding the start of the COC episode and new users had no combined hormone contraceptives use in the preceding 12 weeks. Each Seasonique treatment episode was propensity score-matched to up to 4 comparator treatment episodes. Follow-up time was categorized according to time since COC use (current, recent, intermediate, remote), and current use was pre-specified as the primary exposure period. Occurrence of VTE events, including deep venous thrombosis (DVT) and/or pulmonary embolism (PE) were identified using an International Classification of Diseases (ICD)-based algorithm. The validity of the VTE algorithm was assessed using medical records with adjudication for a sample of cases. The relative risk of VTE was estimated using Cox proportional hazards models.

Results: A total of 147,390 women (176,323 treatment episodes) of Seasonique or 28-day COC_{LNG} were identified. The VTE algorithm had a positive predictive value of 76% (95% confidence interval [CI] 66 to 85%). Among naïve and new users, the VTE incidence rate difference comparing current Seasonique use to current COC_{LNG} use was 0.61 per 1,000 person-years (95% CI -0.16 to 1.38). Current Seasonique use had a HR of VTE compared to current 28-day cycle COC_{LNG} of 1.40, 95% CI 0.90 to 2.19. Some sensitivity analyses suggested a possible increased risk among naïve users.

Conclusions: These results are consistent with other literature estimates regarding the risk of VTE with extended compared to traditional, 28-day cycle COC_{LNG} use. Further analyses among naïve users may aid in interpreting the increased VTE risk observed in some sensitivity analyses.

3718 | Utilisation and safety of rivaroxaban for acute coronary syndrome (ACS) in secondary care in the UK: Results from the rivaroxaban observational safety evaluation post ACS (ROSE-ACS) study

Alison Evans[1,2], Sandeep Dhanda[1,2], Vicki Osborne[1,2], Debabrata Roy[1,2] and Saad Shakir[1,2]

[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]University of Portsmouth, Portsmouth, United Kingdom

Background: The ROSE-ACS Specialist Cohort Event Monitoring (SCEM) study was conducted in secondary care to monitor the safety and use of rivaroxaban for the prevention of atherothrombotic events in adults after an ACS. The targeted safety outcome was bleeding risk.

Objectives: To estimate the short-term (12 week) cumulative incidence and incidence rate of major bleeding in patients (pts) prescribed rivaroxaban post ACS and describe drug utilisation in the secondary care setting in England and Wales.

Methods: Pts identified through clinical speciality groups supported by UK Clinical Research Networks Sept 2015 - Oct 2018. Pt characteristics, drug utilisation and bleeding outcomes collected via questionnaires completed by specialists sent at baseline and after 12 weeks of observation. A contextual cohort of pts receiving standard treatment also included in order to compare reasons for choice of anticoagulation type. However the study did not allow any direct comparisons between the two cohorts and therefore bleed incidence results are not presented.

Results: The final cohort consisted of 124 pts; median age was 59.5 years [IQR 51-68] and the majority were male (83.1%). Most pts were initiated treatment with rivaroxaban for ST-elevation myocardial infarction (STEMI) (n=64, 51.6%) with 53 (42.7%) treated for Non-ST-elevation myocardial infarction (NSTEMI). Rivaroxaban was largely prescribed in accordance with the product label; 116 pts (93.5%) initiated on a daily dose of 5mg. The majority of pts were started rivaroxaban within 3 days of being admitted (n=102, 82.3%), with the highest frequency on day 2 (n=39, 31.5%). One major bleed was reported which was within the gastrointestinal site (cumulative incidence 0.8%, 95% CI [0.0, 4.4]; incidence rate 4.2 per 100 person years, 95% CI [0.6, 29.6]). A further 13 bleeds were reported as requiring medical attention (10.5%, 95% CI [5.7, 17.3]; 54.3 per 100 person years, 95% CI [31.5, 93.5]) and 2 were classified as minimal bleeds (1.6%, 95% CI [0.2, 5.7]; 8.3 per 100 person years, 95% CI [2.1,33.4]). There were 3 (2.4%) deaths (all as a result of myocardial infarction) and no reported pregnancies.

Conclusions: The ROSE-ACS study shows that although use of rivaroxaban for ACS in the UK is low, it is largely being prescribed to populations in accordance with prescribing recommendations. Frequency of reported bleeding events were low and no new safety signals were identified. The SCEM design provides a framework suitable to evaluate the safety of newly marketed medicines in the secondary care setting.

3769 | Effect of tramadol, dabigatran and concomitant use on the risk of hospitalised bleeding using BIFAP database in Spain

Consuelo Huerta[1], María José Peñalver Jara[2], Isabel Herrera Marcos[3], Natalia Gutierrez Albadalejo[3], Airam de Burgos[1,3] and Lucia Cea Soriano[3]

[1]Spanish Agency for Medicines and Medical Devices (AEMPS), Madrid, Spain; [2]Consejería de Salud de la Región de Murcia, Murcia, Spain; [3]Faculty of Medicine, Complutense University of Madrid, Madrid, Spain

Background: Tramadol, a weak opioid, inhibits the reuptake of serotonin, a key feature on vascular homeostasis. A suspected interaction exists between dabigatran and tramadol, which might trigger an excess on risk of bleeding however, there is a gap in knowledge on this topic

Objectives: To estimate the effects of tramadol, dabigatran and concomitant use on the risk of hospitalized bleeding (Gastrointestinal bleeding and intra-extracranial bleeds)

Methods: Among a validated established cohort of new users of oral anticoagulants for atrial fibrillation (AF) aged 18 years or older with at least one year recorded, we identified all hospitalized bleed episodes (GIB and extra/intracranial bleeds) within 2008-2015. Nested case-control analyses were conducted using conditional logistic regression. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated for dabigatran, tramadol and concomitant use

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: aORs (95%CIs) for current use of dabigatran, tramadol and concomitant users were 1.71 (1.37-2.13) and 1.22 (0.87-1.71) and 2.38 (0.72-13.30) compared with non-users of both drugs (>365 days). ORs for current continuers and non-continuer users of dabigatran were 1.36 (1.00-1.86) and 2.19 (1.61-2.98), respectively. There was not an increased risk with concomitant use of tramadol and rivaroxaban (0.49 (0.11-2.27)), or antagonist of vitamin K (1.17 (0.77-1.78)).

Conclusions: Although tramadol was not associated with an increased risk of bleeds, there was a trend towards and increased risk of excess bleeds when using concomitantly with dabigatranv

3856 | The association between initiation statins and fluid retention treated with loop-diuretics - A symmetry analysis

Daniel P. Henriksen[1,2] and Jesper Hallas[1]

[1]*University of Southern Denmark, Odense, Denmark;* [2]*Odense University Hospital, Odense C, Denmark*

Background: HMG-CoA reductase inhibitors, or statins, are widely used in the general population. In the summary of products characteristics of the different types of statins, peripheral oedema is mentioned, with different adverse effect frequencies. The adverse effect could lead to prescribing loop-diuretics - a so-called prescription cascade. However, this association has not been quantified on a population-based level.

Objectives: To assess the association between initiation of a statin and lower-extremity fluid retention treated with loop-diuretics, in a self-controlled design.

Methods: We conducted a symmetry analysis on all adults living on the island of Funen (total pop: 493 000 in 2016), who filled in their first prescription of a statin (ATC C10AA) in the period of 2000-2016 and initiated a loop-diuretic (ATC C03C) three months prior to or after this date. Patients with a diagnosis of heart failure or chronic kidney disease were excluded from further analysis. A symmetrical distribution of prescriptions before and after initiation of statins is expected if no association between statins and loop-diuretics exist (i.e. a sequence ratio (SR) of 1.0). The symmetry analysis design is robust to confounders that are stable over time. Sensitivity analyses were performed in regard to the observation window time (one month, six months, and one year).

Results: A total of 1329 patients filled in their first-ever prescription of both a statin and loop-diuretics within a 3-month interval; 771 patients filled their prescription of a statin prior to their prescription of loop-diuretics, and 558 patients redeemed their prescriptions in the opposite order (SR 1.38, 95%CI 1.24-1.54). We observed no difference in SR, when stratifying on the two most widely prescribed statins - simvastatin and atorvastatin ($SR_{simvastatin}$ 1.40, 95%CI 1.25-1.59; $SR_{atorvastatin}$ 1.48, 95%CI 1.09-2.08). Older age (above or equal to 65 years) was associated with a slightly increased SR compared to younger age (SR_{older}: 1.47, 95%CI 1.28-1.71 versus $SR_{younger}$: 1.26, 95%CI 1.07-1.50). When restricting the time window to 30 days and 180 days prior to and after statin-initiation, the SRs were also increased ($SR_{30\ days}$: 1.16, 95%CI 0.98-1.38, $SR_{180\ days}$: 1.37, 95%CI 1.26-1.49).

Conclusions: We found an increased risk of treatment with loop-diuretics after initiating statins, possibly be due to a prescription cascade.

3885 | Incidence of arrhythmia and cardiac conduction disorder among dulaglutide initiators: Results from a multi-country post authorization safety study (PASS)

Miranda Davies[1,2], Lorna Hazell[1,2], Sandeep Dhanda[1,2], Vicki Osborne[1,2], Ayad K. Ali[3], Jonas Reinold[4], Susann Grill[4], Jetty A. Overbeek[5], Edith M. Heintjes[5], Ron M.C. Herings[5,6], Janet Sultana[7], Gianluca Trifirò[7] and Saad Shakir[1,2]

[1]*Drug Safety Research Unit, Southampton, United Kingdom;* [2]*University of Portsmouth, Portsmouth, United Kingdom;* [3]*Eli Lilly and Company, Indianapolis, IN;* [4]*Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany;* [5]*PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands;* [6]*University Medical Center, Amsterdam, Netherlands;* [7]*BIOMORF Department, University of Messina, Messina, Italy*

Background: Dulaglutide is a once-weekly injectable glucagon-like peptide-1 receptor agonist authorised in Europe (2014) for the treatment of type 2 diabetes mellitus (T2DM). Cardiovascular effects were an important potential risk of dulaglutide at the time of marketing authorisation from clinical trial data.

Objectives: To assess the incidence of arrhythmia and/or cardiac conduction disorder during the first twelve months of dulaglutide treatment among patients with T2DM.

Methods: New user cohorts of dulaglutide were identified (2015-2019) from electronic healthcare databases in Germany (BIPS), the Netherlands (PHARMO), Italy (CASERTA) and England (DSRU). Outcome data were obtained from codes (in databases) or from data collection forms sent to prescribers in England (Modified Prescription-Event Monitoring, M-PEM). Patients were followed up for 12 months (censored at death, loss to follow up or end of treatment, whichever occurred first). The primary analysis included patients with a report of arrhythmia and/or conduction disorder in the follow up period, and with no prior history of the event. Country specific risk estimates were calculated. A sensitivity analysis (M-PEM only) looked at the incidence of this outcome amongst patients both with and without a prior history of the event

Results: A total of 21,907 patients with T2DM who started dulaglutide were identified, corresponding to 13,651 in BIPS; 296 in PHARMO; 671 in CASERTA; and 7,289 in DSRU M-PEM. The distribution of dulaglutide initiators with full 12 months of observation was: 41.7% in BIPS; 35.5% in PHARMO; 55.9% in CASERTA; and 100% in DSRU M-PEM. During the follow up period, a total of 62 incident events were reported (22 in BIPS, 1 in PHARMO, 3 in CASERTA, and 36 in M-PEM). The risk estimates in corresponding databases

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

were 0.2% (95% CI = 0.2%-0.4%), 0.4% (95% CI = 0.0%-2.1%), 0.5% (95% CI = 0.1%-1.4%), and 0.5% (95% CI = 0.4% - 0.7%). Across all data sources the most commonly reported type of arrhythmia was supraventricular arrhythmia (21 in BIPS, 1 in PHARMO, 3 in CASERTA, and 20 in M-PEM); corresponding risk estimates were 0.2%, 0.4%, 0.5% and 0.3%. The inclusion of prevalent cases of arrhythmia/conduction disorder (M-PEM, sensitivity analysis) increased the risk estimate to 0.8% (95% CI = 0.6%-1.1%).

Conclusions: This multi-country European PASS showed that the incidence of arrhythmia and cardiac conduction disorder among dulaglutide initiators was observed to be consistent with rates observed in clinical trials (premarketing, and one post marketing cardiovascular outcomes trial).

4178 | Percutaneous transluminal septal myocardial ablation and common procedural complications: A descriptive study

John G. Connolly[1], Laura Hou[1], Justin Bohn[1], Talia Menzin[1], Ting-Ying Huang[1], Fortunato Senatore[2], Efe Eworuke[2] and Marie Bradley[2]
[1]*Harvard Pilgrim Healthcare Institute, Boston, MA;* [2]*US Food and Drug Administration, White Oak, MD*

Background: Percutaneous transluminal septal myocardial ablation (PTSMA) is an alternative to surgery for the treatment of left ventricular outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy. Dehydrated alcohol, used to conduct PTSMA, was not approved by the U.S. Food and Drug Administration (FDA) until June 21st, 2018. Data on frequency of PTSMA and suspected complications prior to that date are limited.

Objectives: To estimate the frequency of PTSMA and the rate of common suspected complications following PTSMA.

Methods: We identified patients undergoing incident PTSMA in inpatient and outpatient care settings in the Sentinel Distributed Database between January 1st, 2014 and June 21st, 2018. Eligible patients were 18 years or older with continuous medical and drug coverage for at least 183 days prior to their index PTSMA. We followed patients for common complications including: permanent pacemaker placement, ventricular arrhythmia, heart failure, as well as septal myectomy and repeat PTSMA for up to 365 days after the index procedure and up to 30 days for atrioventricular (AV) block. We calculated a rate of diagnoses or procedures per person time for each outcome and care setting.

Results: We identified 376 patients who underwent inpatient PTSMA and 852 who underwent outpatient PTSMA. Inpatients were younger (mean age 69 vs. 72 years) and more likely to be female (62% vs. 72%) than outpatients. In both settings, the most common post-PTSMA diagnosis was atrioventricular block (7106/1000 person-years (PY) inpatient vs. 7254/1000 PY outpatient), followed by heart failure (1132/1000 PY inpatient vs. 894/1000 PY outpatient). Patients undergoing inpatient PTSMA were more likely to have a repeat procedure (10.4% inpatient vs. 4.9% outpatient). The most commonly co-occurring diagnoses within the same patient were ventricular arrhythmia and heart failure (35 patients across both care settings).

Conclusions: Cardiovascular conditions suspected to be complications of PTSMA, particularly AV block, are common following the procedure. Future research will examine how FDA approval of dehydrated alcohol impacted the number of PTSMA procedures and the post-PTSMA complication rate.

4229 | Risk of aortic aneurysm and aortic dissection with use of fluoroquinolones in Korea

Nayeong Son, Jeongeun Oh, Eunmi Choi, Bonggi Kim, Soo Yeon Chung and Soon Young Han
Korea Institute of Drug Safety and Risk Management, Anyang, Republic of Korea

Background: Fluoroquinolones (FQ) are among the most widely used antibiotics in Korea. Recent studies have raised concern that fluoroquinolones could be associated with an increased risk of aortic aneurysm (AA) and aortic dissection (AD). However, It has not yet been established whether FQ use increase the risk of AA/AD in Korean population.

Objectives: The aim of this study is to evaluate the association between FQ use and risk of AA/AD in patients over 40 in Korea.

Methods: We conducted a nested case-control study using the National Health Insurance Service (NHIS) Database from 2013 to 2017 in Korea. The underlying study cohort included the patients older than 40 years, and excluded patients who used FQ or experienced AA/AD or related diseases during a year before cohort entry date. For each case of AA/AD, we used risk-set sampling and randomly matched 4 population controls by same sex, age and cohort entry date. The first date of AA/AD diagnosis is defined as the index date. We defined FQ use that it is investigated whether each subjects used FQ during a year before index date. Using conditional logistic regression model, we assessed the association of FQ use and AA/AD adjusted for the potential confounders(age, sex, history of disease, medication use and surgery).

Results: A total of 29,638 AA/AD patients were identified between 2014 and 2017. In the main analysis, use of FQ within a year was found to be associated with a 10% increase of risk of AA/AD(adjusted odds ratio(aOR:1.10, 95% CI:1.07-1.14), compared with non-users. Especially, the risk was higher in patients used FQ within 60 days (aOR:1.53, 95% CI:1.46-1.62). In dose-response analysis and duration-response analysis, the risk of AA/AD increased as the cumulative dose and length of FQ therapy increased(p-trend<0.001). In subgroup analysis, there were no significant differences of the risk among sex and age group. In sensitivity analysis, the result supported main analysis substantiating robustness.

Conclusions: Our study provides considerable evidence for the risk of AA/AD by FQ in Korean population. Patients and medical professionals should be aware that FQ use can increase the risk of AA/AD, and high dosage and duration of use may aggravate the risk.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4252 | Worth a second look: pharmacovigilance data support current concerns for JAK inhibitors

Enriqueta Vallejo-Yagüe[1], Stefan Weiler[1,2] and Andrea M. Burden[1]
[1]*ETH Zurich, Zurich, Switzerland;* [2]*National Poisons Information Centre, Tox Info Suisse, Associated Institute of the University of Zurich, Zurich, Switzerland*

Background: The Janus Kinase (JAK) inhibitors, tofacitinib and baricitinib, are new targeted treatments for rheumatoid arthritis (RA). Recent concerns regarding the risk of thromboembolism have led to warnings by competent regulatory authorities.
Objectives: To examine the thromboembolic safety signal for tofacitinib and baricitinib.
Methods: Individual case safety reports (ICSRs) for tofacitinib and baricitinib were retrieved from the World Health Organization global database, VigiBase, in April 2019. Primary outcomes were deep vein thrombosis (DVT) and pulmonary thrombosis (PT) or pulmonary embolism (PE). Patient demographics were summarized, stratified by outcome. A disproportionality analysis was conducted by estimating the reporting odds ratio (ROR) and 95% confidence intervals (CIs). The ROR were calculated worldwide and stratifying by reporting from Europe or the US.
Results: In both tofacitinib (n=40,017) and baricitinib (n=2,138) ICSRs, patients with reported DVT or PT|PE were older and had higher reporting of pro-thrombotic medications (e.g., contraceptives) or indicators of thromboembolic risk (i.e., antithrombotic treatment). The use of tofacitinib was associated with increased reporting odds for DVT (ROR: 2.37 95% CI 1.23-4.56) and PT|PE (ROR 2.38 95% CI 1.45-3.89) in Europe. For Baricitinib, a 3-fold increased reporting odds was observed for DVT (ROR: 3.47 95% CI 2.18-5.52) and PT|PE (ROR: 3.44 95% CI 2.43-4.88) in Europe. In the US, tofacitinib was only associated with an elevated reporting odds of PT (ROR: 2.05 95% CI 1.45-2.90) and no baricitinib ICSRs were reported.
Conclusions: In our analysis, a higher frequency of thromboembolic risk factors was observed in those reporting DVT or PT|PE, vs the total reported cases for the studied drugs. While RA patients have an elevated risk for thromboembolisms, and large-population based studies are needed, the results of this study provide further support to the current recommendation for cautious use in patients with a high thromboembolic risk profile. Moreover, a potential class effect of JAK inhibitors cannot be ruled out.

4302 | Association between desloratadine use and incidence of cardiac outcomes - A Nordic cohort study

Annette Kjær Ersbøll[1], Thora Majlund Kjærulff[1], Kaushik Sengupta[1], Eero Pukkala[2], Kristian Bolin[3], Martha Emneus[4], Dena Rosen Ramey[5], Joanne E. Brady[5], Daniel Mines[5], Kristian Aasbjerg[6], Christian Vestergaard[7] and Gunnar Gislason[8]
[1]*University of Southern Denmark, Copenhagen, Denmark;* [2]*Tampere University, Tampere, Finland;* [3]*University of Gothenburg, Gothenburg, Sweden;* [4]*Applied Economics and Health Research Aps (ApHER), Copenhagen, Denmark;* [5]*Merck & Co., Inc., Kenilworth, NJ;* [6]*Aarhus University Hospital Skejby, Aarhus, Denmark;* [7]*Aarhus University Hospital, Aarhus, Denmark;* [8]*Gentofte Hospital, Copenhagen, Denmark*

Background: Desloratadine (DL) is a non-sedating antihistamine, first marketed in 2001. Adverse events of supraventricular tachycardia (SVT), and atrial fibrillation and flutter (AFF) have been reported among individuals using DL. The European Medicines Agency requested MSD conduct a post-authorization safety study.
Objectives: To assess the association between DL use and incident SVT, and AFF
Methods: We conducted a cohort study including individuals with a first prescription redemption of DL in 2001-2015. A Nordic registry-based study was conducted using health registries in Denmark, Finland, and Sweden. A common individual-level database was established. Current DL exposure was a time-varying variable defined for each prescription redemption as days' supply plus a 4-week grace period. Unexposed periods (remote prior exposure) were defined as starting 26 weeks after the date of prescription redemption. Outcomes were incident SVT and AFF assessed separately. We analyzed the association between DL use and incidence rate (IR) of SVT and AFF using Poisson regression of number of seizures as outcome and logarithmic transformation of follow-up time as the offset. Potential confounders were identified using causal diagrams and included country, calendar year, sex, seasonality, and history of asthma, severe rhinitis and chronic urticaria. Results are presented as IR per 100,000 person-years (PY) and incidence rate ratio with a corresponding 95% confidence interval (IRR, 95% CI).
Results: In total, 1,833,337 and 1,822,783 incident DL users were included in the study of which 2,864 and 12,378 were diagnosed with incident SVT and AFF in the primary analyses, respectively, during the study period. The IRs of SVT were 31.1 and 31.6 per 100,000 PY during DL exposed and DL unexposed periods. No significant association was seen between DL use and incidence of SVT (Unadjusted: IRR=0.99, 95% CI: 0.89; 1.10 Adjusted: IRR=1.03, 95% CI: 0.92; 1.15). The IRs of AFF were 142.8 and 136.2 per 100,000 PY during DL exposed and DL unexposed periods. A significant association between current DL exposure and IR of AFF was seen (unadjusted IRR=1.05, 95% CI: 1.00; 1.10). A 6% increase in the IR of AFF during the exposed periods was seen for the adjusted analysis (IRR=1.06, 95% CI 1.01; 1.12). The association was strongest following the first prescription (IRR=1.24 95% CI 1.13;1.36).
Conclusions: A 6% increase in the IR of AFF was seen among individuals currently exposed to DL. No association between current DL exposure and SVT was found.

4357 | Dronedarone-induced hyperkalemia

Qun-Ying Yue
Uppsala Monitoring Centre, Uppsala, Sweden

Background: Dronedarone is an anti-arrhythmic agent indicated for atrial fibrillation. In signal detection of VigiBase, the WHO global

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

individual case safety report database at Uppsala Monitoring Centre, dronedarone associated hyperkalemia was identified as a signal.

Objectives: To assess causality and possible risk factors for dronedarone associated hyperkalemia.

Methods: Reports of dronedarone associated hyperkalemia in VigiBase up to April 2019 were reviewed. The Bradford-Hill criteria were applied in the assessment of the case series.

Results: VigiBase contained 18 unique cases of hyperkalemia with dronedarone as a suspected or interacting drug (expected 8). Dronedarone was single suspected in 12 cases. The reports came from 10 countries involving 5 females and 13 males, age range 45 to 86 years (mean 71). The dronedarone dose (known in 10) was 400 mg twice daily in nine cases. Most of the cases (89%) were serious with four life-threatening and one fatal. The time from dronedarone start to the event onset (TTO) was 19 days (mean, n=11) ranging from 3 days to 9 weeks. Positive dechallenge was reported in six cases when information was available. Based on the temporal relationship including positive dechallenge, there seems to be a possible causal relation for dronedarone associated hyperkalemia. In 11 cases, (acute) renal failure was a co-reported event, with creatinine increased in two other cases, while in five there were no co-reported renal events and in four of these dronedarone was single suspected. While creatinine increased is clearly included in the label as an adverse reaction of dronedarone, renal failure is not. Other drugs known to cause hyperkalemia were reported as suspected (four cases) or concomitant (10 cases) drugs: such as beta-blockers and calcium channel blockers (alter transmembrane potassium movement); ACE-inhibitors, angiotensin-II receptor blockers, NSAIDs, potassium-sparing diuretics (impair renal potassium excretion); and potassium-containing agents (increase supply).

Conclusions: Based on the Bradford-Hill criteria, and especially the reporting disproportionality, close temporal relationship including positive dechallenge, and similar literature cases, a causal relationship for dronedarone and hyperkalemia seems possible. The mechanism is unclear, but likely multifactorial: e.g. renal failure with dronedarone and concomitant medications known to cause hyperkalemia as contributing factors. Health care professionals should be aware of this possible risk. Renal function should be monitored periodically as recommended during dronedarone treatment.

4389 | Post authorization safety study of pitavastatin: A disproportionality analysis in FDA adverse event reporting system database (FAERS)

Subeesh Kulangara Viswam, Neha Reddy, Alekhya Mandepudi, Gayathri Padmanabuni, Vasista Sharma and Nair Gouri
M.S. Ramaiah University of Applied Science, Bangalore, India

Background: Signal detection is one of the most advanced and promising technique in the field of pharmacovigilance. Pre-approval clinical trials are limited in their ability to detect certain adverse effects and, therefore, the FDA and pharmaceutical sponsors collect and monitor reports of Adverse Events (AEs) following approval. Pitavastatin is a HMG-CoA reductase inhibitor which received FDA approval in the year 2009.

Objectives: This study aimed to screen the FDA's Adverse Event Reporting System (AERS) database for novel AEs that may be attributed to pitavastatin

Methods: Publicly available FAERS data was used for analysis. Most commonly used data mining algorithms, Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) were selected for the study. A value of ROR-1.96SE>1 and PRR≥2, count of co-occurrences ≥3 and chi-square ≥4 was considered as threshold value, above which it was considered as positive signal. The AEs associated with pitavastatin identified earlier in clinical trials and that have been listed in the "adverse effects", "post-marketing reports", "warnings and precautions" and "black-box warning" sections of Micromedex® and DailyMed were omitted from the study.

Results: FAERS database had a total of 5,035 reports for pitavaststin. 53.59% of reports were associated with females and 46.24% of reports with males. Physicians reported the highest number of AE reports (44%), followed by consumers (35%). There were 371 (7.89%) death reports and non-death serious reports included hospitalization (40%), life-threatening (6.19%), disability (4.23%), congenital anomaly (0.06%) and other serious AEs (41.60%). The disproportionality indicators showed a positive signal for cerebral infarction (PRR: 12.77; ROR-1.96SE: 10.59), anaemia (PRR: 4.35; ROR-1.96SE: 3.95), cardiac failure (PRR: 3.62; ROR-1.96SE: 2.92) and platelet count decreased (PRR: 3.68; ROR-1.96SE: 3.05).

Conclusions: This disproportionality analysis identified four clinically important unlabelled AEs, which if confirmed in future studies would have potential implications for the use of pitavastatin in clinical practice.

4399 | Statins-associated myopathy

Thierry Trenque, Camille Douilly, Elise Lepoix, Agathe Trenque, Aurore Morel and Brahim Azzouz
CHU, Reims, France

Background: Immune-mediated necrotizing myopathy (IMNM) is a subgroup of idiopathic inflammatory myopathies, different from other myositis. IMNM is a form of statin myopathy characterized by the presence of antibodies against 3-Hydroxy-3-Methyl-Glutanyl-Coenzyme A Reductase (anti-HMGCR antibody) and elevated creatine kinase.

Objectives: The aim of this study was to establish a relationship between the different statins and the risk of IMNM, and to evaluate the informations Registered.

Methods: We conducted an analysis of the French national pharmacovigilance database (FPVD) over the period 1985 - 31st July 2019. In order to identify the relevant cases, we identified two MedDRA Preferred Terms (PTs) related to IMNM. The PTs were "necrotizing myopathy" and "immune-mediated myositis". We performed a

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

quantitative and qualitative review of individual case safety reports (ICSRs) recorded in French vigilance spontaneous reporting system. The association between IMNM and statins exposure was assessed using the case/non case method. The Reporting Odds Ratio (ROR) was calculated.

Results: A total of 30 ICSRs were found in FPVD corresponding to the PT terms of which 17 related to IMNM. All cases were serious. Patients studied (10 men, 7 women), the median age was 73 years (range: 42-85 years). Mean latency time between start of statin treatment and diagnosis was 21 months (range: 4-66). The suspected statins were atorvastatin (n= 15), pravastatin (n= 1) and simvastatin (n=1). The ROR was respectively 448.32 (95% CI: 102.5-1960.7), 6.92 (95% CI: 0.9-52.2) and 6.8 (95% CI: 0.9-51.3) for atorvastatin, pravastatin and simvastatin. In all cases (n= 15), Creatine Kinase levels were high, with a 81 times the upper limit of normal. Muscle biopsies were available and positive in 13 cases. Anti-HMGCR antibody was documented in 12 cases and positive in all of these cases in accordance with the biopsy result.

Conclusions: Atovastatin presents the highest risk. Muscle biopsy is not required to confirm the diagnosis of IMNM in the presence of anti-HMGCR antibodies. A class-effect cannot be excluded.

4720 | What drugs are associated with orthostatic hypotension?: An overview of findings from randomised controlled trials

Cini Bhanu, Irene Petersen, Danielle Nimmons, Daniel Davis, Mine Orlu and Kate Walters

University College London, London, United Kingdom

Background: Orthostatic hypotension is a prevalent condition associated with increased risk of falls and mortality, characterised by a reduction in blood pressure on standing upright, and it is commonly caused by drugs. To date, no studies have reviewed high-quality Randomised Controlled Trial (RCT) evidence on drugs associated with orthostatic hypotension.

Objectives: To determine which drugs are associated with orthostatic hypotension as an adverse effect, using RCTs

Methods: *Design*: A comprehensive review of the literature. MEDLINE, EMBASE and Web of Science were systematically searched from inception to 3 January 2020. PROSPERO ID 168697. We conducted searches using standard search terms for orthostatic hypotension and medications. We additionally used an automated macro program to search for individual drug names from the British National Formulary 77. We included all RCTs reporting on orthostatic hypotension associated with any drug (identified by International Nonproprietary Name) in adults over 18 years, in any language, with a clear comparator group: a) without drug exposure; b) on placebo or c) with a comparator drug. We excluded studies on non-humans, pregnant women and on the drug treatment of orthostatic hypotension. Two independent reviewers conducted screening, quality evaluation and risk of bias assessment. Analysis of the data included a narrative synthesis of findings. Heterogeneity of methods, outcomes and populations will be assessed for subsequent meta-analysis using a random-effects model.

Results: In total, 9,251 unique citations were identified from the electronic database searches. Of the 9,251 titles and abstracts screened, 580 full texts were included. A range of RCT evidence of variable quality, reporting on orthostatic hypotension as an adverse drug effect, is available. The top three drug groups reporting orthostatic hypotension are cardiac drugs, antidepressants and antipsychotics. A broad range of other drug groups report associations with orthostatic hypotension, including Parkinson's, anti-retroviral, anti-malarial, chemotherapy, anxiolytic, adrenergic antagonist, anti-diabetic, anti-epileptic, analgesic, immunomodulatory and antibiotic medications.

Conclusions: A broad range of drug groups show potential to increase risk of orthostatic hypotension in adults, including some which are not widely considered by clinicians in routine practice. This is of particular importance when assessing risk-benefit profiles of medications in the clinical setting, particularly for older people who are at greatest risk of orthostatic hypotension.

5026 | Ivabradine registry: An assessment of the effectiveness of ivabradine restricted access program in three cardiac centers in Saudi Arabia

Amal Alshatri Almotiry, Wed AlGannam, Budur Alshuraihi, Naser Aljaser and Adel Alrwisan

Saudi Food and Drug Authority (SFDA), Riyadh, Saudi Arabia

Background: Ivabradine was approved in Saudi Arabia in 2007 for the treatment of chest pain in angina pectoris and chronic heart failure. In 2015, the Saudi Food and Drug Authority (SFDA) revoked the marketing authorization of ivabradine due to reports of serious cardiac adverse events. Subsequently, in 2017, Ivabradine was re-registered under an SFDA-approved restriction program, in which Ivabradine was restricted to the indication of chronic heart failure and only permitted in 22 cardiac centers. New risk minimization measures (RMMs) were also implemented including a requirement for the enrolment of patients in a registry.

Objectives: To evaluate prescribers' adherence to the RMMs in Saudi Arabia.

Methods: This retrospective cohort study collected data from medical records in a drug registry of patients initiating ivabradine in three cardiac centers in Saudi Arabia. Data were collected at ivabradine initiation and patients were followed for up to 6 months after starting the treatment. This study analyzed the data available from November 2018 until February 2020. The primary outcome was the adherence with the following components of the RMMs: using ivabradine only in patients with a heart rate ≥ 70bpm at time of initiation, not exceeding the recommended initiation and maintenance dosing (5 mg and 7.5 mg twice daily, respectively) during the ≤6 months of follow-up, and the absence of concomitant use of verapamil or diltiazem.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: A total of 245 patients were included in the study. The percentages of patients who had a heart rate of ≥70 bpm at the time of initiating ivabradine were 90.2%. While 90.6% of patients did not receive a starting dose higher than 5mg. The maintenance dosing information was available in 70 patients, none of them had a maintenance dose exceeding the recommended. Among the patients, only one (0.4%) used verapamil or diltiazem concomitantly with ivabradine.
Conclusions: The RMMs and the restriction program for ivabradine were well implemented in Saudi Arabia, suggesting a favorable safety profile of ivabradine in chronic heart failure.

5062 | Evaluation of the beta blocker - edema - loop diuretic prescribing cascade among adults: A prescription sequence symmetry analysis

Earl J. Morris, IV[1], Xinyi Jiang[1], Carl J. Pepine[2], Steven M. Smith[1] and Scott M. Vouri[1]
[1]University of Florida College of Pharmacy, Gainesville, FL; [2]University of Florida College of Medicine, Gainesville, FL

Background: Beta blockers reduce blood pressure via multiple mechanisms, including vasodilation, which can manifest in clinical edema in up to 8% of patients. Some patients with edema may enter a prescribing cascade, whereby they receive additional treatment (e.g., a diuretic) explicitly for the edema. Accordingly, we sought to examine whether a prescribing cascade exists between beta-blockers and loop diuretic therapy.
Objectives: To examine whether beta blocker initiation is associated with subsequent increased loop diuretic initiation.
Methods: We performed a prescription sequence symmetry analysis (PSSA) to assess new use of a loop diuretic in relation to new use of a beta blocker among adults aged ≥18 years using the IBM MarketScan® Commercial Claims and Medicare Supplemental Database from 2005 to 2018. We excluded prevalent users of calcium channel blockers and individuals with a diagnosis of heart failure 720 days before or 360 days after new use of beta blocker and/or loop diuretic. Secular trend-adjusted sequence ratios (aSR) with 99% confidence intervals (CI) were calculated within ± 360 days of beta blocker initiation. Stratified analyses were performed on age (18-49 years, 50-64 years, and ≥ 65 years), sex, and individual beta-blockers.
Results: Among 1,590,803 beta blocker initiators, 79,760 (5.01%) had a new loop diuretic prescription within ± 360 days of beta blocker initiation, resulting in an aSR of 1.66 (99% CI 1.63-1.69). The estimated incidence of the prescribing cascade was 1.27%. The aSR was highest among beta blocker initiators aged ≥ 65 years (aSR 1.76 [99% CI 1.70-1.80]) and among men (aSR 1.84 [99% CI 1.79-1.89]). The prescribing cascade was most prominent with metoprolol tartrate (aSR 2.12 [99% CI 2.04-2.19]) and metoprolol succinate (aSR 1.88 [99% CI 1.81-1.96]). Positive associations were also found for atenolol (aSR 1.77 [99% CI 1.67-1.87]), bisoprolol (aSR 1.76 [99% CI 1.52-2.04]), carvedilol (aSR 1.17 [99% CI 1.12-1.22]), labetalol (aSR 1.77 [99% CI 1.57-2.00]), and propranolol (aSR 1.27 [99% CI 1.16-1.39]). No association was found in acebutolol, betaxolol, nadolol, nebivolol, pindolol, or timolol initiators.
Conclusions: Our findings suggest that a beta blocker-edema-loop diuretic prescribing cascade is present in a small but significant number of adults. Older adults are at highest risk for this prescribing cascade even slightly exceeding the incidence seen in calcium channel blockers. Differences in the pharmacology of beta blockers may result in differing risks of edema and subsequently differing risks of prescribing cascades.

Pharmacovigilance -> Diabetes

3774 | Incidence of acute pancreatitis among dulaglutide initiators: Results from a multi-country post authorization safety study (PASS)

Miranda Davies[1,2], Lorna Hazell[1,2], Sandeep Dhanda[1,2], Vicki Osborne[1,2], Ayad K. Ali[3], Jonas Reinold[4], Susann Grill[4], Jetty A. Overbeek[5], Edith M. Heintjes[5], Ron M.C. Herings[5,6], Janet Sultana[7], Gianluca Trifirò[7] and Saad Shakir[1,2]
[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]University of Portsmouth, Portsmouth, United Kingdom; [3]Eli Lilly and Company, Indianapolis, IN; [4]Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany; [5]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands; [6]University Medical Center, Amsterdam, Netherlands; [7]BIOMORF Department, University of Messina, Messina, Italy

Background: Dulaglutide is a once-weekly injectable glucagon-like peptide-1 receptor agonist authorised in Europe (2014) for the treatment of type 2 diabetes mellitus (T2DM). Acute pancreatitis (AP) is an important identified risk of dulaglutide from clinical trial data.
Objectives: To assess the incidence of AP during the first twelve months of dulaglutide treatment among patients with T2DM.
Methods: New user cohorts of dulaglutide were identified (2015-2019) from electronic healthcare databases in Germany (BIPS), the Netherlands (PHARMO), Italy (CASERTA) and England (DSRU). Outcome data were obtained from codes (in databases) or from data collection forms sent to prescribers in England (Modified Prescription-Event Monitoring, M-PEM). Patients were followed up for 12 months after starting dulaglutide (censored at death, loss to follow-up or end of treatment, whichever occurred first). The primary analysis included patients with a report of AP in the follow up period, and with no prior history of AP. Risk estimates for AP (country specific and combined) were calculated. A sensitivity analysis (M-PEM data only) looked at the incidence of AP amongst patients both with and without a prior history of AP. Univariate analysis was performed on selected variables to identify risk factors for AP among dulaglutide initiators.
Results: A total of 21,907 patients with T2DM who started dulaglutide were identified, corresponding to 13,651 in BIPS; 296 in PHARMO; 671 in CASERTA; and 7,289 in DSRU M-PEM. The distribution of dulaglutide initiators with full 12 months of observation was: 41.7% in BIPS; 35.5% in PHARMO; 55.9% in CASERTA; and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

100% in M-PEM. Cases of AP were reported in BIPS (n=22), CASERTA (n=2), and M-PEM (n=6) data. Incident risk estimates in corresponding data sources were 0.2% (95% CI = 0.1%-0.3%), 0.3% (95% CI = 0.0%-1.1%), and 0.1% (95% CI = 0.0%-0.2%), respectively. The combined risk was 0.1% (95% CI = 0.1% to 0.2%). The sensitivity analysis did not change the risk estimate from the primary analysis. Univariate analysis suggested that AP was more likely to occur amongst smokers (OR = 3.9) and patients with a history of gallstones, biliary colic or cholecystitis (OR = 4.8). Compared to dulaglutide initiators with T2DM duration of < 4 years, the risk of AP was lower for patients with > 10 years of T2DM duration (OR = 0.3).

Conclusions: This multi-country European PASS showed that the incidence of AP among dulaglutide initiators was observed to be consistent with rates observed in clinical trials; however, the risk estimates should be interpreted with caution due to heterogeneity of data sources.

3902 | Sodium-glucose co-transporter 2 inhibitors and the risk of early breast cancer among women with type 2 diabetes

Melanie Suissa[1], Hui Yin[2], Oriana Yu[3], Stephanie Wong[4] and Laurent Azoulay[5]

[1]Department of Epidemiology, Biostatistics and Occupational Health, McGill University; Department of Medicine, University of Montreal, Montreal, QC, Canada; [2]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [3]Division of Endocrinology, Jewish General Hospital; Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [4]Division of Surgery and Oncology, Jewish General Hospital Segal Cancer Centre, McGill University, Montreal, QC, Canada; [5]Department of Epidemiology, Biostatistics and Occupational Health, McGill University; Department of Oncology, McGill University, Montreal, QC, Canada

Background: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are the newest class of antidiabetic drugs shown to have cardiovascular benefits. However, numerical imbalances in breast cancer events were observed with certain SGLT-2 inhibitors (i.e., dapagliflozin) in premarketing trials, all occurring within one year of randomization. While this may have been a chance finding, it remains unclear whether use of SGLT-2 inhibitors, either as a class or by individual molecule, is associated with an early increased risk of breast cancer.

Objectives: To determine whether the use of SGLT-2 inhibitors is associated with an early increased risk of breast cancer among female patients with type 2 diabetes.

Methods: We used the UK Clinical Practice Research Datalink to identify a cohort of female patients newly treated with either a SGLT-2 inhibitor or a dipeptidyl peptidase 4 (DPP-4) inhibitor between 2013 and 2018. Cohort entry was defined as the date of first prescription of either drug during the study period, and patients were followed using both intention-to-treat and as-treated approaches. Propensity score fine stratification was used to control for confounding and Cox proportional hazards models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of breast cancer incidence, comparing new users of SGLT-2 inhibitors with new users of DPP-4 inhibitors. In secondary analyses, we investigated the incidence of breast cancer by specific SGLT-2 inhibitor molecule (dapagliflozin, empagliflozin, canagliflozin).

Results: The cohort included 9,938 SGLT-2 inhibitor users and 36,631 DPP-4 inhibitor users. After a median follow-up of 2.6 years, these groups generated 67 and 382 breast cancer events, respectively. In the intention-to-treat approach, use of SGLT-2 inhibitors was not associated with an increased risk of breast cancer, compared with DPP-4 inhibitors (incidence rates 2.8 vs 3.7 per 1000 person-years, respectively; HR: 1.00, 95% CI 0.77-1.30). Similar findings were observed in the as-treated approach (HR: 0.98, 95% CI: 0.72-1.32). In secondary analyses, use of dapagliflozin was associated with an overall HR above the null (HR: 1.16, 95% CI 0.86-1.57), with cumulative incidence curves diverging at 1.5 years after treatment initiation. The HRs for the other molecules were all around the null.

Conclusions: In this first population-based study, use of SGLT-2 inhibitors was not associated with an overall increased risk of early breast cancer, when compared to DPP-4 inhibitors. Additional studies are needed to investigate a possible association with dapagliflozin.

4243 | Risk of genital and urinary tract infections associated with SGLT2 inhibitors as an add-on therapy to metformin in patients with type 2 diabetes mellitus

Eunjun Park, Hyeri Yang, Eonji Na, Eunmi Choi, Bonggi Kim, Soon Young Han and Soo Yeon Chung

Korea Institute of Drug Safety and Risk Management, Anyang-si, Republic of Korea

Background: Sodium glucose cotransporter-2 (SGLT-2) inhibitor is an anti-diabetic drug which lowers the blood glucose level by promoting urinary excretion of glucose. Regarding this, the safety issues about the risk of genital and urinary tract infections have been concerned. However, most of the previous studies are focused on the Western population.

Objectives: This study aimed to assess the risk of genital and urinary tract infections of SGLT-2 inhibitors as an add-on therapy to metformin in patients with type 2 diabetes mellitus (T2DM) compared to dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylurea (SU) and thiazolidinedione (TZD) in Korean population.

Methods: We conducted a retrospective cohort study using the National Health Insurance Service (NHIS) database in Korea from 2013 to 2017. Patients aged ≥19 years and those diagnosed with T2DM prior to drug prescription (metformin + either SGLT-2 inhibitor, DPP-4 inhibitor, SU or TZD) were enrolled in this study. The outcomes were genital infections (including candidial infections, vaginitis, vulvitis and other inflammatory disease of uterus for female, and candidial balanitis, orchitis, epididymitis, balanoposthitis for male) and urinary tract infections. Primary analysis was performed using Cox's proportional hazard model after 1:1 propensity score (PS) matching to

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

calculate the hazard ratio (HR) with 95% confidence interval (CI). Sensitivity analysis was conducted by limiting follow-up period (≤1 year) and age (≥60 years).

Results: 7,738, 7,145 and 2,175 patients were matched in DPP-4 inhibitor, SU and TZD comparator group, respectively. SGLT-2 inhibitors were associated with a higher risk of genital infections compared to DPP-4 inhibitors (HR: 2.39, 95% CI: 2.07-2.76), SU (HR: 3.23, 95% CI: 2.73-3.81) and TZD (HR: 2.23, 95% CI: 2.35-4.44) as an add-on therapy to metformin, and findings were similar with the risk of urinary tract infections. Subgroup analyses were done on sex and age groups, showing increased risk in women and patients aged over 60 years. Results of sensitivity analyses were consistent, and even showed higher HRs in most of the results compared to the primary analysis.

Conclusions: Our study found that SGLT-2 inhibitors are significantly associated with higher risk of genital and urinary tract infections compared to those of DPP-4 inhibitors, SU and TZD. In particular, women and patients over 60 years of age tend to have a higher risk, so careful monitoring can be recommended.

Pharmacovigilance -> Neurological/Mental Health

29 | Adherence to laboratory monitoring among people taking oral drugs for multiple sclerosis: A population-based study

Huah Shin Ng[1], Elaine Kingwell[1], Feng Zhu[1], Tingting Zhang[2], Ruth Ann Marrie[3], Robert Carruthers[1] and Helen Tremlett[1]

[1]University of British Columbia, Vancouver, BC, Canada; [2]Brown University School of Public Health, Providence, RI; [3]University of Manitoba, Winnipeg, MB, Canada

Background: The oral disease-modifying therapies (DMTs) for multiple sclerosis (MS) are associated with improved drug adherence relative to the injectable DMTs. However, it is not known how well MS patients adhere to the blood and urine tests that are required for safety monitoring.

Objectives: We examined adherence to recommended laboratory testing by persons who initiated an oral DMT for MS.

Methods: Population-based health administrative and laboratory data were accessed. All people in the province of British Columbia, Canada, filling their first prescription for dimethyl fumarate, fingolimod or teriflunomide (2011-2015) were identified. The proportion of people adherent to each drug monograph's recommended laboratory monitoring schedule, pre- and on-DMT, was estimated for lymphocytes, liver enzymes, and urine protein. The association between adherence and sex, age, socioeconomic status, comorbidity and previous exposure to non-oral DMT were examined using the generalized estimating equation and multivariable logistic regression.

Results: Overall, 1016 people were included (dimethyl fumarate n=567; fingolimod n=253; and teriflunomide n=196). The proportions of people who were adherent to the recommended laboratory monitoring schedule prior to oral DMT initiation was 88-91% for liver tests and 91-94% for lymphocyte tests (dimethyl fumarate, fingolimod and teriflunomide), and 77% for urinalysis (dimethyl fumarate only). Adherence to the first on-DMT liver test was 89% for dimethyl fumarate (within 6 months); 61% for fingolimod (within 3 months); and 40% for teriflunomide (within 1 month). For dimethyl fumarate, adherence was 90% for the first lymphocyte test and 75% for urinalysis (each within 6 months). Men were less likely than women to have a urinalysis (adjusted odds ratio [aOR]=0.61; 95%CI:0.40-0.95) before initiating dimethyl fumarate, or liver (aOR=0.46; 95%CI:0.23-0.95) or lymphocyte (aOR=0.47; 95% CI:0.22-0.98) tests while taking dimethyl fumarate.

Conclusions: Adherence to recommended laboratory testing was high (>77%) before oral DMT initiation, but lower once on drug. There is a need to understand the long-term consequences of suboptimal laboratory monitoring in the DMT-treated MS population. The sex differences also warrant further investigation.

36 | Fingolimod associated with molluscum contagiosum virus infection as adverse events: Safety review

Abdulrahman Alomair, Abdulziz Alaqeel, Mohammed Fouda, Adel Alrwisan and Hajer Al-saleh

Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: Fingolimod is sphingosine 1-phosphate receptor modulator indicated to treat Relapsing Remitting Multiple Sclerosis (RRMS). Molluscum Contagiosum (MC) is benign skin disease caused by a poxvirus. It is characterized by small pearly papules with core that may produce a white cheesy material. Saudi Food and Drug Authority (SFDA) has initiated a safety review based on detected signal from Saudi National Pharmacovigilance center database (NPC).

Objectives: This review aim to evaluate the risk of MC associated with Fingolimod.

Methods: SFDA team performed a safety review on July 16, 2019 using NPC database, WHO database (VigiBase), and literature screening to retrieve related information would be beneficial to assess the causality between MC and Fingolimod.

Results: **Local Cases:** NPC database has only one case report of Fingolimod associated with MC. After applying WHO causality assessment, the case has possible association. **Global Cases:** WHO database (VigiBase) searched for all individual case safety reports (ICSRs) reported MC with Fingolimod yielded to 48 ICSRs. Initial review revealed that 32 cases were not sufficiently documented for medical assessment. However the rest 16 cases has been evaluated resulted in one positive dechallenge and one negative dechallenge, after applying WHO causality assessment, all cases showed possible association. Moreover, Fingolimod was the most reported medication with the adverse reaction term MC in WHO database when compared with all other medications in VigiBase. **Literature:** Only one case report has founded support the possible association between the use of Fingolimod and the risk of MC. 18 year old man with history of RRMS who developed MC infection shortly after starting Fingolimod. **Datamining:** Information Component (IC) developed by Uppsala Monitoring Centre has been used to calculate the reporting ratio between drug and event. The combination of Fingolimod and MC has observed

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

more than expected (IC 4.88) when compared with other medications in VigiBase. **Biological plausibility:** Fingolimod has immunosuppressive effect which can increase the risk of opportunistic infections that include MC viral infection.

Conclusions: Several cases of MC have been reported with the use of Fingolimod. However, the mechanism of MC with Fingolimod use is unclear but it could be due to immunosuppressive effect of the drug. The evidence identified in this review is sufficient to support a causal association between MC and Fingolimod. Therefore, health care professionals should be aware of this possible risk and may consider to monitor any signs of MC in patients treated with Fingolimod.

2404 | Evaluation of spontaneous adverse event reports for alopecia attributed to erenumab within the FDA adverse events reporting system

Mohamed Mekkawy
High Institute of Public Health, Alexandria University, Alexandria, Egypt

Background: Erenumab is a monoclonal antibody that blocks the activation of calcitonin gene-related peptide (CGRP) that can produce a migraine attack, it was approved for the preventive treatment of migraine in adults in May 2018 and post-marketing experience is still lacking.

Objectives: To describe and evaluate the spontaneous adverse event reports of alopecia attributed to erenumab in the FDA adverse events reporting system (FAERS).

Methods: The published database quarterly files starting from the third quarter of 2018 till the third quarter of 2019 were queried for reports listing alopecia attributed to erenumab administration as the primary suspected drug. We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR).

Results: We identified 793,104 reports in the period between January 2018 and September 2019: 13,069 (1.6%) reports mentioned erenumab. On the other hand, there were 6,810 (0.86%) alopecia reports during the same period of which 360 (5.3%) were attributed to erenumab administration. The PRR and ROR were as following: PRR: 3.3, 95% CI: 3.0 - 3.7, ROR: 3.4, 95% CI: 3.1-3.8.

Conclusions: Although FAERS is subject to many limitations such as under-reporting, the results suggest that erenumab is associated with a higher risk of alopecia which needs further studies to confirm or deny this claim.

2439 | Role of dopamine D3 and serotonin 5-HT_{2A} receptors in antipsychotic associated hyponatraemia: A Pharmacovigilance-pharmacodynamic assessment through an analysis of the US food and drug administration adverse event reporting system (FAERS) database

Faizan Mazhar, Carla Carnovale, Vera Battini, Sonia Radice and Emilio Clementi
University of Milan, Milan, Italy

Background: Hyponatraemia induced by antipsychotic drugs is a rare but potentially life-threatening adverse reaction (ADRs); underlying pharmacological mechanisms of this association remain unclear suggesting the need for further investigations for guiding antipsychotic therapies, especially in patients with electrolytic imbalances.

Objectives: To investigate the putative relationship between different antipsychotic pharmacological targets and the risks of hyponatraemia induced by antipsychotic drugs by using information reported to the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: A nested case-control was conducted using FAERS database. From the base cohort consisting of ADRs for antipsychotic drugs, we selected cases, i.e. ADRs of hyponatraemia/ Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), and controls, i.e. all other ADRs. Multiple logistic regression with the adjustment for covariates (sex, age and concomitant medications associated with hyponatraemia/SIADH), completed by disproportionality analysis were used to determine the associations between antipsychotics' receptor occupancy (dopaminergic D_1, D_2, D_3, D_4, histamine H_1, muscarinic M_1, M_2, adrenergic α_1, α_2, serotonin 5-HT1A, 5-HT2A, 5-HT_2C) and reporting of hyponatraemia.

Results: During the study period, 139,816 reports involved at least one antipsychotic. Hyponatraemia/ SIADH was reported in 1,521 (1.1%) patients. Olanzapine was the most frequently suspected drug (n=410; 27%). A significant positive association was found between dopamine D3, D4 and reports of hyponatraemia, while adrenergic α_1, serotonin 5-HT1A, 5-HT2A receptor occupancies showed a significant negative association. A multivariable stepwise regression model showed that only dopamine D3 (AOR=1.21, CI 95% 1.09-1.34; $p<0.05$) predicted the risk for hyponatraemia ($p<0.05$) while serotonin 5-HT2A occupancy (AOR=0.78, CI 95% 0.68-0.91; $p<0.01$) exhibit a protective effect against hyponatraemia.

Conclusions: Our findings supports that antipsychotic drugs blocking D3 receptors are more frequently associated with hyponatraemia reports in FAERS while 5-HT2a blockade appears to have a protective effect against hyponatraemia. Our PV-PD analysis suggest that serotonin-mediated effects on central 5-HT2 and 5-HT_{1c} receptors may not be involved in the hyponatraemia linked to the use of Hyponatraemia drugs.

2507 | Comparative pharmacovigilance analyses of pimavanserin and mortality in Parkinson's disease

Joshua Brown[1], Brian Cicali[1], Carl Henriksen[1], Irene Malaty[2], Michael Okun[2] and Melissa Armstrong[2]
[1]*University of Florida College of Pharmacy, Gainesville, FL;* [2]*University of Florida College of Medicine, Gainesville, FL*

Background: Pimavanserin is approved for treatment of Parkinson's disease (PD)-related psychosis but has been associated with an increased risk of death. Media reports regarding this association have not taken into account limitations of the data source nor relevant comparisons to treatment alternatives.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: This study aimed to conduct a comparative pharmacovigilance assessment of pimavanserin versus treatment alternatives.

Methods: This was a retrospective analysis of adverse event case reports submitted to the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) from 2016 through Q3/2019. Reports were assessed for exposure to pimavanserin, clozapine, quetiapine, haloperidol, and other antipsychotics. PD-specific medications were used to restrict the base population to those with confirmed PD. The outcome of interest was all-cause death. A Proportional Reporting Ratio (PRR) and 95% confidence limits were calculated for each two-by-two contingency of outcome (death) and exposure (pimavanserin, etc.). For each outcome/exposure pair, the baseline population was altered to include the full FAERS sample, only reports with PD treated with levodopa, and only reports with PD treated with multiple medications. The sample was also stratified by time period before April 2018 and after September 2018 to capture periods of public knowledge and federal response. A lower confidence limit (LCL) of ≥2 was considered as the commonly accepted threshold for a drug safety signal.

Results: As of Q3/2019, there were 2,287 reports of death associated with pimavanserin. In the full FAERS base population, pimavanserin yielded a PRR LCL=2.08 but was smaller when restricted to those with PD treated with levodopa (LCL=1.15) or multiple PD medications (LCL=1.63). Stratification by time showed a possible reporting bias associated with pimavanserin. Pimavanserin metrics were similar in direction and magnitude to clozapine and quetiapine.

Conclusions: Compared in context to treatment alternatives, pimavanserin was not associated with excess risk of death in patients with PD. Given the severity of PD-related psychosis, treatment options are needed for shared decision-making between physicians and patients that balances both risks and benefits.

2567 | Time to onset analysis of montelukast associated suicidal ideation using data from FDA adverse event reporting system database (FAERS)

Subeesh Kulangara Viswam[1], Neha Reddy[1], Jahnavi Yalamanchili[1], Prizvan Lawrence Dsouza[1], Faizan Mazhar[2] and Nair Gouri[1]
[1]M.S. Ramaiah University of Applied Sciences, Bangalore, India; [2]L. Sacco, "Luigi Sacco" University Hospital, Università Di Milano, Milan, Italy

Background: Montelukast is used for the treatment of chronic asthma and for the symptomatic relief of allergic rhinitis. The association of montelukast use and suicidal ideation is being discussed in the recent past. However, the time-to-onset for such event is seldom investigated.

Objectives: To examine the time-to-onset profile of montelukast associated suicidal ideation using Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: A systematic data mining was performed in FAERS Database (Q4/2003-Q3/2019) using OpenVigil 2.1, a pharmacovigilance analytical tool. Cumulative incidences of suicidal ideation were assessed using the Kaplan-Meier method and Log-rank test was used to compare the cumulative incidences of suicidal ideation between patients treated with montelukast and those treated with all the other drugs. Time-to-onset profiles were analyzed using the Weibull shape parameter test. A larger value of scale parameter stretches the distribution, whereas a smaller value shrinks the distribution. shape parameter <1, ~1 and >1, the hazard was considered to have early failure-type profile, random failure type profile and wear-out failure-type profile respectively. Shape and scale parameter of montelukast was also compared with all the other drugs reported for suicidal ideation.

Results: We identified a total of 30,408 reports for suicidal ideation of which 1,531(5%) were attributed to montelukast. The median time-to-onset of the event associated with montelukast was 8 (range: 3-31) days. Patients treated with other drugs showed almost similar time-to-onset, 6 days (range: 3-21). The cumulative incidence of suicidal ideation significantly differed between patients treated with montelukast and other drugs (log-rank test, $P < 0.002$). Montelukast associated suicidal ideation (shape:0.453, scale:37.1) and other drug-associated suicidal ideation (shape: 0.48, scale: 17.1) indicated early failure-type profile, which means the event is more of acute and early onset in nature. However, the time to onset data is more widely distributed in both instances.

Conclusions: Montelukast associated suicidal ideation had an onset profile that was similar to that of other drugs. As montelukast associated suicidal ideation is more of acute and early onset in nature, attention should be more focused on the earlier stages of treatment especially in patients with baseline risk.

2616 | Comparative risk of parkinsonism associated with olanzapine, risperidone and quetiapine in older adults

Te-yuan Chyou[1], Revathi Nishtala[2] and Prasad Nishtala[3]
[1]University of Otago, Dunedin, New Zealand; [2]University of Leeds, Leeds, United Kingdom; [3]University of Bath, Bath, United Kingdom

Background: In New Zealand (NZ), clinical trials provide limited information on the comparative risk of Parkinsonism associated with second-generation antipsychotics (SGAs) in older adults.

Objectives: This study examines the incidence of Parkinsonism in new users of SGAs in older adults (≥ 65 years). As secondary analyses, we examined the risk of Parkinsonism by type and dose of SGA and also the age-sex interactions.

Methods: We used the NZ national minimum data set and the pharmaceutical collections to identify older adults who had a diagnosis of Parkinsonism and who started taking olanzapine, risperidone or quetiapine between 01/01/2005 and 31/12/2016. Confounding was mitigated using propensity score methods. The Cox proportional hazard (COXPH) regression model with inverse treatment probability weighting (ITPW) was used to evaluate the risk of Parkinsonism associated with SGAs, using quetiapine as the reference. We used the generalized propensity score method, where daily doses as

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

continuous variables were used as exposure variables, to evaluate the dose-response risk of Parkinsonism associated with SGAs.

Results: After ITPW adjustment for confounders including comorbidity, the COXPH model showed that compared to quetiapine, the use of olanzapine and risperidone were associated with an increased risk of parkinsonism (ITPW-adjusted hazard ratio (ITPW-HR) 1.76, 95% confidence interval 1.57 to 1.97; and ITPW-HR 1.31 (1.16 to 1.49) respectively). The dose-response risk of Parkinsonism was highest for olanzapine (HR 1.69 (1.40 to 2.05)) and the least for quetiapine (HR 1.22 (1.14 to 1.31)). Age-sex interactions revealed risk of Parkinsonism in the 65-74yr group was higher for both sexes with risperidone compared to olanzapine, but the risk increased significantly with olanzapine for both sexes in the 85yr+ group.

Conclusions: The study found that quetiapine use might be associated with a relatively lower risk of Parkinsonism than olanzapine or risperidone in older adults. Prescribers should exercise caution when using olanzapine in the oldest old.

2656 | Evaluation of spontaneous adverse event reports for drug abuse, misuse, dependence or off-label use attributed to pregabalin within the FDA adverse events reporting system (FAERS)

Ahmed M. Elkersh[1], Mai M. Salama[2] and Mohamed A. Mekkawy[1]
[1]*High Institute of Public Health, Alexandria, Egypt;* [2]*Medical Research Institute, Alexandria, Egypt*

Background: Pregabalin abuse and dependence have become increasingly reported. However, no study has analyzed spontaneous reports of adverse events with this drug in the most recent years that led to worldwide regulatory actions.

Objectives: To describe and evaluate spontaneous adverse event reports of drug abuse, misuse, dependence or off-label use attributed to pregabalin.

Methods: We identified adverse events reports listing pregabalin in the FDA Adverse Events Reporting System (FAERS) from January 2014 to September 2019. We used the terms "pregabalin," and "Lyrica," to identify pregabalin. The "Intentional product misuse," "drug abuse," and "off-label use" MedDRA terms were used to identify the drug abuse, misuse, dependence and off-label use events. We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) for this drug.

Results: Among 3,351,770 FAERS reports between January 2014 and September 2019, around 28890 (1%) reports mentioned pregabalin. There were 168064 (5%) drug abuse, misuse, dependence and off-label use reports during the same period of which 3723 (2%) was attributed to pregabalin. The PRR was 2.605 (95% CI: 2.527, 2.685), and the ROR was 2.843 (95% CI: 2.746, 2.943).

Conclusions: Although FAERS is subject to significant limitations, the results suggest that pregabalin has a statistically significant association with an increased incidence of drug abuse, misuse, dependence and off-label use. pregabalin prescribers should evaluate the patient's history of drug abuse and monitor carefully all possible adverse effects.

3745 | Concomitant use of gabapentinoids and opioids following surgery and the risk of opioid-related adverse events

Katsiaryna Bykov, Brian T. Bateman, Jessica M. Franklin and Elisabetta Patorno
Brigham and Women's Hospital, Boston, MA

Background: Gabapentinoids (pregabalin and gabapentin) are commonly used as part of multimodal postoperative analgesia. However, when co-administered with opioids, these drugs may potentiate central nervous system and respiratory depression.

Objectives: To assess whether co-administration of gabapentinoids with opioids is associated with increased risk of opioid-related adverse outcomes, including overdose, in surgical patients.

Methods: Using Premier inpatient research database, we conducted a cohort study of US adults who underwent a major surgery between October 2007 and December 2017 and compared patients who received gabapentinoids + opioids to patients who received opioids only. The primary outcome was opioid overdose, identified based on discharge diagnoses and naloxone (opioid antagonist that reverses overdose) use, which was used to define the outcome date. Secondary outcomes were respiratory depression, unspecified adverse effects (AEs) of opioids, and a composite of these three outcomes. Patients were followed from the day of surgery for 30 days or until discharge in intent-to-treat analysis (ITT); in as-treated analyses, we censored patients upon therapy modification. To adjust for confounding, we used propensity score (PS) fine stratification (PSS) with asymmetric trimming and weighting. A weighted Cox proportional hazard model estimated the hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Following PS trimming, there were 737,383 gabapentinoid-exposed patients and 3,002,480 patients in opioids-only group. Mean age was 64 years old and 41% were male. We identified 327 overdose events, 9126 respiratory depression events, and 3041 events of opioid AEs. Patient, surgery, and initial opioid characteristics, including mean morphine milligram equivalents administered on the day of surgery, were well balanced between the exposure groups after PSS weighting. The PSS-weighted HR for overdose was 1.72 (95% CI 1.36 - 2.19) in ITT analysis and 1.95 (95% CI 1.53 - 2.49) in as-treated analysis. For secondary outcomes, ITT HRs (95% CIs) were 1.65 (1.57 - 1.73) for respiratory depression, 1.69 (1.56 - 1.83) for opioid AEs, and 1.65 (1.58 - 1.73) for the composite outcome. As-treated analyses yielded similar results.

Conclusions: In this real-world cohort of patients undergoing a major surgery, concomitant use of gabapentinoids with opioids was associated with higher risk of opioid overdose and other opioid-related adverse events, including respiratory depression. The absolute risk of adverse events was low.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4053 | Risks of adverse cardiovascular outcomes associated with antipsychotic use in people with dementia

Pearl L.H. Mok[1], Matthew J. Carr[1], Bruce Guthrie[2], Daniel Morales[3], Tjeerd van Staa[4], Antony J. Avery[5] and Darren M. Ashcroft[1]
[1]*Division of Pharmacy and Optometry, University of Manchester, Manchester, United Kingdom;* [2]*College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, United Kingdom;* [3]*Population Health and Genomics, University of Dundee, Dundee, United Kingdom;* [4]*Division of Informatics, Imaging & Data Sciences, University of Manchester, Manchester, United Kingdom;* [5]*Division of Primary Care, University of Nottingham, Nottingham, United Kingdom*

Background: Behavioural and psychological symptoms associated with dementia are sometimes treated with antipsychotics (AP). There is a known risk of stroke and death linked with AP use that regulatory warnings are largely focussed on, but far less is known about other potentially important cardiovascular-related risks associated with their use.

Objectives: To investigate risks of serious cardiovascular outcomes - stroke, venous thromboembolism (VTE), myocardial infarction (MI), and heart failure - associated with AP use in people with dementia.

Methods: We conducted a population-based cohort study using data from Clinical Practice Research Datalink (CPRD GOLD) linked to hospital and mortality records. The cohort included 35,055 patients aged 50 years or over, and with a first dementia diagnosis between January 1998 and May 2018. Follow up began from the date of dementia diagnosis until the date of the cardiovascular event, death, transfer out of general practice, last data collection date of the general practice, or 31st May 2018, whichever came first. Exposure to AP was treated as time-varying defined as: current use - date of prescription + 90 days, recent use - 1-180 days after current use ended, past use - over 180 days after current use ended, and unexposed. For sensitivity analyses, the definitions of current and recent use were varied using 30 or 60 days after prescription date, up to 60 or 120 days after current use ended, respectively. Hazard ratios (HR) were estimated using Cox models.

Results: Compared with periods unexposed to AP use, current and recent use of AP were associated with significantly elevated risks for stroke and VTE - stroke: current use HR 1.65 (95% CI 1.46-1.87), recent use HR 1.79 (1.38-2.33); VTE: current use HR 1.59 (1.29-1.96), recent use HR 1.81 (1.18-2.77). Current use of AP, but not recent use, was also linked with elevated risks for MI: HR 1.33 (1.09-1.62), and for heart failure: HR 1.21 (1.04-1.40). Past exposures to AP was not associated with elevated risks for any of the four outcomes. Similar results were observed in sensitivity analyses when different definitions of AP exposure were applied.

Conclusions: Use of AP was associated with elevated cardiovascular risks in patients with dementia. Our findings suggests that these risks need to be considered when prescribing AP to these patients, especially for those without psychotic symptoms, and to be included in warnings from regulatory authorities.

4086 | Association between desloratadine use and incidence of non-febrile seizure - A Nordic cohort study

Annette Kjær Ersbøll[1], Thora Majlund Kjærulff[1], Kaushik Sengupta[1], Eero Pukkala[2], Kristian Bolin[3], Martha Emneus[4], Daniel Mines[5], Dena Rosen Ramey[5], Joanne E. Brady[5], Kristian Aasbjerg[6], Christian Vestergaard[7] and Gunnar Gislason[8]
[1]*University of Southern Denmark, Copenhagen, Denmark;* [2]*Tampere University, Finland, Tampara, Finland;* [3]*University of Gothenburg, Gothenburg, Sweden;* [4]*Applied Economics and Health Research Aps, Copenhagen, Denmark;* [5]*Merck & Co., Inc., Kenilworth, NJ;* [6]*Aarhus University Hospital, Skejby, Denmark;* [7]*Aarhus University Hospital, Aarhus, Denmark;* [8]*Gentofte Hospital, Copenhagen, Denmark*

Background: Desloratadine (DL) is a non-sedating antihistamine first marketed in 2001. Seizure has been reported in children using DL. We conducted a post-authorization safety study in individuals with no history of seizure.

Objectives: To assess the association between DL use and incidence of non-febrile seizure.

Methods: We conducted a Nordic registry-based cohort study among individuals with a first prescription redemption of DL in 2001-2015. Individual-level data from health registries in Denmark, Finland, and Sweden were used to derive a common database. DL exposure was a time-varying variable defined for each prescription redemption as days' supply plus a 4-week grace period. Unexposed periods (remote prior exposure) were defined as starting 26 weeks after date of prescription redemption. The outcome was incident non-febrile seizure. The association between DL exposure and incidence rate (IR) of seizure was analyzed using Poisson regression of number of seizures as outcome and logarithmic transformation of follow-up time as the offset. Potential confounders were identified using causal diagrams and included country, calendar year, sex, age, seasonality, and history of asthma, severe rhinitis and chronic urticaria. Results are presented as IR per 100,000 person-years (PY) and incidence rate ratio with corresponding 95% confidence interval (IRR, 95% CI).

Results: The study included 1,561,410 incident DL users of all ages of which 2,297 individuals were diagnosed with incident seizure in the primary analysis. The IRs of seizure were 39.9 and 30.1 per 100,000 PY for currently DL exposed and unexposed periods. A significant association between current DL exposure and incidence of non-febrile seizure was seen (IRR 1.32 95% CI 1.19; 1.48). The adjusted association between being currently DL exposed and incidence of non-febrile seizure showed an increase of 17% in the IR of non-febrile seizure during the exposed periods (IRR 1.17 95% CI 1.05; 1.31). The association was strongest among children 0-4 years of age (IRR=1.47; 95% CI: 1.16; 1.87).

Conclusions: A 17% higher IR of non-febrile seizure was seen in individuals comparing current DL exposed and unexposed periods. The finding is consistent with pharmacovigilance data. DL should be administered with caution in patients with personal or family history of seizures.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4137 | Safety profile of ocrelizumab for the treatment of multiple sclerosis: A systematic review

Huah Shin Ng, Constanza Luzon and Helen Tremlett
University of British Columbia, Vancouver, BC, Canada

Background: Ocrelizumab has been approved for the treatment of relapsing and primary progressive multiple sclerosis (MS).
Objectives: This review aims to provide a comprehensive summary of reported adverse events for ocrelizumab, using a systematic approach.
Methods: We searched four biomedical databases (Medline, Embase, Web of Science and Toxicology Data Network-TOXLINE) from their inception to May 2019, using search terms "multiple sclerosis, clinically isolated syndrome and ocrelizumab". We also searched clinical trial registries, drug company websites and product monographs of ocrelizumab. We included studies which reported participants 18 years of age or older with a diagnosis of MS or clinically isolated syndrome. The outcomes of interest included any adverse events reported in a broad range of study designs including clinical trials, observational studies and case reports. The searches and data extraction were conducted independently by two authors and any disagreements were resolved by consensus with the third author.
Results: Our search identified 1417 records (as of May 2019). Overall, 48 records were included, which accounted for 15 unique studies (4 randomized control trials (RCTs), 2 open-label trials and 10 observational studies) and 6 case reports. Adverse events were identified in 1226 out of 1437 patients treated with ocrelizumab (85.3%). The most common adverse event reported in the ocrelizumab group was infection (n=1002, 48.1% of patients treated), followed by infusion-related reaction (n=764, 27.3% of patients treated). The most common infections reported were nasopharyngitis, upper respiratory tract infections and urinary tract infections. Overall, 178 (9.9%) patients with serious adverse events were identified in the ocrelizumab treated groups and 134 (2.8%) patients discontinued ocrelizumab due to adverse events.
Conclusions: This systematic review collated serious and total adverse events among patients treated with ocrelizumab for MS, including not only those reported in published clinical trials, but also adverse events from ongoing studies, case reports and post-marketing surveillance. Our observations may help guide future post-marketing surveillance initiatives and pharmacovigilance studies.

4578 | Risperidone and methylphenidate: Case reports and pharmacovigilance safety reports on adverse motor effects

Andrea Michelle Burden[1], Dominik Stämpfli[1] and Stefan Weiler[1,2]
[1]*Swiss Federal Institute of Technology, Zurich, Switzerland;* [2]*Tox Info Suisse, Zurich, Switzerland*

Background: A combination of the psychostimulant methylphenidate and the second-generation antipsychotic risperidone may be prescribed to treat attention deficit hyperactivity disorder with comorbid conduct-dissocial disorder. Pharmacodynamic considerations indicate a high potential for interacting adverse motor effects.
Objectives: We aimed (1) to summarise published case reports with both methylphenidate and risperidone and (2) to analyse pharmacovigilance data to investigate adverse motor effects when methylphenidate and risperidone are reported in combination for young patients.
Methods: PubMed, Google Scholar, and Qinsight were searched for published case reports on adverse motor effects under the combination of methylphenidate and risperidone. Pharmacovigilance data consisted of aggregated information on individual case safety reports (ICSRs) within the WHO Uppsala Monitoring Centre's VigiBase for reported ages > 0 days and < 18 years. We calculated reporting odds ratios (RORs) and corresponding 95% confidence intervals (CIs) for the pharmacovigilance data, and summarised ICSR characteristics.
Results: We identified eight case reports from our literature review in which both methylphenidate and risperidone were used in combination. In all reports adverse motor effects were described when the dosing of risperidone was intentionally or accidentally modified. VigiBase contained 25,556 ICSRs (16,118 for methylphenidate, 8,614 for risperidone, and 824 for both). Of these, adverse motor effects were reported in 953 (5.9) ICSRs with methylphenidate, 1,356 (5.9%) ICSRs with risperidone, and 159 (19.3%) ICSRs where combination use was reported. The 159 ICSRs on combination use included 136 (85.5%) males and 21 (13.2%) females; gender was not reported in 1.3% of cases. Mean age was of 10.2 (± 2.9) years. RORs showed a disproportionality in reporting for adverse motor effects when both drugs were reported, compared to methylphenidate (ROR = 3.80, 95% CI: 3.16 - 4.58) or risperidone (ROR = 1.28, 95% CI: 1.07 - 1.54).
Conclusions: The potential of adverse motor effects might be amplified when methylphenidate and risperidone are used in combination. The over-arching narrative of the identified case reports underlines the necessity of caution and patient monitoring when risperidone dosing is modified during methylphenidate therapy.

4601 | Antipsychotics and the risk of catatonia

Julien Da Costa[1,2], Etienne Very[1,2], Vanessa Rousseau[1,2], Jordan Virolle[2], Maximilien Redon[2], Simon Taïb[1,2], Alexis Revet[1,2] and François Montastruc[1,2]
[1]*Paul Sabatier University, Toulouse, France;* [2]*Toulouse University Hospital, Toulouse, France*

Background: Catatonia associated with antipsychotic drugs is a severe psychomotor syndrome including several symptoms such as motor, behavioural or affective disturbances. Although some case reports argue that first generation antipsychotics (FGA), by their higher blockade of the dopamine D2 receptor, are more likely to induce a catatonic syndrome than second generation antipsychotics (SGA), no large observational study confirm this hypothesis, nor evaluate whether differences exist between each antipsychotic drug.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To investigate whether FGAs were associated with an increased risk of reporting catatonia including neuroleptic malignant syndrome and malignant catatonia when compared with SGAs.

Methods: We performed a pharmacovigilance study within VigiBase, the World Health Organization's global database of individual case safety reports, from 1968 to 2018 to compare the cases of catatonia reported in patients exposed to FGAs with those reported in patients exposed to SGAs. We conducted disproportionality analyses (case non-case method) allowing the estimation of reporting odds ratios (RORs) with 95% CIs of the exposure odds among spontaneous reports of catatonia to the exposure odds among other reported adverse effects.

Results: We identified 60,443 adverse effects reported in patients who received FGAs and 253,067 adverse effects reported in patients treated with SGAs. Compared with SGAs, the use of FGAs was associated with an increased risk of reporting catatonia (1,862 reports for FGAs and 3,557 for SGAs (ROR 2.2; 95% CI 2.0, 2.3)). Consistent results were observed when the analysis was restricted to reports generated from physicians, from the US and to reports with the highest completeness score. The highest RORs of catatonia were found for molindone (6.0; 95% CI 3.1, 10.4) and haloperidol (3.8; 95% CI 3.5, 4.0).

Conclusions: In this real-world study including more than 300,000 reports of patients exposed to antipsychotics from any country in the world, the use of FGAs was associated with an increased risk of reporting catatonia compared to the use of SGAs. This increased risk is consistent with the pharmacodynamic hypothesis of catatonia induced by antipsychotic drugs since it suggests that the greater dopamine D2 receptor activity is, the higher catatonia are reported. Our results warrant replication in population-based studies.

4645 | Impact of clinical pharmacists interventions on pharmacotherapy management of ambulatory psychiatry patients through JSS MINDS initiative

Srikanth Siddalingegowda[1], P.B. Samaksha[1], Ramesh Madhan[1], M. Kishor[2] and Raman Rajesh[2]

[1]JSS College of Pharmacy, Mysuru, India; [2]JSS Medical College & Hospital, Mysuru, India

Background: Nonadherence in psychiatric patients contributes to increase with the number of psychotic illness and mortality. Clinical pharmacist role in psychiatry is mainly focused in patient education, medication adherence, helping to ensure the safe use of medication; providing comprehensive drug information to patients; and supporting primary prevention.

Objectives: This study was conducted to identify the nonadherence to medication for ambulatory psychiatry patients.

Methods: A prospective interventional study was conducted in psychiatry outpatient department of JSS hospital, Mysuru over a period of eleven months. All the enrolled patients were followed on their scheduled visits of ambulatory psychiatric patients. Customized patient medication counseling was provided to both patient and caretaker. Patient were followed and follow up will be reminded through telephonic contact. Hepler and Strands classification was adopted to identify drug related problems. Drug interactions were checked using Micromedex and Statistical analysis was carried categorically.

Results: : The study included 1074 patients (mean age = 36.6, 44% women) and 793 patients were under the age group of 20-40 years. A total of 1160 clinical pharmacy services were provided to 639 patients that includes patient counseling (n= 639, 55.1%), pharmacist interventions (n= 367, 31.6%) and drug information (n= 154, 13.2%). Amongst the pharmacists interventions, majority were related to dose correction (n= 128, 35%), drug-drug interactions (n=114, 31%) and rest were adverse drug reactions (ADRs) (n=67, 18%), and remaining were drug interactions. Musculoskeletal system (n= 21, 31%) and neurological class (n= 13, 19%) were affected due to ADRs. Majority of the ADRs had possible causality association (n= 48, 72%), moderately sever (Level 4a & 4b: 51% & 20%), predictable (n = 37%, 55%) but not preventable (n=41, 61%). While majority of the DDIs were moderate (n=79, 69%) in nature. Most of the interventions (n= 319, 89%) were accepted by the psychiatrists and implemented. Further, 36% of bipolar disorder, 21 % of schizophrenia, 23% of depression and 21% of other disorders were found to be poorly adherent to medications and their care givers were trained for the same.

Conclusions: Coordinated and dedicated approaches by clinical pharmacists can help in improve the better medication adherence in psychiatry patients with decreased mortality. Clinical pharmacist services were appreciated by psychiatrist.

5048 | Evaluation of a potential gabapentinoid - somnolence - stimulant prescribing cascade among adults: A prescription sequence symmetry analysis

Earl J. Morris, IV, Brianna Costales, Xinyi Jiang, Amie Goodin and Scott M. Vouri

University of Florida College of Pharmacy, Gainesville, FL

Background: Gabapentinoids (e.g., gabapentin, pregabalin) are frequently used off-label for pain and psychiatric conditions. Gabapentin alone rose from the seventh most prescribed medication in 2017 to the fourth most prescribed medication in the United States by January 2019. Gabapentinoid-associated somnolence (i.e. drowsiness and fatigue) has an estimated incidence of over 20% in adults. While gabapentinoids have demonstrated efficacy for some pain conditions, this must be weighed against the potential for development of daytime somnolence. Subsequent treatment of these symptoms with a stimulant is possible, resulting in a potential prescribing cascade. A gabapentinoid-somnolence-stimulant cascade is not only avoidable but also presents a drug safety concern as both medication classes have misuse and abuse potential, especially when used in combination.

Objectives: To examine whether gabapentinoid initiation is associated with excess initiation of stimulant therapy.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: We performed a prescription sequence symmetry analysis (PSSA) to assess new use of a gabapentinoid relative to new use of a stimulant among adults aged ≥ 18 years using the IBM MarketScan® Commercial Claims and Medicare Supplemental Database from 2005 to 2018. Secular trend-adjusted sequence ratios (aSR) with 99% confidence intervals (CI) were calculated within ±360 days of gabapentinoid initiation. Stratified analyses were performed on age (18-49, 50-64, ≥ 65 years), sex, and individual gabapentinoids.

Results: Among 1,355,734 gabapentinoid initiators, 14,004 (1.03%) had a new stimulant prescription within ± 360-days, resulting in aSR of 1.12 (99% CI 1.07-1.16). The estimated incidence of the potential prescribing cascade was 0.06%. A positive association was found for adults aged 18-49 (aSR 1.11 [99% CI 1.05-1.17]) and aged 50-64 (aSR 1.13 [99% CI 1.04-1.23]); however, no association was found in adults aged ≥ 65 (aSR 1.18 [99% CI 0.97-1.44]). The aSRs among gabapentinoid initiators did not appear to differ among age sex (males: aSR 1.10 [99% CI 1.02-1.18]; females: aSR 1.13 [99% CI 1.07-1.19]). The prescribing cascade did not differ among pregabalin initiators (aSR 1.18 [99% CI 1.06-1.31]) vs. gabapentin initiators (aSR 1.11 [99% CI 1.05-1.16]).

Conclusions: Our findings suggest that a gabapentinoid-somnolence-stimulant prescribing cascade is rarely observed among gabapentinoid new users. However, given the widespread use of gabapentinoids, many patients may still be impacted.

5057 | Evaluation of a potential atypical antipsychotic - diabetes - antidiabetic agent prescribing cascade among adults: A prescription sequence symmetry analysis

Earl J. Morris, IV[1], Zachary A. Marcum[2], Xinyi Jiang[1] and Scott M. Vouri[1]

[1]*University of Florida College of Pharmacy, Gainesville, FL;* [2]*University of Washington College of Pharmacy, Seattle, WA*

Background: Atypical antipsychotics are used to treat symptoms of various psychiatric conditions, including schizophrenia, bipolar disorder, depression, dementia, and Alzheimer's disease. While these drugs are generally efficacious for treatment of psychiatric symptoms, they pose a risk of hyperglycemia and diabetes. Furthermore, current evidence is contradictory regarding differential effects on development of diabetes among different atypical antipsychotics.

Objectives: To examine whether atypical antipsychotic initiation is associated with excess initiation of antidiabetic medications.

Methods: We performed a prescription sequence symmetry analysis (PSSA) to assess new use of an atypical antipsychotic in relation to new use of an antidiabetic agent among adults aged ≥ 18 years using the IBM MarketScan® Commercial and Medicare Supplemental Database from 2005 to 2018, excluding those with a diagnosis of type 1 diabetes mellitus, schizophrenia, or polycystic ovary syndrome. Secular trend-adjusted sequence ratios (aSR) with 99% confidence intervals (CI) were calculated within ± 360 days of atypical antipsychotic initiation. Stratified analyses were performed on age categories (18-49, 50-64, ≥ 65 years), sex, and individual atypical antipsychotics.

Results: Among the 448,665 atypical antipsychotic initiators, 8,853 (1.97%) had a new antidiabetic prescription within the ±360-day window, resulting in aSR of 1.16 (99% CI 1.09-1.22). The estimated incidence of the potential prescribing cascade was 0.19%. Atypical antipsychotic initiators aged 18-49 had the highest aSR 1.49 (99% CI 1.35-1.61) compared to other age groups (age 50-64: aSR 1.19 [99% CI 1.08-1.30]; age ≥ 65: aSR 0.75 [99% CI 0.67-0.84]). Additionally, females had a positive association (aSR 1.22 [99% CI 1.14-1.30]), while males showed a null association (aSR 1.06 [95% CI 0.97-1.17]). Among individual drugs, positive associations were found for aripiprazole (aSR 1.33 [99% CI 1.20-1.46]) and olanzapine (aSR 1.32 [99% CI 1.11-1.56]). No association was found for clozapine, iloperidone, lurasidone, paliperidone, quetiapine, or risperidone.

Conclusions: Our findings suggest excessive use of antidiabetic agents following initiation of atypical antipsychotics occurs in a small number of adults and may be more common in younger adults. Aripiprazole and olanzapine initiation resulted in positive aSRs. Given the uncertainty of differential risk of diabetes among individual atypical antipsychotic agents, more research is needed to better understand these differences.

Pharmacovigilance -> Other

35 | Potential association of aromatase inhibitors and osteonecrosis of jaw: Signal refining to identify false positive/ pseudo signal

Subeesh Kulangara Viswam[1], Neha Reddy[1], Eswaran Maheswari[1], Ann Mary Swaroop[1], Nair Gouri[1] and Faizan Mazhar[2]

[1]*M.S Ramaiah University of Applied Sciences, Bengaluru, India;* [2]*Università Di Milano, Milan, Italy*

Background: Signal generation through data mining algorithms is an innovative and emerging field in pharmacovigilance. However, it is important to consider confounding factors that significantly influence the signal. Aromatase inhibitors are being reported for possible association with osteonecrosis of jaw. However, this signal was calculated without adjusting the possible confounding factors.

Objectives: Our study aimed to identify potential signals of Aromatase inhibitors associated osteonecrosis of jaw and assess the possibilities of the safety signal to be a pseudo signal/false positive in FDA Adverse Event Reporting System (FAERS).

Methods: A systematic data mining was performed in the FAERS database using OpenVigil 2.1, a pharmacovigilance analytical tool. Drugs included in the analysis were Letrozole, Anastrozole and Exemestane and event of interest was osteonecrosis of jaw. Reporting Odds Ratio (ROR) was used to assess the relation between the drug and adverse event. A value of ROR-1.96SE >1, (SE- standard error) was considered positive. The confounding factor considered in this study was other drugs that are known to cause osteonecrosis of jaw, co-administered with the drug of interest. Through data mining and literature search, bisphosphonates and denosumab were identified as possible confounding factors. The signal strength of drug of interest

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

were calculated with and without the presence of confounding factors.

Results: FAERS database had a total of 15,178 reports for osteonecrosis of jaw. Amongst which 1,061 (6.99%) reports were associated with aromatase inhibitors. The number of reports for letrozole, anastrozole and exemestane were 448 (42.22%), 251 (23.65%) and 362 (34.11%) respectively. Signal strength (ROR-1.96SE) for letrozole, anastrozole and exemestane associated osteonecrosis of jaw without any background correction was 8.34, 6.64 and 15.14 respectively. Upon removing the reports of bisphosphonates and denosumab, signal strength drastically decreased to 0.03, 0.36 and 0.47 for letrozole, anastrozole and exemestane respectively. The signal strength of bisphosphonates and denosumab associated osteonecrosis of jaw did not change significantly (104.06 to 93.2 and 37.1 to 36.1, respectively) upon removal of aromatase inhibitors.

Conclusions: Our study suggested that the signal generated for aromatase inhibitors associated osteonecrosis of jaw in FAERS database can be false positive. Careful background corrections with the identification of those confounding factors are imperative to exclude false-positive results.

74 | Classification and disproportionality analysis of medication errors reported to the drug commission of German pharmacists

Natalie Parrau[1], André Said[1], Matthias Ganso[1] and Martin Schulz[1,2]
[1]*Drug Commission of German Pharmacists, Berlin, Germany;* [2]*Freie Universität Berlin, Berlin, Germany*

Background: Medication errors (ME) may occur in every step of the medication process and can lead to preventable harm. As a national pharmacovigilance center, the Drug Commission of German Pharmacists (AMK) collects and evaluates risks associated with medicinal products, including ME.

Objectives: We classified spontaneously reported ME and used disproportionality analysis to detect safety signals.

Methods: Spontaneous reports from January 2013 to December 2018 were considered as (potential) ME when reporters clearly pointed this out, or when the follow up of reports revealed evidence for ME. We used the European Medicines Agency's (EMA) classification of ME reports, supplemented by coding the affected medication process: prescribing, storing, dispensing, preparation, and administration (with or without use of a drug delivery device). In addition, we analyzed ME in children. The reporting odds ratio (ROR) and its 95% confidence interval (95% CI) were determined on the 5th level of the Anatomical Therapeutic Chemical classification system, German version. We calculated ROR if at least four cases were reported and regarded a ROR as a signal if the lower 95% CI was greater than 1.

Results: Within six years, 1398 (potential) ME reports were obtained. 395 ME (28.3%) were reported as potential or intercepted errors. In 759 cases (54.3%), no harm or adverse events (AEs) were reported. However, 224 ME (16.0%) led to harm or AEs, with n=58 being serious. Regarding the medication process, ME mostly occurred while administering medicinal products by using a drug delivery device (46.8%, n=654). In total, 123 reports (8.8%) were related to the treatment of children; administering (37.4%, n=46) or preparing errors (35.0%, n=43) were mostly reported. ME affecting children mainly referred to the systemic use of anti-infectives (46.3%, n=57). Disproportionality analysis generated 55 signals. Signal validation yielded that a majority of the signals (n=34) involved ME using a drug delivery device, e.g. an inhaler device for respiratory diseases or devices for insulin injection.

Conclusions: Classification and evaluation of ME with respect to the medication process is a prerequisite for effective risk minimization measures. The use of anti-infective suspensions for children and of certain drug delivery devices seems to be error-prone. Thus, continuous patient and caregiver education provides a reasonable measure for health-care professionals to prevent ME.

108 | Prescribing and non-medical use of tramadol and other opioid analgesics: U.S., 2009-2018

Saranrat Wittayanukorn, Ibrahim Ibrahim, Rose Radin, Sara Karami, Rajdeep Gill, Grace Chai and Jana McAninch
Food and Drug Administration, Silver Spring, MD

Background: Whereas most commonly prescribed opioid analgesics (OAs) are Schedule II controlled substances in the U.S., tramadol is Schedule IV. Given the evolving U.S. opioid crisis, it is important to surveil U.S. tramadol dispensing and nonmedical use trends.

Objectives: 1) To estimate patterns of dispensing of tramadol and the commonly prescribed Schedule II oral OAs: hydrocodone, morphine, and oxycodone; 2) to describe the frequency, trends, and clinical characteristics of poison control center (PCC) calls and emergency department (ED) visits involving nonmedical use of these OAs.

Methods: We analyzed IQVIA data to examine outpatient utilization patterns from 2009-2018. We conducted descriptive analyses of the National Poison Data System (NPDS; 2014-2018) and National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES; 2016-2017) to examine the frequency of PCC calls and ED visits associated with nonmedical use of tramadol and the other selected OAs, and to describe the medical severity and route of nonmedical use.

Results: Since 2013, immediate-release (IR) tramadol single-entity (SE) has been the second most dispensed OA. Tramadol prescriptions declined from an estimated 42 million in 2014 to 33 million in 2018; while its market share percentage among OA prescriptions increased (13.6% in 2012 to 18.7% in 2018). Prescriptions dispensed for IR formulations of hydrocodone, morphine, and oxycodone also decreased from 2014 to 2018. The annual number of U.S. PCC calls involving tramadol nonmedical use declined from 1,713 calls in 2014 to 929 in 2018, which remained higher than that of morphine (n=292) but lower than that of hydrocodone (n=1,674) or oxycodone (n=2,054) in 2018. The oral route was the most commonly reported for nonmedical use

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

calls involving tramadol (>98% of reported routes), hydrocodone (98.5%), morphine (82.8%), and oxycodone (88.8%). Among 3,983 calls involving tramadol nonmedical use, approximately 90% of medical outcomes were categorized as minor or moderate effect (symptoms that were non-life-threatening). Of U.S. ED visits attributed to nonmedical use of any prescription OAs, an estimated 3.3% (95% CI: 2.4-4.2) involved tramadol, the lowest of the OAs examined.

Conclusions: The number of dispensed prescriptions of IR tramadol SE increased from 2009-2014, then gradually declined through 2018. PCC calls involving nonmedical use of tramadol or selected Schedule II OAs all declined from 2014-2018. Tramadol was less frequently implicated in PCC calls and ED visits involving nonmedical use than were the Schedule II OAs hydrocodone and oxycodone.

2355 | Effect of tenofovir containing first-line art in patients with moderate/severe reduced creatinine clearance at baseline: A retrospective study at two referral hospitals in Namibia

Francis Kalemeera[1], Brian Godman[2,3], Andy Stergachis[4] and Tim Rennie[1]

[1]University of Namibia, Windhoek, Namibia; [2]Strathclyde University, Glasgow, United Kingdom; [3]Karolinska Institute, Stockholm, Sweden; [4]University of Washington, Seattle, WA

Background: Caution is advised against the use of tenofovir disoproxil fumarate (TDF) in patients with baseline creatinine clearances (CrCl) <60ml/min, for concerns of increased risk of further decline in CrCl. However, TDF containing ART is recommended for management of HIV/Hepatitis-B co-infected patients.

Objectives: To find out if the use of TDF in patients (pts) with a CrCl <60ml/min at baseline was associated with more improvement than further decline; to identify the factors associated with improvement; and to compare decline rates between the <60ml/min group (gp I) and the ≥60ml/min group (gp II).

Methods: A retrospective cohort study at two referral hospitals. Included pts16 yrs. or older, and received TDF-containing ART. The difference in CrCl between baseline and follow-up values identified improvement or decline. Improvement defined: a ≥25% increase in CrCl, was assessed for gp I pts. Decline defined: a ≥25% drop in CrCl, was evaluated for both gp I and II patients. Binary logistic regression was performed to identify factors that were associated with improvement. Kaplan-Meier analysis was used to evaluate the difference in cumulative hazard rates of migration to lower stages of CrCl between gp I and II.

Results: Groups I and II had 2861 and 7526 pts, respectively. Amongst gp I pts, improvement and increases in CrCl >3ml/min/year, were observed in 40.1% (n=1,146) and 60.4% (n=1728), respectively. Decline occurred in 2.3% (n=65). Improvement was associated with severely low CrCl (adjusted hazard ratio [aHR]=13.4 [95%CI: 6.7 - 26.9, p<0.001]); male pts (aHR=1.8 [95%CI: 1.5-2.2, p<0.001]); HIV-related clinical disease (aHR=1.2 [95%CI: 1.0 - 1.4], p=0.033) and a longer duration of ART (aHR=1.1 [95%CI: 1.05 - 1.2, p<0.001]). The proportion of pts who migrated to lower CrCl stages in gp I was approximately 1/6 of the corresponding proportion in gp II (2.3% vs. 13.1, p<0.001). The cumulative hazard rate was significantly lower in gp I. The proportion of pts who migrated to the severe reduced CrCl stage in gp I was approximately 2.0 times the corresponding proportion in gp II (1.0 vs. 0.5; p<0.001). The cumulative hazard rate was higher in gp I.

Conclusions: Improvement was more likely than decline in gp I pts. Significantly more decline events were observed amongst pts in gp II. Greater proportions migrated to a lower CrCl stage in gp II. Although, gp I pts were more likely to experience new onset severe reduced CrCl than gp II pts, the absolute proportions were low. TDF should not be withheld from HIV-positive pts with a baseline CrCl <60ml/min.

2358 | Drug dispensing errors in a regional hospital: Challenges for promoting patient safety

Amanda de Araújo[1], Isabela Vieira[1], Carolina Santos[2], Mário Rosa[3], Karla Almeida[4], Cláudia Carneiro[5] and Renata Nascimento[6]

[1]School of Pharmacy, Federal University of Ouro Preto (UFOP)., Ouro Preto/Minas Gerais, Brazil; [2]School of Medicine, Federal University of Ouro Preto (UFOP) and Santa Casa da Misericórdia de Ouro Preto (SCMOP), Ouro Preto/Minas Gerais, Brazil; [3]Institute for Safe Medication Practices (ISMP) Brazil, Belo Horizonte/Minas Gerais, Brazil; [4]Santa Casa da Misericórdia de Ouro Preto (SCMOP), Ouro Preto/Minas Gerais, Brazil; [5]School of Pharmacy, Federal University of Ouro Preto (UFOP) and Center for Research in Biological Sciences (NUPEB), UFOP, Ouro Preto/Minas Gerais, Brazil; [6]School of Pharmacy, Federal University of Ouro Preto (UFOP) and Institute for Safe Medication Practices (ISMP) Brazil, Ouro Preto/Belo Horizonte, Brazil

Background: Patient safety is a foremost attribute of quality of healthcare systems worldwide. In hospital settings most errors are related to the prescription, administration and use of medicines.

Objectives: The aim of this study was to analyse drug dispensing errors in a Brazilian regional hospital and identify opportunities to improve the medication process.

Methods: This is a cross-sectional study conducted at a medium-sized regional hospital (118 beds), located in the Southeast Region of Brazil. Dispensing error was defined as the discrepancy between the written instruction on the drug prescription and the accomplishment of this instruction by the hospital pharmacy, during the dispensation process. Data were collected at the time of error identification (delivery of items to nursing staff), in the period spanned from January to May 2019. Variables were presented as absolute and relative frequencies. The research was approved by the Research Ethics Committee of the Federal University of Ouro Preto.

Results: There were identified 233 drug dispensing errors in the 8,707 prescriptions attended during the study period, a prevalence of 2.7%. Most errors (65.2%) corresponded to prescribed but not dispensed medications and medical supplies. Approximately 10.5% of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

dispensing errors were related to medication dosing errors and 2.0% to delivery of switched medications. The higher notification rate was observed in April 2019. Although the hospital has adopted a computerized system (Spdata) since June 2018, continuous training began only in March 2019, focus on raise awareness among health professionals about the importance of reporting errors.

Conclusions: Drug dispensing errors are a challenge for the hospital pharmacy. The identification of the main errors and their causes are essential for amending work processes and, consequently, improving patient safety and qualifying hospital care.

2363 | Patient safety: Diagnostics of prescription in microregional hospital

Isabela Vieira
UFOP, Ouro Preto, Brazil

Background: Patient safety is a priority attribute of the quality of healthcare systems worldwide. Most errors that occur in the hospital environment related to the prescription, administration and use of medicines. In this way, understand the prescription process in hospitals and detect errors that are caused by essential actions to prevent errors.

Objectives: The present study was to analyze the medication errors identified in the prescriptions by the Santa Casa de Misericórdia Pharmacy of Ouro Preto (SCMOP), in Ouro Preto/MG.

Methods: This was a cross-sectional study conducted in a mid-sized regional hospital (118 beds), from August to October 2019. Prescription error was defined as the discrepancy between the order prescribed in the prescription and the care of this order. Data were collected in a proper table, at the time of analysis of the prescriptions performed by SCMOP Pharmacy and tabulated in Excel® spreadsheet.

Results: During the quarter evaluated, 634 prescribing errors were identified in the 4,620 prescriptions met, a prescribing error rate of 13.7%. High prevalence of errors was identified in the age group 65 years or older (48.2%). Regarding the classification of errors, the main occurrence was prescription drugs with inadequate administration time (52.3%). We identified 73 drugs involved with errors, two of which (enoxoparin and heparin) belong to the list of potentially dangerous drugs.

Conclusions: Prescription errors are a reality in SCMOP and may be related to work process failures. Professional awareness and continuing education activities are essential to reduce prescribing errors and thus improve patient safety and quality of hospital care.

2366 | Linezolid induced skin reactions in a multidrug-resistant infective endocarditis patient: The first case with systematic review

Jose J. Kochuparambil[1], Asha K. Rajan[2], Muhammed Rashid[3], Ananth Kashyap[4] and Manik Chhabra[5]
[1]*St. Joseph's College of Pharmacy, Cherthala, Alappuzha, India;* [2]*Jaya College of Pharmacy, Chennai, India;* [3]*Sri Adichunchanagiri College of Pharmacy, BG Nagara, India;* [4]*Sarada Vilas College of Pharmacy, Mysuru, India;* [5]*Indo-Soviet Friendship College of Pharmacy, Moga, India*

Background: There are no cutaneous adverse reactions (CARs) reports available in the literature on linezolid (LNZ) induced reactions in multidrug-resistant (MDR) infective endocarditis (IE) patient. So, there is a lack of information on the management of such incidents. Here we report the first case of CARs in an MDR IE patient by LNZ administration with a systematic review.

Objectives: To report a case on linezolid induced cutaneous adverse reactions (CARs) and to critically evaluate the literature.

Methods: Descriptive studies addressing LNZ induced CARs in MDR patient were considered for review retrieved from PubMed database using keywords based search. Study selection, data abstraction and quality assessment were performed.

Results: Case report: A 24-year-old female patient admitted to the hospital with complaints of fever (101° F)associated with chills, rigors, and shortness of breath for 4 days. She was an MDR IE patient with a history of rheumatic heart disease, currently, on LNZ 600mg IV BD against *Staphylococcus* coagulase-negative as that was the only sensitive option. The patient experienced flares of cutaneous reactions with multiple hyper pigmented maculopapular lesions all over the body after one week of LNZ therapy. LNZ dose was tapered gradually and discontinued by ensuring that the patient receives appropriate corticosteroids. Her reactions were completely subsided and an improvement in infection was observed after 1 month of therapy. **Systematic Review:** A total of 4 reports from the PubMed database were included in the final review with 2 male and 2 female patients. LNZ was immediately stopped in all the cases due to spontaneous reporting of CARs and the reaction was progressively resolved.

Conclusions: Healthcare professional should be aware of the CARs especially on MDR patients as they are exposed to multiple drugs. More spontaneous monitoring and reporting required for better quantification.

2430 | Liver injury associated with lipid emulsions

Xiao-Xiao LI[1,2], Yin-Chu Cheng[1,3], Suo-Di Zhai[1], Peng Yao[2], Si-Yan Zhan[3,4] and Luwen Shi[2]
[1]*Peking University Third Hospital, Beijing, China;* [2]*School of Pharmaceutical Sciences, Peking University, Beijing, China;* [3]*School of Public Health, Peking University, Beijing, China;* [4]*Peking University Third Hospital, Beijing, China*

Background: Patients dependent on total or partial parenteral nutrition are at increased risk of developing parenteral nutrition-associated liver disease or cholestasis, which present as a wide range of disruption to liver function, namely, intestinal failure-associated liver disease. No large population-based studies have been conducted in adults to quantify the risk of IFALD following the initiation of lipid emulsions (LEs).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To determine the risk of liver injury associated with the use of different intravenous LEs in large populations given parenteral nutrition in a real world setting in China.

Methods: A prescription sequence symmetry analysis (PSSA) was performed using data from Chinese Basic Health Insurance for Urban Employees (1 Jan 2015-31 Dec 2015). Patients newly prescribed both intravenous LEs and a set of hepatic protectors (treated for liver injury determined by literature review and expert consultation) within time windows of 7, 14, 28, 42 and 60 days between each other were included. The washout period was set to one month according to the waiting-time distribution. After adjusting for prescribing time trends, we quantify the deviation from symmetry of patients initiating parenteral nutrition first and those initiating hepatic protectors first, by calculating adjusted sequence ratios (ASRs) and relevant 95% confidence intervals (CI). Analyses were further stratified by age, gender, and different generations of LEs developed.

Results: In total, 416, 997, 1697, 2072 and 2342 patients filled their first prescriptions with both drugs within 7, 14, 28, 42 and 60 days, respectively. Significantly increased risks of liver injury were found across all time windows, and the strongest effect was observed in the first 2 weeks (ASR 6.97 [5.77-8.42] ~ 7.87 [6.04-10.61]). In subgroup analyses, female gender, age more than 60 years, soybean oil-based and alternative LEs showed higher ASRs in all time windows.

Conclusions: A strong association was found between LEs use and liver injury through PSSA in a real-world setting, which aligns with trial evidence and clinical experience. Differences revealed in the risks of liver injury among various LEs needs further evaluation.

2468 | Drug-induced vitamin B12 deficiency: A population-based hypothesis-free symmetry analysis screening

Daniel P. Henriksen[1], Jesper Hallas[2], Mads Nybo[2], Per Damkier[2] and Lars Christian Lund[3]

[1]Odense University Hospital, Odense, Denmark; [2]University of Southern Denmark, Odense, Denmark

Background: Vitamin B12 is a water-soluble vitamin required for formation of hematopoietic cells. Several drug-classes have been associated with vitamin B12 deficiency, but the evidence is typically based on spontaneous adverse event reportings, or case reports.

Objectives: To perform a population-based hypothesis-free symmetry analysis screening of drug-classes associated with laboratory confirmed vitamin B12 deficiency.

Methods: The study population consisted of all subjects living on the island of Funen (pop: 493 000 in 2016) who had at least one creatinine measurement between 2000-2016 as well as a vitamin B12 measurement. Subjects were included at the first occurrence of vitamin B12 deficiency (<130 pmol/L), given they had at least one vitamin B12 measurement within normal range (>=130 pmol/L) within 365 days up to the date of their initial measurement indicating de novo vitamin B12 deficiency. We then performed a symmetry analysis screening of all newly initiated drug classes (ATC fourth level) one year prior to and after the date of the vitamin B12 deficiency measurement, anchoring the date to the date of the initial prescription of the given drug class. A symmetrical distribution of the number of patients with vitamin B12 deficiency before and after date of the prescription of the given drug class is expected if no association exist (i.e. a sequence ratio (SR) of 1.0). The symmetry analysis design is robust to confounders that are stable over time. We took only SRs into account if the difference between groups ($dif_{presc,before/after}$), that is persons who filled a prescription before versus after vitamin B12 deficiency date, was above 10.

Results: A total of 1738 persons were included for further analysis, 1014 (58%) were female, and the median age was 68 years (47-79 years). The drug-class with the largest $dif_{presc,before/after}$ was proton pump inhibitors ($N_{presc->B12def}$: 173/94, SR 1.84, 95%CI 1.44-2.39), followed by loop-diuretics ($N_{presc->B12def}$: 111/63, SR 1.76, 95%CI 1.31-2.44), paracetamol ($N_{presc->B12def}$: 144/113, SR 1.27, 95% CI 1.00-1.64), and angiotensin converting enzyme (ACE) inhibitors ($N_{presc->B12def}$: 63/34, SR 1.85, 95%CI 1.26-2.90). Metformin yielded an SR of 3.78 (95%CI 1.99-8.96), but the number of persons were low ($N_{presc->B12def}$: 34/9).

Conclusions: Using the symmetry analysis to screen a large population-based cohort for laboratory-confirmed vitamin B12 deficiency confirmed several well-known adverse drug reactions, but also identified unknown but biologically plausible signals. The next step is to explore these more in depth.

2496 | Using natural language processing to improve patient age ascertainment from adverse event reports

Phuong Pham[1,2], Carmen Cheng[2], Eileen Wu[2], Ivone Kim[2], Rongmei Zhang[2], Yong Ma[2], Cindy M. Kortepeter[2] and Monica A. Muñoz[2]

[1]University of Florida, Gainesville, FL; [2]US Food and Drug Administration, Silver Spring, MD

Background: Missing information in structured data fields is a significant challenge when conducting analyses of adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS). Age is a critical data element because age-related physiological changes can affect the pharmacokinetics and pharmacodynamics of drugs. While demographic data is often missing in the report's structured data fields, it may be found in the report's free-text narrative. Natural language processing (NLP) has been leveraged to extract patient demographic information from unstructured clinical text in electronic health records. However, the potential for NLP to improve the identification of patient age from FAERS reports has not been previously evaluated.

Objectives: Evaluate the performance of a rule-based NLP tool to extract patients' age from the report narrative and its potential impact on addressing missing age in the structured data field.

Methods: Using all FAERS reports received from January 1, 2002 through December 31, 2018, we evaluated the annual proportion of reports missing an age in the structured field before and after the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

application of the NLP tool. A random sample of 1500 reports was selected from the dataset for reviewers to manually identify patients' age from the report narrative (gold standard). Reviewers were blinded to the structured field and NLP output. Each report was read by two different reviewers and disagreements were adjudicated by a third reviewer. The gold standard of manually extracted ages was then compared to the NLP output. Sensitivity, specificity, positive predictive value (PPV), and F-measure (a metric accounting for both sensitivity and PPV) were calculated.

Results: Of 10,300,609 reports received in the study period, the overall percentage of reports missing age in the structured data field was 32%. The percentage of reports missing age in the structured field increased over time, from 21.9% in 2002 to 43.8% in 2018. The NLP tool achieved high performance, with sensitivity of 98.5%, specificity of 92.9%, PPV of 94.9%, and F-measure of 96.7%. When the NLP algorithm was applied to reports without age in the structured data field from 2002 to 2018, the tool identified age for an additional one million reports (10% of the total number of reports).

Conclusions: NLP has potential utility to extract patients' age from report narratives of postmarketing adverse event reports. The use of this tool would help facilitate pharmacovigilance and research using FAERS data.

2545 | Knowledge and practice of adverse drug reporting among healthcare workers in Ekiti State, South-west Nigeria

Joseph O. Fadare, 360001[1,2], Theophilus Adegbuyi[1], Ebisola J. Araromi[1] and Abayomi Sijuade[1]

[1]Ekiti State University College of Medicine, Ado-Ekiti, Nigeria; [2]Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria

Background: Adverse drug reactions (ADRs) constitute significant healthcare challenge worldwide with associated morbidity, mortality and increasing healthcare cost Prevalence studies in different settings show that approximately 5 to 35% of many preventable hospital admissions are due to adverse drug reactions (ADR). There is a need for healthcare professionals at all levels of care to be knowledgeable about adverse drug reactions and it's reporting.

Objectives: The main objective of this study was to assess the knowledge of ADR and its' reporting among of all cadres of healthcare workers (physicians, nurses, pharmacists and community health extension workers) working at the primary, secondary and tertiary levels of care in Ekiti State, South-west Nigeria.

Methods: This was a cross-sectional and questionnaire-based study conducted among healthcare workers during the month of September, 2019. The site selection was done using systematic sampling and included two primary- level comprehensive health centres, two secondary- level general hospitals and one tertiary- level facility each in all three senatorial districts of the state. The questionnaire had a sub-section on the knowledge (10 statements/questions scored @1 point each for correct answer) with a total score of 10 points and other sections on attitude and practice of ADR reporting. The knowledge level was classified as poor (<4 points), average (5-6) and good (>6).

Results: A total of 300 healthcare workers comprising of nurses (112;37.3%), physicians (75;25.0%), pharmacists (53;17.7%) and community health extension workers (40;13.3%) completed the questionnaire. The mean score for physicians, pharmacists, nurses and community health extension workers was 6.2 ± 1.5, 7.0 ± 1.6, 5.6 ± 1.8 and 5.3 ± 1.6 respectively. Respondents had poor (65;21.7%), average (119;39.7%) and good (116;38.7%) knowledge about ADRs. Majority (228;76%) have observed incidents of ADRs during their professional practice, however only 75 (25%) have ever reported it. Only 113 (37.7%) had seen the yellow reporting form while only 53(17.7%) had ever used it. The reporting method preferred by respondents were through email (102;34.0%), phone (78;26.0%) and direct contact (95;31.7%).

Conclusions: Healthcare workers in tertiary-level facilities and pharmacists had higher knowledge scores than colleagues working in lower level facilities. There was evidence of poor ADR reporting practice among respondents especially non-familiarity with yellow card. There was also a preference for other methods such as email and phone for reporting over the traditional yellow form.

2557 | Medication error reporting by African countries to VigiBase

George Tsey Sabblah[1], Delese Mimi Darko[1], Mahama Duwiejua[2], Florence van Hunsel[3], Katja Taxis[4] and Eugène van Puijenbroek[4,4]

[1]Food and Drugs Authority, Accra, Ghana; [2]University of Ghana, Accra, Ghana; [3]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, Netherlands; [4]University of Groningen, Groningen, Netherlands

Background: Thirty-seven African countries are full members of the World Health Organisation (WHO) Programme for International Drug Monitoring (PIDM) and may contribute medication error (ME) reports to VigiBase, the WHO global database of individual case safety reports. Currently, there is limited information on the number of ME reports submitted by these countries, the type of medicines contributing to these errors, the characteristics of these events and the type of reporters. These pieces of information will help in formulating educational strategies and interventions to prevent harm associated with MEs.

Objectives: The objective of this study is to determine the frequency of ME reports submitted by African countries to VigiBase and to describe their characteristics.

Methods: ME cases from African countries in VigiBase from 1st January 1997 to 31st December 2018 were retrieved in January 2020 using the narrow Standard Medical Dictionary for Regulatory Activities (MedDRA) Queries. Descriptive statistics were used to summarize key variables of interest, namely, number of reports submitted by each country; year the reports were first submitted to VigiBase; the source of reports; reporter type; most reported events classified at the preferred term (PT) level and most reported medicine classified by the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

fourth level ATC codes. Spearman's ρ was used to determine the relationship between the number of reports and the year of joining PIDM.

Results: A total of 3,388 ME reports were retrieved from VigiBase, which is 0.4% of all ME reports in the database. Out of the 37 full members of the PIDM, only 15 contributed ME reports with 3,338 (98.5%) of these reports submitted by three countries; Morocco (56.8%), Egypt (24.6%) and South Africa (17.1%). There was no statistically significant relationship between the year of joining PIDM and number of reports (r= 0.44, p=0.0973). The majority of reports were from spontaneous reporting system, 2,825 (83.5%) and studies 540 (15.9%). Patients submitted 1326 (30.1%) of the ME reports. Top five medicine classes with most frequently reported MEs were Insulins and analogues, Immunostimulants, Other analgesics and antipyretics, Direct acting antivirals and Immunosuppressants. The top five reported MedDRA PTs in decreasing order were Incorrect dose administered, Inappropriate schedule of product administration, Product administration error, Product dose omission and Medication error.

Conclusions: There is a relatively small number of ME reports from a limited number of African countries. Low reporting puts patients at risk of experiencing preventable MEs. Low rate of reporting from patients' needs further investigation.

2562 | Twenty years of modified prescription- event monitoring: Summary of studies conducted between 2000 and 2020

Vicki Osborne[1,2] and Saad AW Shakir[1,2]

[1]*Drug Safety Research Unit, Southampton, United Kingdom;* [2]*University of Portsmouth, Portsmouth, United Kingdom*

Background: Modified Prescription-Event Monitoring (M-PEM) is the only national system in England developed solely to prospectively monitor the utilisation and safety of recently marketed medicines available to all primary care physicians (GPs). It is not a spontaneous reporting system and is a pharmacoepidemiological method based on the fundamental concept of monitoring events regardless of relatedness to drug exposure. Where drugs are of the same class, direct comparisons between drugs are possible. Alternatively, within cohort comparisons are possible using 1) different exposure time periods and 2) pre and post exposure time periods.

Objectives: We aimed to summarise the studies that have been conducted using M-PEM methodology between 2000 and 2020, to quantify the contribution of this method to pharmacoepidemiology and pharmacovigilance.

Methods: M-PEM uses an observational cohort design in England. All dispensed primary care National Health Service prescriptions for a target medication are obtained for the required study period. Data collection forms (DCFs) are sent to GPs for individual patients dispensed these prescriptions. These are sent after a pre-specified study observation period following the date of dispensing (e.g.12 months) and request data on drug utilisation (DU) characteristics and events during the observation period. Summary descriptive statistics were calculated for completed M-PEM studies.

Results: Over the past 20 years, 20 M-PEM studies were completed on 19 different medications. These included 3 inhaled corticosteroids, 2 antipsychotics, 2 antidiabetics and 2 opioids. A variety of different therapeutic areas were covered including 7 central nervous system, 4 respiratory and 3 cardiovascular medications. Median response rate for M-PEM DCFs was 55.3% (IQR: 44.8, 62.1%). Median cohort size was 5687 patients (IQR: 1554, 11316), with a minimum cohort size of 63 patients and a maximum cohort size of 17546 patients. After stratification by sex, median number of males was 3371 (IQR: 822, 5219) and median number of females was 2390 (IQR: 602, 6834). In total, M-PEM contributed DU and safety data on 132078 patients in the post-marketing setting.

Conclusions: M-PEM is a prospective cohort methodology that can collect DU and safety data on medicines prescribed in primary care, covering a wide variety of therapeutic areas. Over the past 20 years, M-PEM has collected data on large numbers of patients, with response rates higher than other GP postal surveys. Overall, M-PEM has contributed important data for the post-marketing assessment of medicines.

2565 | Estimating patient satisfaction from disease blog texts on the internet: A pilot study for patient-centric pharmacovigilance

Shinichi Matsuda[1], Takumi Ohtomo[1], Masaru Okuyama[2], Hiraku Miyake[2] and Kotonari Aoki[1]

[1]*Chugai Pharmaceutical Co., Ltd., Tokyo, Japan;* [2]*Initiative Inc., Tokyo, Japan*

Background: While adverse event reporting databases and healthcare databases have played a central role in the current pharmacovigilance system, it is faced with a challenge how to obtain feedbacks directly from patients who are the main stakeholders for healthcare services. As an example of conventional researches to receive the feedbacks, there is a survey using a QOL questionnaire. However, because most of the QOL questions are developed from the perspective of healthcare professionals, it tends to focus only on the pre-specified intentions of the questioners. Although such questionnaires partly evaluate patient satisfaction, it may overlook important patient opinions. Therefore, we thought that an analysis based on the data of patients' actual narratives can enhance the understanding of whether patients are satisfied or unsatisfied with the treatments. Using disease blog texts on the Internet, we conducted a pilot study to estimate patient satisfaction on their treatments.

Objectives: To visualize and evaluate patient satisfaction by applying natural language processing and machine learning approaches to patient-written disease blog texts.

Methods: We analyzed textual data collected from the Japanese disease blogs on the Internet: *tōbyōki* blogs, which translate literally as a diary-like account of a struggle with disease (Matsuda, *et al*. JMIR Public Health Surveill 2017). Using supervised machine learning approach, we not only created a model to estimate patient satisfaction index (PSI) based on the patients' texts but also evaluated the validity of the model.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Our preliminary model showed moderately good result in classifying patient satisfaction (positive or negative) for each sentence. For instance, the sentence "During that time, the nurse was stroking my back all the time." showed positive PSI (+0.4375); in contrast, the sentence "And next is muscle injection, so it hurts again." showed negative PSI (-0.99805) as expected. These results suggested that PSI becomes a useful indicator to identify the transition of patient satisfaction before and after the critical event of the patient journey such as disease notification or initiation of the drug treatment.

Conclusions: Patient satisfaction could be estimated based on the text data written by patients. Patient-generated data on the Internet should be a promising data source to implement patient-centric pharmacovigilance.

2568 | Ten years of specialist cohort event monitoring: Summary of studies conducted between 2010 and 2020

Vicki Osborne[1,2] and Saad A. W. Shakir[1,2]

[1]*Drug Safety Research Unit, Southampton, United Kingdom;* [2]*University of Portsmouth, Portsmouth, United Kingdom*

Background: Specialist Cohort Event Monitoring (SCEM) is a national system in the UK developed to prospectively monitor the utilisation and safety of recently marketed medicines available in specialist care settings (e.g. hospitals and specialists' clinics). SCEM are formal pharmacoepidemiological studies; events are monitored regardless of relatedness to drug exposure. SCEM can collect information on both the study drug of interest and a reference (contextual) cohort of patients using another drug (i.e. standard of care), to allow contextualisation of drug utilisation (DU) characteristics.

Objectives: We aimed to summarise the studies that have been conducted using SCEM methodology between 2010 and 2020, to quantify the contribution of this method to pharmacoepidemiology and pharmacovigilance.

Methods: SCEM uses an observational cohort design in the UK. Prescribers are identified through clinical research networks and patients are subsequently identified by specialist prescribers. Informed consent is obtained for participation. Research personnel are used to aid with recruitment of prescribers, although only prescribers have any contact with patients. Data are sampled at national level and research personnel recruit in all areas of the UK. Data collection forms (DCFs) are sent to prescribers for individual patients. These are sent at baseline and after a pre-specified study observation period following the medication start date (e.g. 12 weeks). Data is collected on DU characteristics and events during the observation period. Summary descriptive statistics were calculated for completed SCEM studies.

Results: Over the past 10 years, 4 SCEM studies were completed between 2010 and 2020 on 5 different medications (cohort sizes n=124, 125, 528, 845, 2067 and 2542; 1 medication was examined in 2 different studies for different indications). Medications studied were 2 antipsychotics, 2 oral anticoagulants and 1 antiplatelet. Median number of prescribers for these studies was 235 (IQR:43, 1196). Median completion rate for SCEM DCFs (completion of both forms) was 98.9% (IQR:98.1, 100.0%). After stratification by sex, median number of males was 339 (IQR:103, 1149) and median number of females was 443 (IQR:62, 918). In total, SCEM have contributed DU and safety data on 6231 patients in the post-marketing setting.

Conclusions: SCEM is a prospective cohort methodology that can collect DU and safety data on medicines prescribed in specialist settings. Over the past 10 years, SCEM has collected data on large numbers of patients and has contributed important data for the post-marketing assessment of medicines.

2626 | Knowledge, attitude and practice of healthcare professionals towards pharmacovigilance in Alexandria, Egypt: A cross sectional survey

Mai M. Salama[1], Omaima G. Yassine[1], Iman El Sayed[1], Sherif Abdelmonem[2] and Fayek S. Elkhwsky[1]

[1]*Biomedical Informatics and Medical Statistics Department, Medical Research Institute, Alexandria University, Alexandria, Egypt;* [2]*Department of Critical Care Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt*

Background: The concept of Pharmacovigilance is still new to healthcare professionals (HCPs) in Arabian countries.

Objectives: To compare the knowledge, attitude and practice towards pharmacovigilance between health care professionals in Alexandria, Egypt.

Methods: A cross-sectional survey was conducted among 547 pharmacists and physicians in three different health sectors in Alexandria, Egypt from August 2017 to March 2018. The questionnaire consisted of 20 questions. The data were analyzed using SPSS version 20. Bivariate analysis using Chi-square test and multivariate logistic regression were used. The main outcome was measuring knowledge, attitude and practice towards pharmacovigilance. Pareto chart was used to determine the most common barriers affecting the reporting of adverse drug reactions (ADRs).

Results: The survey was completed by 232 (42.4 %) physicians and 315 (57.6 %) pharmacists. The odds of high knowledge and positive attitude were around 6 times more among pharmacists than that among physicians (OR= 6.60, 95% CI: 2.31-18.85), and (OR= 5.66, 95% CI: 2.26-14.15) respectively. The odds of high practice was more than twice among pharmacists than that among physicians (OR= 2.62, 95% CI: 1.35-5.05). Major barriers against reporting ADRs were lack of time and difficulty in deciding whether ADR has occurred or not.

Conclusions: The limited knowledge about pharmacovigilance among physicians could have affected ADRs reporting incidence. Educational intervention and a practical training program need

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

to be applied by the health authority to physicians in order to enhance the pharmacovigilance and drug safety culture in Egypt.

2663 | Quantification of adverse drug reactions related to drug switches in the Netherlands

Pieter J. Glerum[1,2], Marc Maliepaard[3,4], Vincent de Valk[5], Joep HG Scholl[6], Florence PAM van Hunsel[6], Eugène P van Puijenbroek[6,7], David M Burger[8] and Cees Neef[9]

[1]CBG-MEB, Utrecht, Netherlands; [2]Maastricht University Medical Centre +, Maastricht, Netherlands; [3]CBG-MEB, Utrecht, Netherlands; [4]Radboud University Medical Centre, Nijmegen, Netherlands; [5]National Health Care Institute, Diemen, Netherlands; [6]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, Netherlands; [7]Groningen Research Institute of Pharmacy, University of Groningen, Groningen, Netherlands; [8]Radboud University Medical Centre, Nijmegen, Netherlands; [9]CARIM, Maastricht University, Maastricht, Netherlands

Background: From a pharmacological perspective, it is unexpected that a different clinical profile is observed for a generic drug as compared to a brand-name drug. Nor that an adverse drug reaction (ADR) is experienced following a switch between bioequivalent drug products. However, ADRs related to drug switching are reported and there is a need to systematically study these, to elucidate points for improvement on the pharmacological and psychological assumptions of generic interchangeability.

Objectives: The primary aim is to calculate the relative number of reported ADRs per number of drug switches, for active substances for which a relatively high number of ADRs was reported in the Netherlands. In addition, we examined whether different peaks of ADRs would be observed using the absolute number of ADRs or using switch-corrected number of ADRs.

Methods: This is a retrospective cohort study in the Dutch patient population on active substances for which a relatively high number of ADRs related to drug switching was reported. For this, we analyzed drug switches from the National Health Care Institute in the Netherlands and reported ADRs related to switching from Lareb, the Netherlands Pharmacovigilance Centre, between June 1, 2009 and December 31, 2016 for a selection of 20 active substances. We also compared pharmacovigilance analyses based on the absolute, switch-corrected and user-corrected numbers of ADRs.

Results: For our selection of 20 active substances, 1,348 reported ADRs and over 23.8 million drug switches were identified. There was no overall correlation between the number of ADRs and the number of switches, but on average we found 5.7 reported ADRs per 100,000 switches. The number was relatively high for rivastigmine, levothyroxine, methylphenidate and salbutamol, with 74.9, 50.9, 47.6 and 26.1 ADRs per 100,000 switches, respectively. When comparing analyses using the absolute number and the switch-corrected number of ADRs, we demonstrate that different active substances would be identified as having a relatively high number of ADRs, and different time periods of increased numbers of ADRs would be observed. We also demonstrate similar results when using the user-corrected number of ADRs instead of the switch-corrected number of ADRs, allowing for a more feasible approach in pharmacovigilance practice.

Conclusions: The number of drug switch-related ADRs is relatively high for rivastigmine, levothyroxine, methylphenidate and salbutamol. Further, we demonstrate that analyses of drug switch-related ADRs leads to different results when the number of reported ADRs is corrected for the number of drug switches.

3864 | Detection on safety alerts of non-fluoroquinolones antibiotics using tree-based scan statistics with propensity score matching

Miyuki Hsing-Chun Hsieh and Edward Chia-Cheng Lai

Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background: Quinolone antibiotics includes fluoroquinolones (FQs) and non-fluoroquinolones (non-FQs). Non-FQs were largely used especially in primary healthcare facilities in Taiwan but not in North America or European countries. Drug safety of FQs and their potential adverse events were relatively known; however, limited safety information for non-FQs was available.

Objectives: Using tree-based scan statistics (TBSS) to detect safety alerts for non-FQs.

Methods: We analyzed the Taiwan's National Health Insurance Database (NHID) and selected patients newly received FQs or non-FQs between 2008 and 2012. We 1:1 matched non-FQs users to FQs users by propensity score, considering patients' baseline characteristics including age, sex, comorbidities and healthcare resource utilization. We followed patients for a year from initiation of FQs or non-FQs. We censored patients at the date of drug discontinuation or switching. We defined all events by 3-digit ICD-9 codes. We screened and classified safety alerts by 3-level diagnostic tree with ICD-9 codes system. We used TreeScan software version 1.4 and applied unconditional Bernoulli analysis to detect safety alerts of non-FQs compared to FQs. Alpha level at 0.01 was considered as significance.

Results: We included 40,803 non-FQs users matched to 40,803 FQs users. We identified a total of 468,134 diagnoses and 17,587 nodes within diagnostic tree. Among 63 nodes reached statistical significance, 39 related to infection and were considered as indications of non-FQs. Because non-FQs were more likely to be prescribed in obstetrics and gynecology clinics compared to FQ, 14 obstetrics and gynecology related nodes were not considered as safety alerts due to potential confounding effects. We found 3 nodes for anxiety and 7 nodes for relatively general symptoms, such as headache, back pain, abdominal pain and dizziness, which were considered as safety alerts of non-FQs.

Conclusions: In addition to the safety information from FQ, we detected some safety alerts for non-FQs including anxiety and some

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

general symptoms, which warrant future studies to confirm. This study provided experiences to apply TBSS to Taiwan's NHID for signal detection.

3883 | Signals from a national spontaneous reporting system: What regulatory action do they lead to?

Florence van Hunsel[1], Liana Gross-Martirosyan[2] and Jarno Hoekman[3]
[1]*Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, Netherlands;* [2]*Medicines Evaluation Board, Utrecht, Netherlands;* [3]*Utrecht University, Utrecht, Netherlands*

Background: Signals from the Dutch Spontaneous Reporting System (SRS) can lead to regulatory actions, after decision making by the Dutch Medicines Evaluation Board. The nature and timing of these regulatory actions is likely to be dependent on the characteristics of the safety signals, including whether drugs are authorized via the centralized authorization procedure (CAP) or not.

Objectives: to characterize signals based on the Dutch SRS and to determine the nature and timing of regulatory actions based on these signals.

Methods: This study evaluates the signals disseminated from the Dutch SRS in the period from 2008 - 2017. Characteristics of the signals to be studied were selected based on key aspects of the drug used, the adverse event (AE), and the reports. To determine which regulatory action(s) took place (such as evaluating the signal in next PSUR review, asking for an update of the product information or sending the signal to the Reference Member State (RMS)), the minutes of the MEB and PRAC meetings were searched until April 2018. For drugs with a centralized authorization procedure, the timing between discussion at the MEB and SmPC update was determined.

Results: In the study period a total of 206 signals were disseminated based on the Dutch SRS. Most signals concerned a small molecule drug (93.6%). For 75.9% of signals a possible class effect was reported. The mechanism of the AE was suggested in 75.4%. The most reported ATC class code for drugs was N 'Nervous system' in 24.5% of the reports. The most frequently reported AE in the signals was related to Skin and subcutaneous tissue disorders (26 signals, 13%). Almost 70% of the signals from the Dutch SRS concerned non-centrally authorized products. 72.4% of the signals were related to not serious AEs,. 87.4% of the signals concerned AEs of drugs that had been on the market for $\geq$10 years. 88.7% of the signals from the Dutch SRS in the study period led to a regulatory action by the MEB other than routine pharmacovigilance. Forwarding the signal to the RMS was the most frequent action (30%). No significant differences in characteristics were seen between signals leading to product information (PI) update and those that led to other regulatory actions, except for time on the market for non-CAPs. For signals on CAPs; in 34% PI was updated following the signals from Dutch SRS. The time to update was on average 1.7 years.

Conclusions: 88.7% of signals from the Dutch SRS lead to a regulatory action. These signals often concerned non-serious ADRs, which can nonetheless be burdensome for patients. Signals were mostly on non-centrally authorized products, that had been on the market for more than 10 years.

3897 | Are further interventions needed to prevent hospital-acquired hyponatraemia? A cross-sectional survey of IV fluid prescribing practices in Denmark

Per Sindahl
Danish Medicines Agency, Copenhagen, Denmark

Background: Hyponatraemia is associated with increased morbidity and mortality and is frequently hospital-acquired due to administration of hypotonic intravenous (IV) fluids. Despite several attempts to minimise hospital-acquired hyponatraemia, it continues to be a safety concern and further interventions, such as educational material, may be necessary.

Objectives: To explore IV fluid prescribing practices and relevant knowledge in order to support decision-making as to whether further interventions to reduce the risk of hospital-acquired hyponatraemia are warranted.

Methods: A cross-sectional survey approaching all physicians working at emergency departments (estimated n=348) in Denmark was conducted in 2019. To measure IV fluid prescribing practices, we developed four clinical scenarios describing common clinical situations encountered in the emergency department where IV fluids are administered. The clinical scenarios selected represented conditions associated with increased ADH secretion where the risk of developing hyponatraemia has been well documented. After each scenario physicians were asked to select one IV fluid out of eight. The scenario questions were followed by 13 multiple-choice knowledge questions pertaining to IV fluids and hyponatraemia. Correct answers to all questions were summarised using descriptive statistics and logistic regression was used to identify if responder characteristics were associated with correct prescribing practice.

Results: Among the 201 respondents (response rate 57.8%), 1.5% answered all four clinical scenario questions correctly, 5.0% three, 59.2% two, 27.9% one, and 6.5% answered none correctly. 24.8% of physicians indicated to use hypotonic fluids in patients with potentially increased intracranial pressure and 29.4% to use hypotonic maintenance fluids in children, both of which are against guideline recommendations. More than half of the respondents were unaware of the impact of strong hypotonic fluids on plasma sodium in acutely ill patients. Only 29.4% knew how to treat a patient with severe symptoms of hyponatraemia, which is a medical emergency. The regression analysis showed no significant differences in prescribing practices between senior and junior doctors and other selected characteristics.

Conclusions: Inappropriate prescribing practices and limited knowledge of a large number of physicians working at emergency departments in Denmark calls for further interventions to protect patients against the risk of hospital-acquired hyponatraemia.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3939 | Complementary and alternative medicine indicated for immune system health: A shelf inspection in a sample of community pharmacies in South Africa

Cassim M. Mandlazi[1], Dayna L. Thomas[1], Nonjabulo Ndaba[1], Anthony Torcida[1], Ilse Truter[1] and Raj Naidoo[2]
[1]*Nelson Mandela University, Port Elizabeth, South Africa;* [2]*Nelson Mandela University, Port Elizabeth, South Africa*

Background: A wide variety of Complementary and Alternative Medicine (CAM) products are sold in the front-shops of community pharmacies. Many of these products are currently not registered, and may lack essential information on the outer package to enable consumers to make informed decisions on their appropriateness and safety. Immune system CAM products are popular in a country with a high prevalence of infectious diseases and many immunocompromised patients as a result of HIV.
Objectives: The primary aim was to determine the information available on the outer package label of CAM products for immune system health sold in pharmacies in Port Elizabeth, South Africa.
Methods: A data collection sheet was developed in MS Excel® and pilot tested. Variables included, for example, manufacturer, active ingredient(s), dosage, dosage form, directions for use, warnings/contraindications and regulatory authentication. Data on the outer labels of 36 commonly sold immune system CAM products were collected between June and September 2019 in five community pharmacies, representative of the community pharmacy categories in South Africa.
Results: Nearly half (44%) of the 36 products were classified as vitamins and minerals. Most of the products (92%) had no product registration number (that is, these products were not formally registered with the medicines regulatory authority in South Africa). All the products had the manufacturer indicated. The active ingredients, dosage forms and quantities appeared on all product outer package labels. All products stated the dosage and dosing frequency, and 72% indicated age-related indications. Active ingredients included inter alia vitamin C (in 42% of products), zinc, selenium and omega 3. None of the products listed any side effects, and 56% had no warnings. Most products stated that efficacy could vary between users, and that they were not intended for therapeutic use. Nearly half (47%) had no manufacturing dates, and 76% used plastic primary packaging which can affect product integrity. All products did include some information about storage conditions. The average cost per product was ZAR128.
Conclusions: Most products indicated for immune system health were not registered for medicinal purposes and contained insufficient data on their safety and efficacy. This exploratory study raised serious concerns regarding products that are easily available to the general population. There is an urgent need for CAM products to be formally regulated, to ensure manufacturing practices meet minimum standards for safety and quality.

3958 | Pattern of adverse drug reaction reporting by community pharmacist in Dharan Nepal

Kadir Alam[1] and Yogendra Baral[2]
[1]*B. P. Koirala Institute of Health Sciences, Dharan, Nepal;* [2]*Purbanchal University, Goath Gaun, Nepal*

Background: In the USA, adverse drug reaction positioned as the 6th driving reason for mortality. In the UK, around 6.5% of hospital affirmations were expected to an ADR. In Sweden 12.0% of the patients' admissions due to pharmaceutical were the consequences of ADRs. In developing countries like Nepal, there are weak regulatory systems to monitor ADR. Studies suggests that 0.64%-0.86% of the hospital admission were identified with drugs in the past. Although, there are 11 regional pharmacovigilance centers to report ADR, all of them are located in tertiary care hospital and most of them are non functional. ADR reporting from community where majority of population reside are lacking.
Objectives: Aimed to study pattern of ADR reporting, common drugs causing the ADRs, types of ADRs and causality, severity and preventability assessments of the reported ADRs.
Methods: A descriptive cross sectional study was conducted from June to September, 2018. Potential 15 community pharmacies were identified from the list of registered community pharmacies in Dharan. Selected community pharmacists from those pharmacies were provided one day training on identification and reporting system of ADR. Self developed ADR collection form was distributed those community pharmacies. The trained pharmacists were requested to report ADR through ADR reporting form. Researcher visited the trained community pharmacists every alternate day and collected the filled ADR reporting forms. Ethical approval was obtained from Nepal Health Research Council.
Results: Altogether 200 ADRs were reported by community pharmacist. Common drug causing ADRs were antibacterial 28.0 % (n=56) followed by non-steroidal anti-inflammatory drugs 25.5% (n=51)]. The most common type of ADR was Nausea/Vomiting [27.71 % (n=92), followed by abdominal discomfort [19.28 % (n=64)]. About 35.5% (n=71) of the patients required medical treatment to manage the ADRs. Over 72.5 % of the ADRs had a 'possible' association with the suspected drugs and 71.5% was of 'mild (level 1)' type. All of the ADRs reported were 'definitely preventable'.
Conclusions: Study suggests ADRs are very much prevalent in community which remains unnoticed. Strengthening this program might improve ADR reporting system and help safe use of medicines in the community.

3996 | The Australian pharmacoepidemiology research landscape: The more things change the more they stay the same

Claudia Bruno, Juliana de Oliveira Costa, Smriti Raichand and Sallie-Anne Pearson
UNSW Sydney, Sydney, Australia

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Australia's Pharmaceutical Benefits Scheme (PBS) dispensing data represents a significant resource for whole-of-population pharmacoepidemiology research. Our previous review of 228 published studies spanning 1987-2013 using PBS data highlighted significant blind spots with respect to the populations under study (with limited studies on adults <65 years using individual-level data, children, and pregnant women). Other knowledge gaps include exposure outcome studies and specialist-initiated medicines.

Objectives: Our updated review examines published literature using PBS data from 2014-2018.

Methods: We searched MEDLINE, Embase and conducted author searches for studies published from 2014 to 2018; eligible studies used PBS dispensing data alone or linked to other collections to measure patterns and/or outcomes of prescribed medicines use. Independent reviewers screened abstracts of 4,996 articles and 311 full-text manuscripts. We also extracted items pertaining to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) checklist.

Results: We identified 180 eligible studies, 55 (30%) were published in 2018. 72% of studies used individual-level data, and 51% linked PBS claims to other health claims data at the individual-level. Study population included: veterans (31%), people eligible for social security support (20%), children and pregnant women (<3%). The studies' primary focus were: clinician and patient practices (33%), drug utilization trends (21%), drug use and outcomes (12% linked, 4% ecological, 3% dispensing data), and methodological studies (14%). The most commonly studied drug classes were: nervous system (38%) and cardiovascular medicines (23%). Under-reporting most commonly related to the study design (abstract - 29%; methods - 20%), type of data used (26.7%) and population selection (17.4%).

Conclusions: This updated review sheds light on contemporary pharmacoepidemiological research in Australia. We observed an exponential increase in research based on PBS claims (228 over 26 years versus 180 in the recent 5 years). Population coverage is expanding but there is limited research in children and pregnant women. The increase in methodological research including validation studies is encouraging. However, exposure outcome studies investigating real-world medicines safety and effectiveness remain stagnant. Recent reforms around data availability and use in Australia are likely to bolster the availability of PBS data linked to collections with outcomes data and further increase research capacity in the field.

4005 | Predictors of post marketing regulatory actions concerning hepatotoxicity

Saja Alhabardi*, Mona Almaghrabi* and Adel Alrwisan
Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: Drug-induced liver injury is one of the leading causes of acute liver failure, resulting in regulatory actions ranging from warnings to withdrawals from the market.

Objectives: To investigate predictors for regulatory actions related to hepatotoxicity after drugs reach the markets, that may help in a better allocation of resources to monitor medicines after approval.

Methods: Data source: we examined approval documents for systemic drugs approved from 2011 to 2016 by the Food and Drug Administration (FDA). Extraction of liver toxicity information pre and post-approval was from medical reviews and post-marketing safety information published on the FDA's website and was completed by end of November 2019. **Outcome measure:** we defined post-marketing regulatory actions as any action that would result in marketing withdrawal, black-box warning, or updates to warning/precaution or adverse effects sections. **Statistical analysis:** we conducted Cox regression model to examine predictors for regulatory actions including accelerated approval status, meeting Hy's law prior to marketing, and history of regulatory actions.

Results: During the study period, 193 new drugs were approved, and mostly were antineoplastic and immunomodulating agents (n=68), alimentary tract and metabolism agents (n=29), and anti-infective drugs (n=23). About one fifth (n=43) of products met accelerated approval designation. A total of 48 products met Hy's law criteria before approval. There was 17 regulatory actions pertaining hepatotoxicity after approval (market withdrawal n=1, black-box warning n=2, and updates to warning/precautions or adverse effects sections n=14). The hazard ratio (HR) for regulatory action for products met Hy's criteria at approval was 0.61 (95% confidence interval [CI], 0.17-2.23). No increased hazard of regulatory action for product with accelerated approval designation (HR, 0.93; 95%CI, 0.29-2.92), nor for products with hepatotoxicity labeling information listed at approval (HR, 0.91; 95%CI, 0.33-2.56).

Conclusions: Factors such as Hy's criteria, accelerated approval status, or availability of labeled liver toxicity information at approval were not predictors for post-marketing regulatory actions concerning hepatotoxicity.

4026 | A Semantic-based visualization of drug safety profiles

Chen Yanover, Karni Marcus and Pini Akiva
KI Research Institute, Kfar Malal, Israel

Background: Qualitative, and in some cases quantitative, information about drugs' adverse events (ADEs) and side effects, is abundant, but typically unavailable to clinicians in an accessible and comprehensible way. Semantically guided visualization of such information may improve prescription and reduce ADEs.

Objectives: To visualize drug safety profiles in a semantically meaningful manner, allowing straightforward comparison of multiple treatment choices (drugs or drug classes) and focusing on clinically relevant ADEs.

Methods: As a test-case, we processed the SIDER database, version 4.1 (Kuhn et al., 2016), comprising 1,430 compounds (or drug ingredients), 5,805 ADEs (MedDRA®, the Medical Dictionary for Regulatory Activities, lowest level terms) and 138,899 drug-ADE pairs. Of these,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

occurrence frequency is also available for 55,677 (40%) drug-ADE pairs. MedDRA terminology is, by construction, hierarchical, linking lowest level terms to preferred terms, high level terms, high level group terms and, finally, system organ class. Similarly, drug ingredients are mapped to the Anatomical Therapeutic Chemical (ATC) Classification system, thus associating each ingredient with chemical, pharmacological, therapeutic subgroups and, on the top level, to anatomical main group. We represented SIDER information as a heatmap, with entities ordered according to the corresponding classification system, color coding occurrence frequency, where available, and, otherwise, indicating a known drug-ADE pair.

Results: Specific slices of the heatmap, showing risks of a subset of (related) ingredients (e.g., statins) on a class of ADEs (for example, lower respiratory tract and lung infections), can be presented to clinicians when considering multiple drug choices, allowing side-by-side comparison of the potential ADEs (and their frequency). Additionally, the proposed representation may help inferring missing drug-ADE information based on adjacent, same-class pairs (Spiro et al., 2019).

Conclusions: Semantic-based visualization of known drug-ADE data may lead to more educated prescription, hence reducing ADE burden, increasing adherence, and, importantly, improving treatment outcome. We experienced with such visualization on drug-ADE data extracted from drug labels (SIDER database); supplementing such info with risk estimations inferred from observational health data (as described in our concurrently submitted abstract) can further increase the visualization utility by filling gaps in the current knowledge, obtaining estimations for subpopulations of interest, and inferring risks, collectively, for classes of drugs or ADEs.

4035 | Prevalence of potential drug-drug interactions during hospital discharge in a tertiary care center in Nepal

Bijay Bhandari[1], Pratik Lamichhane[2], Dipendra Yadav[1] and Sangha Ratna Bajracharya[1]

[1]*Institute of Medicine, Tribhuvan University, Kathmandu, Nepal;* [2]*Institute of Medicine, Tribhuvan University, Kathmandu, Nepal*

Background: In our setup, potential drug-drug interactions (pDDIs) are overlooked in routine clinical practice. Treatment failure or inefficacy or suboptimal treatment due to drug-drug interactions can increase the duration of treatment ultimately leading to increase healthcare costs.

Objectives: To find out the prevalence and anticipate potential drug-drug interactions in the prescribed drugs during discharge from the hospital.

Methods: A cross-sectional study was conducted in a University teaching hospital in Kathmandu, Nepal. Ethical approval was taken from IRC-Institute of Medicine, Kathmandu. Through simple random sampling, the data about drug prescription was collected from the patient discharged record, from different units of the Department of Internal Medicine. The sample size was calculated using a 50% prevalence at a 95% confidence interval with a 5% margin of error and a 10% nonresponse rate. A data abstraction form was developed and used to collect the data and was transferred to electronic format after verifying. The handwritten prescription's where spellings were illegible, was clarified from the prescribers of the concerned unit. pDDIs were checked by using Lexicomp® drug interactions. The severity of pDDIs was classified as Major Moderate and Minor according to per Lexicomp®. The data were analyzed using Statistical Package for Social Science (SPSS) version 20 for descriptive statistics.

Results: We collected 401 discharge prescriptions, out of which 19 were invalidated due to exclusion criteria. We analyzed 382 discharge prescriptions, out of which the total prevalence of potential drug-drug interactions was 78.27% (74.23-82.30) with 95% CI. The mean age of the population was 53.8 ± 20 years and the mean number of medications was 6.3 and the mean duration of hospital stay was 7.9±5.7 days and the average number of interactions equal to 3.9. Severity rating as major, moderate and minor pDDIs was found to be 10.7%, 76.5%, 11.7% respectively. Among different units of Internal Medicine, pDDIs in discharged prescriptions from the Cardiology ward was in the top with 36.7% while it was around half of this (19.1%) in Pulmonology discharged prescriptions with Gastroenterology unit (7%) being least in the row. In patients with 5 drugs, pDDIs were 6.91% whereas in the case of 7 drugs pDDIs were found to be more than double (14.41%).

Conclusions: There is a high prevalence of pDDIs in the Internal Medicine wards in a tertiary care center in Nepal. The use of drug-drug interactions checker database before discharge with computer-based discharge prescriptions are recommended.

4039 | Measuring the impact of calcitonin marketing authorisation withdrawal on public health in France, Germany and UK

Samantha Lane[1], Elizabeth Lynn[1], Jim Slattery[2] and Saad Shakir[1]

[1]*Drug Safety Research Unit, Southampton, United Kingdom;* [2]*European Medicines Agency, Amsterdam, Netherlands*

Background: Impact of pharmacovigilance actions such as marketing authorisation (MA) withdrawal on public health (PH) is not normally measured quantitatively. Removing a medicine from market may significantly benefit PH by avoiding unnecessary adverse drug reactions (ADRs), which should be measured quantitatively if possible. Calcitonin-containing products, used to treat osteoporosis, demonstrate the model. Calcitonin was withdrawn EU-wide in 2012 due to evidence of increased cancer risk, including but not limited to prostate, breast and skin cancers during long-term exposure in clinical trials.

Objectives: To identify a method to quantify impact of MA withdrawal of calcitonin-containing products in terms of morbidity and mortality changes.

Methods: Patients exposed to calcitonin were counted in quarterly periods for 12 months pre- and post-withdrawal of MA by sex and decade of age, in IQVIA Medical Research Data (IMRD)-France,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

IMRD-Germany and IMRD-UK electronic health record databases; annual exposure was estimated. Reason for MA withdrawal (ADR of interest) was obtained from EMA records. Quantitative research addressing the ADR of interest was identified by systematic review, allowing an estimation of absolute risk in exposed patients. PH impact, expressed as annual number of ADRs avoided as a result of PV action, was estimated by modelling product usage figures and ADR risk. This number of expected ADRs was scaled up to give an approximation for the source population. Background risk put results into context.

Results: No evidence of exposure to calcitonin was found in the IMRD-France population during the 12 months prior to MA withdrawal. At the time of calcitonin withdrawal, 3,047,589 patients were active in IMRD-Germany and 5,258,874 patients in IMRD-UK; prevalence of calcitonin exposure in these populations during the 12 months before withdrawal was 2.6% and 5.4% respectively. Average exposure was 86% lower in IMRD-Germany patients and 97% lower in IMRD-UK patients post-withdrawal, but only in the UK population did the number of exposed patients reach zero, six months post-withdrawal. From published studies, estimated risk of cancer among exposed patients was 7.6%. Based on risk and usage estimates it was estimated that 48 new attributable cases of cancer were prevented annually throughout the IMRD-Germany and IMRD-UK populations due to reduced or eliminated calcitonin exposure.

Conclusions: This model quantifies the PH impact of MA withdrawal of calcitonin in terms of serious morbidity, as exposure was reduced or eliminated. This method can be applied to products in other settings.

4070 | Vortioxetine's post-marketing safety profile determined through cluster analysis of global adverse event reports

Corine Ekhart[1], Florence van Hunsel[1], Eugène van Puijenbroek[1,2], Rebecca Chandler[3], Eva-Lisa Meldau[3] and Niklas Norén[3]

[1]Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, Netherlands; [2]University of Groningen, Groningen, Netherlands; [3]Uppsala Monitoring Centre, Uppsala, Sweden

Background: Vortioxetine, a novel antidepressant, is a multimodal serotonergic drug which has been on the market since late 2013. Although the mechanism of action is unclear, it is hypothesized to work via blockage of serotonin reuptake. However, the Summary of Product Characteristics (SmPC) of vortioxetine is relatively sparse compared with other SSRIs. Although adverse events (AEs) tend to be reported as distinct entities, it cannot be excluded that they share commonalities that might shed a light on for instance the pathogenesis or an unknown underlying factor. Through cluster analysis, we aim to get insight into these commonalities and the pathogenesis of reported adverse events of vortioxetine.

Objectives: To gain insight into commonalities and pathogenesis of adverse events of vortioxetine by clustering global adverse event data.

Methods: Cluster analysis was performed for 5,827 reports on vortioxetine in VigiBase, the World Health Organization's global database of Individual Case Safety Reports. Consensus clustering grouped reports that were repeatedly placed together across a set of mixture model-based cluster analyses. The latter used empirical Bayes estimation for a latent class model with conditionally independent binomial distributions for AEs.

Results: 36 clusters containing at least 5 reports, and 2492 AEs in total, were analyzed. The two largest clusters included 48% of the vortioxetine reports and appeared to describe gastro-intestinal AEs and hypersensitivity AEs. Other distinct clusters were related to fatigue, aggression/suicidality, convulsion, medication errors, arthralgia/myalgia, weight increased, paraesthesia and anticholinergic effects (such as dry mouth, dry eyes, blurred vision). Some of these clusters are not labelled ADRs for vortioxetine, but are known ADRS for other SSRIs such as paroxetine and escitalopram. Some clusters can be explained by the pharmacology of vortioxetine or the pathophysiology of depression. Other clusters seem to be driven by variations in coding practice or might be spurious due to the small number of reports.

Conclusions: Cluster analysis reveals a pattern of co-reported AEs which is consistent with labelled AEs for vortioxetine and the safety profile for SSRIs in general. In addition, clusters of unlabeled AEs were identified that reflect clinical entities and that might represent signals of previously unknown ADRs. Novel analyses of spontaneous reports such as clustering may help to further understand the pathogenesis of ADRs.

4085 | Improved detection statistical signals in pharmacovigilance by combining multiple variables from the reports

Thomas Berbain[1,2], Ismail Ahmed[3], Pascale Tubert-Bitter[3], Serge Brunel[1], Pascal Auriche[1] and Mehdi Benkebil[1]

[1]French Agency for Medicines (ANSM), Saint-Denis, France; [2]University of Toulouse III - Paul Sabatier, Toulouse, France; [3]Inserm U1018: Center for Epidemiology and Population Health (CESP), Villejuif, France

Background: Pharmacovigilance identifies and assesses safety issues related to the use of medicines and ensures that the benefits always exceed the potential risks. Larges collections of individual case safety reports (ICSRs) remain the primary source of information and require effective analytics to identify likely drug safety signals. Disproportionality analysis is based solely on aggregate numbers of ICSRs and naively disregards the content of the ICSRs. Multiple variables are available in French Pharmacovigilance Database (BNPV), including drug causality score, quality and seriousness of ICSRs, as well as trends in time and geographic spread.

Objectives: The objective was to develop and evaluate a predictive statistical model of safety signals (PSMSS) that incorporates these variables from ICSRs.

Methods: PSMSS implemented with logistic regression to identify predictive variables and estimate their respective contributions. A

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

reference set was created based on historical safety signals from 2012 to 2019 of Observational Medical Outcomes Partnership (OMOP), the list of marking ICSRs processed by French Agency for Medicines (ANSM) and the list of signals processed in Pharmacovigilance Risk Assessment Committee (PRAC). It accounts for 468 positive controls, and 3713 negative controls (pairs of drugs and adverse events not listed in the Summary of Product Characteristics of that drug in 2019). Part of the reference set was used for model fitting, the second part was used for model evaluation.

Results: The following variables were selected for inclusion in the PSMSS: numbers of recent reports; with a high causality score; a high quality rating; a positive rechallenge; a serious criteria and reports disproportional reporting. PSMSS provided a statistically significant improvement in area under the receiver operating characteristics curve (AUC) over screening based on an adapted method of the Multi Gamma Poisson Shrinker ((M)GPS), respectively (0.805 vs. 0.568).

Conclusions: Accounting for multiple aspects of ICSRs has clear conceptual and empirical advantages over disproportionality analysis.

4108 | Tramadol (oral and for injection) adverse event spontaneous reports in the World Health Organization programme for international drug monitoring database, VigiBase: 2009-2019

Sydney T. Thai[1,2], Thomas Rhodes[2], Molly Aldridge[2], Suzanne F. Cook[2] and Cynthia J. Girman[2]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]CERobs Consulting, LLC, Wilmington, NC

Background: Tramadol (oral and for injection) formulations are available in over 80 countries worldwide. Little has been published on spontaneously reported adverse events (AEs) for tramadol oral and injection (IV) routes of administration (ROA).

Objectives: To summarize the ten most frequently reported AEs and three AEs of specific interest for tramadol products with oral and IV ROA.

Methods: Using VigiBase (1/2009 to 6/2019), all spontaneous AE reports where oral or IV tramadol, ketorolac/tramadol or paracetamol/tramadol were coded as the suspected or interacting drug were identified. The ten most frequently reported AEs and three AEs of interest (seizure, serotonin syndrome, respiratory depression) globally and for Europe (EU) were summed for oral and IV tramadol using counts and percentages. Demographics of the report and opioid co-use were assessed.

Results: Of 53,303 oral and 41,145 IV tramadol reports, most were from Asia (>65% for oral, >93% for IV). Reports were more often regarding females (65% of oral, 61% of IV) and adults age 45-64 years (34-37%) followed by ages 18-44 years (22-30%). Few reports listed opioid co-use (7% of oral, 3% of IV reports). Nausea, vomiting, and dizziness were the most frequently reported AEs (29%, 20%, and 18% of oral reports; 60%, 35%, and 14% of IV reports, respectively). Other AEs common to both ROAs were pruritis, headache, rash, and urticaria. The ten most frequently reported AEs for oral tramadol included somnolence, constipation, and dyspepsia, while IV tramadol included hyperhidrosis, dyspnea, and retching. AEs of interest were rarely reported; percentages for each were lower for IV (range 0.0-0.3%) compared to oral tramadol (0.2-1.0%). In EU, most reports were for oral tramadol (>93%, n=12,562) compared to IV (n=970). Nausea and vomiting were most common (17% and 16% for oral; 12% and 11% for IV). Other AEs common to both ROA in EU included confusional state, malaise, hyperhidrosis, and pruritis. The ten most frequently reported AEs in EU included dizziness, somnolence, vertigo, and headache for oral tramadol and urticaria, rash, hypotension, and erythema for IV. AEs of interest in EU were reported in a higher percent of IV reports (range 1.0-2.5% vs. 0.5-1.7% for oral). Opioid co-use was listed for 20% of IV reports and 9% of oral reports.

Conclusions: Considering the global and European scope of this study, IV tramadol generally appears to be comparable to oral tramadol with respect to the types of spontaneously reported AEs. For both ROA, AEs of interest were reported infrequently relative to other AEs.

4128 | A tree-based statistic data mining approach to assess the post-marketing safety of new glucose-lowering medications in routine care

Michael Fralick[1], Martin Kulldorff[2], Donald Redelmeier[3], Shirley V Wang[2], Seanna M Vine[2], Sebastian Schneeweiss[2] and Elisabetta Patorno[2]

[1]University of Toronto, Toronto, ON, Canada; [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [3]Institute for Clinical Evaluative Sciences in Ontario, Toronto, ON, Canada

Background: Phase IV cardiovascular outcome trials have shown that SGLT2 inhibitors, a newer class of glucose-lowering medications, produce cardiovascular benefits in patients with type 2 diabetes (T2D). However, clinical trials are underpowered to detect serious but rare adverse events of new medications.

Objectives: We applied a tree-based scan statistic (TreeScan) data mining approach to detect potential adverse events in a cohort of adult patients with T2D initiating canagliflozin, the first marketed SGLT2 inhibitor in the U.S., shortly after its approval (3/2013) and prior to public awareness of specific potential safety concerns.

Methods: In a U.S. commercial claims dataset (3/2013-9/2015), two cohorts of T2D patients initiating canagliflozin or a comparator (i.e., a DPP-4 inhibitor or a GLP-1 receptor agonist), were identified and propensity score matched, adjusting for 23 covariates. Within each cohort, we used 1:4 variable ratio matching. Using TreeScan, we assessed thousands of incident outcomes in canagliflozin vs. comparator initiators during the 180 days after treatment

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

initiation, scanning for statistical alerts for adverse events after adjusting for multiple testing. Incident outcomes were defined by hierarchical groupings of clinically related ICD-9 codes.

Results: We identified two propensity score matched cohorts including 44,733 canagliflozin vs. 99,458 DPP-4 inhibitors initiators (cohort 1), and 55,974 canagliflozin vs. 74,727 GLP-1 receptor agonists PS-matched initiators (cohort 2), with average age of 55 years. When we assessed incident inpatient and emergency department diagnoses, diabetic ketoacidosis was the only severe adverse outcome associated with canagliflozin initiation (p=0.043 in cohort 1 and p=0.0006 in cohort 2). When outpatient diagnoses were also considered, alerts for female and male genital infections emerged in both cohorts (p<0.0005).

Conclusions: In a large population-based study of middle-aged adults with T2D, TreeScan detected known adverse events but identified no other unexpected adverse events associated with the initiation of canagliflozin compared with alternative glucose-lowering strategies. This provides reassurance on the safety of canagliflozin among adult patients with T2D and suggests the tree-based scan statistic may be a useful post-marketing safety monitoring tool for new medications.

4140 | Cannabidiol exposure calls to U.S Poison Control Centers

Sara Karami, Silvia Perez-Vilar and Kira Leishear
U.S. Food and Drug Administration, Silver Spring, MD

Background: Cannabidiol (CBD) is one of over 100 chemical compounds identified in cannabis plants. In June 2018, the U.S. Food and Drug Administration (FDA) approved the first prescription (Rx) CBD drug for the treatment of seizures associated with Lennox-Gastaut or Dravet syndromes.

Objectives: To describe U.S. poison control center (PCC) CBD exposure calls.

Methods: We analyzed PCC call data (2000-2019) involving CBD exposure from the National Poison Data System excluding exposures involving marijuana and nabiximols. We assessed patient characteristics, exposure reasons, medical outcomes, clinical effects and co-exposures.

Results: Beginning in 2014, we identified a total of 2,216 CBD exposure calls to U.S. PCCs with a sharp increase starting in 2016; the bulk of calls occurred in 2019 (N=1,527; 69%). Most calls referred to plant-based non-Rx CBD products (83%), and 6% to Rx CBD products (formulation for 11% of calls was unknown). Classification for the majority of CBD exposures was unintentional (54%), mainly involving children ≤12 years of age (65%). We noted a similar distribution by age category and exposure reason for calls involving Rx CBD products. Among calls reporting use of CBD without other concomitant substances (N=1761, 80%), related medical outcomes for calls where follow-up was available (N=458) were largely classified as minor effects (64%), trailed by moderate (31%) and major (5%). We identified one death reported in temporal association with a non-Rx CBD product. The most frequently reported clinical outcomes included mild central nervous system depression (16%), tachycardia (16%), vomiting (15%), dizziness/vertigo (13%), agitation (13%), nausea (13%), confusion (12%), and drowsiness/lethargy (12%). For calls describing exposure to CBD and at least another substance, co-exposures included marijuana (17%), anticonvulsants (17%), benzodiazepines (15%), antidepressants (12%), ethanol (9%), antihistamines (9%), stimulants and street drugs (8%), and opioids (8%).

Conclusions: We observed a sharp increase of mostly non-Rx plant-based CBD exposure calls to PCCs since 2016. The reported clinical effects have typically been non-serious, though 5% were major; one death was also reported. Our findings are difficult to interpret as the exact contents of retail CBD products are unknown, and a large proportion of CBD calls had missing formulation or clinical and medical outcome follow-up data. Additional follow-up is needed to assess potential clinical effects of retail CBD products and determine how FDA's approval of the first Rx CBD drug may influence CBD poisonings.

4235 | Risk of tympanic membrane perforation with combination quinolone and steroid otic therapy for acute otitis externa

Kiyon Rhew[1], Phuong T Tran[2], Xi Wang[2], Almut G Winterstein[2] and Patrick J Antonelli[3]
[1]*College of Pharmacy, Dongduk Women's University, Seoul, Republic of Korea;* [2]*Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL;* [3]*Department of Otolaryngology, College of Medicine, University of Florida, Gainesville, FL*

Background: Systemic quinolone therapy has been linked to a myriad of soft tissue complications, which can be compounded by systemic steroid therapy. Otic quinolones may cause tympanic membrane perforation (TMP). It is unclear whether combination quinolone and steroid therapy increases this risk.

Objectives: Our study evaluated whether the use of combination otic solution with quinolone and steroids increased the risk of TMP over otic quinolone alone.

Methods: This retrospective cohort study utilized the Korean Health Insurance Review Agency claim database. We included all patients who used otic quinolone +/- steroids following a diagnosis of acute otitis media (AOE) from 2015-2016. We excluded systemic quinolone use within 30 days before or at index date, existing TMP, and patients with disease states that might predispose to TMP during the baseline or follow-up. Included ear drops were quinolone (ofloxacin or lomefloxacin), ciprofloxacin/hydrocortisone, ciprofloxacin/dexamethasone, or ciprofloxacin/fluocinolone. An occurrence of TMP was identified as the presence of two TMP diagnoses at least 30 days apart. A Cox regression model, adjusting for patient demographics (age, sex, and medical insurance type), and the volume of ear drop dispensed (time-varying) was used to compare TMP risk among the ear drop users.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: 112,312 patients were included. The adjusted hazard ratio (HR) of TMP was increased in the patients with ciprofloxacin/dexamethasone compared to the ofloxacin or lomefloxacin (HR 2.38, 95% CI 1.09-5.18). The adjusted HRs of TMP for ciprofloxacin/hydrocortisone were 0.66 (95% CI 0.37-1.18), and for ciprofloxacin/fluocinolone were 1.34 (95% CI 0.59-3.05).

Conclusions: Use of more potent steroids (dexamethasone) in combination quinolone preparations may increase risk of TMP compared to use of otic ofloxacin or lomefloxacin. Larger sample size and careful examination of confounding by severity are needed to confirm this observation.

4259 | Incidence, severity and cost associated with the management of adverse events following anaesthesia: An intensive surveillance in a tertiary care hospital

Ramesh Madhan[1], Resha Dangol[1], Gurudatt C L[2] and Sri Harsha Chalasani[1]

[1]JSS College of Pharmacy, JSS AHER., Mysuru, India; [2]JSS Medical College & Hospital, Mysuru, India

Background: The adverse events following anaesthesia are not only related with deaths, but also with other serious complications such as cardiovascular, respiratory and neurological disorders. Hence an intense surveillance is necessary to promote patient safety.

Objectives: To determine the incidence, severity and cost associated with the management of adverse events following anaesthesia in a tertiary care hospital

Methods: Clinical Pharmacist initiated active surveillance focusing on adverse events following anaesthesia amongst the patients who underwent surgery was carried out for nine months in a tertiary care teaching hospital. Severity of the reaction was assessed using Modified Hartwig and Siegel scale. The direct cost associated with the management of ADRs were calculated and the median cost with the interquartile range (IQR) were determined. All categorical variables were represented as numbers with percentage values.

Results: During the study period, a total of 302 patients were enrolled into the study with a mean duration of surgery 82.07 ± 63.28 minutes. Majority [154 (50.10%)] of patients received spinal anaesthesia followed by general [132 (43.71%)]. A mean of 18.55 ± 5.00 drugs were used. A total of 77 ADRs were reported amongst 65 (22%) patients. The most frequently affected organ system was cardiovascular [33 (43.0%)] followed by gastrointestinal [21 (27.3%)]. The most frequently observed ADRs were bradycardia [17 (22%)] and hypotension [16 (20.8%)]. Majority [51 (66.23%)] of ADRs were moderate in their severity, while two reactions (2.60%) were severe in nature. The direct cost associated with management of ADRs was incurred in 43 (66%) patients. The average cost incurred in the management of ADRs was Rs. 463.50 {[USD 8 (Range: Rs. 3.1 (USD 0.043) to Rs. 9826 (USD 141)]}.

Conclusions: Continuous monitoring and sensitization of healthcare professionals in early detection and management of ADRs associated with anesthesia is imperative. Clinical pharmacists, in close liaison with the anesthesiologists can facilitate early detection and management of adverse events following anesthesia.

4267 | Increased intolerance to angiotensin converting enzyme inhibitors in asthma: A United Kingdom population-based cohort study using electronic medical records

Daniel R Morales[1,2], Brian Lipworth[1], Peter Donnan[1] and Huan Wang[1]

[1]University of Dundee, Dundee, United Kingdom; [2]University of Southern Denmark, Odense, Denmark

Background: Angiotensin converting enzyme (ACE) inhibitors are widely prescribed but intolerance commonly occurs due to cough requiring switching to an angiotensin-II receptor blocker (ARB). ACE-related cough is mediated by bradykinin that may affect airway hyperresponsiveness in asthma.

Objectives: To assess whether switching to ARBs following treatment with ACE inhibitors is more common in people with asthma. To understand in which types of asthma patients this is more likely to occur.

Methods: The UK Clinical Practice Research Datalink was used to identify a cohort of new users of ACE inhibitors. The risk of switching to an ARB was compared between people with asthma and the general population. People with chronic obstructive pulmonary disease (COPD) acted as a negative control. Hazard ratios (HR) were calculated using COX regression adjusting for confounders (age, gender, socioeconomic deprivation, smoking status, hypertension, cardiovascular disease, and body mass index (BMI)). Analyses were stratified by asthma severity defined by British Thoracic Society treatment steps and ACE inhibitor product, with the number needed to harm calculated overall and stratified by age, gender and BMI.

Results: Of 642,336 new users of ACE inhibitors, 40,953 had active asthma (6.4%). The risk of switching to an ARB was significantly greater in people with asthma HR 1.16 (1.14-1.18) and was highest in those with British Thoracic Society step ≥3 asthma HR 1.28 (1.25-1.30). Among individual ACE inhibitor products, risk was highest with enalapril: corresponding numbers 1.25 (1.18-1.34) and HR 1.44 (1.32-1.58) respectively. No significant increased risk was observed in people with COPD. The NNH significantly varied by age, gender and BMI ranging between 21 and 4, being lowest in older women with BMI ≥25.

Conclusions: People with asthma are more likely to switch to an ARB following ACE inhibitor therapy suggesting they are more likely to be intolerant of ACE inhibitors. The NNH varies by age, gender and BMI. ARBs might be considered first-line in people with asthma with such characteristics when treatment with a renin-angiotensin system inhibitor is clinically indicated.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4276 | Ixekizumab and the potential risk of urinary tract infection: A systematic review and analysis of individual case safety reports in the who global database

Mona Almaghrabi and Fawaz Alharbi
Saudi Food and Drug Authoriy, Riyadh, Saudi Arabia

Background: Ixekizumab is a biologic works by binding to interleukin 17A to inhibit its action used in the treatment of plaque psoriasis and rheumatic diseases. The safety of ixekizumab has been intensively reviewed as part of the proactive monitoring initiative conducted by the Saudi Food and Drug Authority.

Objectives: To evaluate the potential risk of urinary tract infection (UTI) with ixekizumab use.

Methods: We searched PubMed, Cochrane and Google scholar for relevant studies and case-reports from inception to March 15th, 2019. Studies in English language and on humans were considered for this review. Search strategies included (Ixekizumab OR Taltz) AND (Urinary tract infection). Moreover, a search was performed in the WHO database (VigiBase) on February 2019, using WHO drug substance term (ixekizumab) and preferred term of Medical Dictionary for Regulatory Activities ((PT) (MedDRA) "urinary tract infection", to retrieve all reported cases of UTI between 1971 and 2019. Cases were assessed using WHO-Uppsala Monitoring Centre causality system.

Results: We included four articles in our review (2 RCTs, 1 open-label extension study, and 1 pooled safety analysis). The studies showed that UTI was one of the most commonly reported ADEs during trials. In integrated safety analysis of clinical trials, data were split into 12-weeks induction period and 12-60-weeks maintenance period, then compared to placebo-group and active-controlled group (etanercept). In induction period, UTI occurred in 2/360 patients in placebo-group (the exposure-adjusted incidence rate, IR 2.4), 5/739 patients in etanercept-group (IR 3.0), 10/734 patients in ixekizumab 80 mg every 2-weeks group (IR 5.9), and 13/729 patients in ixekizumab every 4-weeks group (IR 7.8). In the maintenance period, UTI occurred in 7/402 patients (IR 3.7) in placebo-group, 15/416 patients in ixekizumab 80 mg every 4-weeks group (IR 4.3), and 9/408 patients in ixekizumab 80 mg every 12-weeks group (IR 3.2). 179 of UTI (IR 2.8) occurred among 4209 patients (IR 2.8). We Identified 33 cases of UTI (serious=27) reported to VigiBase suspected with ixekizumab. Causality assessment of the cases was: Likely 3 (9%), probable 4 (12%), and unlikely 1 (3%). However, the majority of the cases were unassessable 25 (75.8%) due to insufficient information.

Conclusions: We believe there is a possible association between ixekizumab and the risk of UTI. The mechanism of occurrence of UTI might be attributed to ixzekizumab immunosuppressant effects. Further studies are needed to assess such risk compared to placebo or comparator drugs.

4287 | Barriers and facilitators of medication error reporting amongst health care professionals

Ramesh Madhan, Gunam Usha Keerthana, Ann Raju Roona, Annu Philip Aleena, Joshy Jiya and Sri Harsha Chalasani
JSS College of Pharmacy, Mysuru, India

Background: Under reporting of medication errors due to fear of sanctions is a major concern against achieving patient safety. Understanding the barriers and facilitators towards voluntary reporting of these errors is key to promote patient safety.

Objectives: The study aimed to understand the barriers and facilitators to medication error reporting amongst healthcare professionals (HCPs).

Methods: Clinical Pharmacists conducted a questionnaire based exploratory research amongst 839 HCPs in a tertiary care teaching hospital. A standardized and validated 35-point questionnaire encompassing the themes of facilitations and barriers was administered. Data was scribed into specially designed electronic data collection form and categorically analyzed.

Results: A total of 712 HCPs returned the filled questionnaire [377 (52.9%) doctors, 324 (45.5%) nurses and 11 (1.5%) pharmacists] giving a response rate of 85%. Of the total respondents, majority [313 (44%)] of HCPs had less than five years of work experience and only 178 [(25%)] reported medication errors. The common reasons for underreporting were disclosure of identity of the person who committed the error [451 (63.4%)], negative peer pressure [353 (49.7%)], fear of blame & shame [308 (43.1%)] and excessive workload [292 (40.8%)]. While, 'Patient Safety' was held as a facilitator amongst majority of HCPs [326 (53.3%)] with permanent embedment of positive patient safety culture in the organization. Supportive working environment [674 (94.7%)], Pressure-free reporting culture [628 (88.3%)], simplicity of ME reporting forms [603 (84.8%)], open encouragement from the peers [510 (68.6%)], and constant reminders about ME reporting [337 (47.4%)] were few other facilitators.

Conclusions: Our study findings revealed that, although the HCPs have a positive attitude towards ME reporting, negative peer pressure & excessive work burden dampens the spirit of reporting ME voluntarily. Sensitizing and strengthening the non-punitive reporting systems through continuous awareness programs will facilitate voluntary ME reporting culture.

4339 | Vaxbatch: A stratified disproportionality analysis tool for batch-related AEFI monitoring in vaccines

Joep Scholl, Florence van Hunsel, Wil Hilgersom and Eugene van Puijenbroek
Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, Netherlands

Background: Because a vaccine is a biological product with a biological manufacturing process, some variability in its composition may

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

exist between batches. This may lead to differences in reactogenicity, and subsequently in differences in the AEFI spectrum between batches within a single product. In order to optimize the safety monitoring for vaccines, a method to monitor possible batch-related issues was warranted.

Objectives: To develop a batch-specific disproportionality analysis tool, allowing for monitoring of possible batch-related issues in vaccines.

Methods: Vaccine reports from the Netherlands national pharmacovigilance database related to the Dutch National Immunisation Programme were included. Each unique AEFI was classified as either a local or a systemic reaction. For each batch within a vaccine, local and systemic reactogenicity was compared with all other batches of the same vaccine, based on the reporting odds ratio (ROR). A batch was classified as having a disproportionate number of reports if the lower limit of the 95%CI of the ROR was above 1. The results were cumulatively stratified by month to allow for longitudinal monitoring. Two different definitions for local/systemic reactogenicity were used and results are to be compared. Disproportionate batches containing reports with new information from the past 30 days were subjected to in depth clinical review.

Results: For the initial run, a total of 8,305 reports were included, containing 24 unique vaccines and 693 batches. In 67% of all reports a valid batch number was present and this has been increasing over the past years. Preliminary results show approximately 4 positive batches per month, where more recent batches seem to be disproportionately present more often than older ones. So far, in depth clinical reviews did not reveal any batch related problems. We found that reports can contribute to multiple positive batches due the administration of more than one vaccine simultaneously. The comparison between the different definitions on local/systemic reactogenicity will be performed 6 months after implementation of the tool.

Conclusions: The results show that longitudinal monitoring of AEFI's in the Dutch National Immunisation Programme for batch related issues is feasible. For systemic AEFI's to be adjudicated to a specific vaccine, in depth clinical review is necessary.

4371 | An empirical evaluation of adverse event cluster analysis in pharmacovigilance

G. Niklas Norén, Eva-Lisa Meldau and Rebecca E. Chandler
Uppsala Monitoring Centre, Uppsala, Sweden

Background: Most analyses in pharmacovigilance are based on single reported adverse event terms and fail to account for the complete sets of signs, symptoms and diagnoses on each report. This makes them vulnerable to jumbling of case series by grouping reports that share single adverse events but describe different clinical conditions and to fragmenting case series which use different terms to describe similar adverse events. Attempts have been made to identify natural groupings of adverse event reports using cluster analysis, but systematic evaluations of performance are lacking.

Objectives: To evaluate the stability and clinical coherence of results from a consensus clustering algorithm applied to individual case reports of suspected adverse drug reactions.

Methods: Consensus clustering was achieved by grouping pairs of reports that were repeatedly placed together in the same clusters across a set of mixture model-based cluster analyses. The latter used empirical Bayes estimation for a latent class model with conditionally independent binomial distributions for adverse events. Three randomly selected drugs in VigiBase, the World Health Organization's global database of Individual Case Safety Reports were analyzed: sumatriptan, ambroxol and tacrolimus. Clustering stability was assessed by the adjusted Rand index, ranging between -1 and +1. Clinical coherence was assessed systematically through an intruder detection analysis, in which each cluster was represented by its three most frequent adverse event terms and an 'intruder' was added. The intruder was randomly selected among commonly reported adverse event terms for the drug not associated with the cluster in question. Clinical coherence was measured as the proportion of clusters for which a domain expert correctly identified the intruder.

Results: Consensus clustering achieved stable and coherent results for all three drugs, with adjusted Rand indices between +0.80 and +0.92, and intruder detection rates between 86% and 94%. Consensus clustering improved both stability and clinical coherence compared to mixture model-based clustering alone.

Conclusions: Consensus clustering for individual case reports can achieve adequate stability and clinical coherence, thereby improving the identification of case series and associated adverse event profiles in pharmacovigilance.

4400 | Incidence of cutaneous small vessel vasculitis associated with oral anticoagulant use

Adebola Ajao[1], Oren Shapira[2], Efe Eworuke[1], Mohamed Mohamoud[1], Rongmei Zhang[1], Joy Kolonoski[2] and John Connolly[2]
[1]Food and Drug Administration, Silver Spring, MD; [2]Harvard Pilgrim Health Care Institute, Boston, MA

Background: Cutaneous small vessel vasculitis (CSVV) was identified as a safety signal among patients treated with Non-Vitamin K Oral Anticoagulants (NOACs). CSVV is a form of vasculitis defined as a single organ, skin isolated leukocytoclastic vasculitis or angiitis without systemic vasculitis or glomerulonephritis.

Objectives: To determine the crude incidence rate of CSVV following initiation of a NOAC, warfarin, or allopurinol (both labelled for vasculitis) among patients with atrial fibrillation (Afib).

Methods: We identified patients 21+ years old, diagnosed with Afib with at least 6 months of continuous medical and drug coverage in the IBM® MarketScan® Commercial and Medicare Supplemental Databases between October 19, 2010 and September 30, 2018. We selected eligible patients who newly initiated NOACs, warfarin, or allopurinol, and did not have any of the following in the 183 days prior to initiating

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

treatment: prior CSVV diagnosis, a dispensing of the other study drugs, select autoimmune disease or autoimmune medications, any cancer diagnoses or treatment, kidney dialysis or transplant, alternative anticoagulation indications, or an institutional (skilled nursing home, hospice, hospital) stay on the treatment initiation date (index date). New users were followed from the index date until a CSVV outcome (primary: outpatient CSVV diagnoses followed by a dispensing of oral or topical prednisone, prednisolone, or select steroid treatments within 90 days; secondary: outpatient CSVV combined with oral or topical prednisone or prednisolone only within 90 days, and tertiary: inpatient principal diagnosis of CSVV), death, disenrollment, end of study period, end of exposure episode, or dispensing of the other study drugs.

Results: We identified 135,858 NOAC new users (mean age ± SD: 67 ± 13 years), 109,241 warfarin new users (mean age ± SD: 72 ± 13 years), and 7,589 allopurinol new users (mean age ± SD: 71 ± 13 years). Baseline patient characteristics were similar across the three patient groups. The crude CSVV incidence rate (events per 10,000 years at risk) of the primary outcome for NOAC, warfarin, and allopurinol users was 3.89, 3.87, 3.97, respectively; secondary outcome was 2.53, 2.76, 3.97, respectively; and tertiary outcome was 0.19, 0.83, 3.97, respectively.

Conclusions: The crude incidence rate of CSVV for NOACs was comparable to warfarin and allopurinol, both of which are labelled for vasculitis. This study will be replicated in the Sentinel Distributed Database. Adjusted studies are planned to further characterize the risk of CSVV among NOAC users to evaluate if there is differential risk by individual NOACs.

4464 | Polypharmacy as an independent risk factor for serious adverse drug reactions: A systematic review

Diogo Mendes[1], Rita Gomes[2], Carlos Alves[3,1] and Francisco Batel Marques[3,1]

[1]*AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal;* [2]*School of Pharmacy, University of Coimbra, Coimbra, Portugal;* [3]*School of Pharmacy, University of Coimbra, Coimbra, Portugal*

Background: The simultaneous use of drugs is common, particularly among the elderly. However, polypharmacy has been associated with an increased risk of adverse effects.

Objectives: This study aims at evaluating if polypharmacy is an independent risk factor for serious Adverse Drug Reactions (ADRs).

Methods: A systematic review was conducted in EMBASE and PUBMED, from January 2008 to May 2019, in order to identify both observational and experimental studies assessing the risk of serious ADRs among patients under polypharmacy versus non-polypharmacy. The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale (observational studies) and the Cochrane Handbook of Systematic Review of Interventions on assessing adverse effects (experimental studies). The EndNote® software tool was used to manage the citations retrieved from the literature search.

Results: Sixteen observational studies were included in this systematic review. Eleven studies evaluated the risk of hospitalization, of which 10 considered polypharmacy as a risk factor for serious ADRs; Three evaluated the risk of death, but the results are conflicting; One study evaluated the risk of the composite outcome of hospitalization or death, 1 the risk of the composite outcome of hospitalization or death or life-threatening events, 1 the risk of disability and one study evaluated the risk of any serious ADRs, and all of these have identifying statistical significant increased risks. Six studies were assessed as having high methodological quality, nine as having moderate methodological quality and one as having poor methodological quality.

Conclusions: According to the results, polypharmacy seems to be an independent risk factor for serious adverse drug reactions, particularly hospitalization. However, there is a lack of a homogeneous methodology across the studies, mainly due to significant differences among the polypharmacy and non-polypharmacy terms adopted.

4479 | Acute pancreatitis associated with methimazole treatment: A population-based study on regional Italian databases

Alessandro Pecere[1], Marina Caputo[2], Andrea Sarro[1], Angelica Zibetti[1], Andrealuna Ucciero[1], Paolo Marzullo[2,3], Gianluca Aimaretti[2] and Francesco Barone-Adesi[1]

[1]*Università del Piemonte Orientale, Novara, Italy;* [2]*Università del Piemonte Orientale, Novara, Italy;* [3]*I.R.C.C.S. Istituto Auxologico Italiano, Ospedale San Giuseppe, Verbania, Italy*

Background: Methimazole (MMI) is a widely used drug for first-line treatment of hyperthyroidism. In 2019, a warning has been issued by the European Medicine Agency (EMA) regarding a potential increased risk of acute pancreatitis (AP) in MMI users, based on evidence from published case reports and post-marketing surveillance.

Objectives: The aim of this study was to investigate the association between MMI treatment and AP onset in a cohort of new users from Piedmont Region, Italy.

Methods: A retrospective analysis of administrative health databases was conducted in the period 2013-2018. In particular, relevant data useful to identify MMI users and AP cases were obtained from: i) inhabitants registry, ii) hospital discharge records (ICD-9-CM 577.0), iii) drug claims registry (ATC H03BB02). General population (non-users) was used as control group. To investigate the association between MMI treatment and AP risk, we identified hospitalizations for AP occurring in each trimester comprised in the first 18 months following the first prescription of MMI. Poisson regression was used to estimate the age- and sex-adjusted Rate Ratios (adjRRs), and the relative 95% confidence intervals (CI), comparing rates of AP between MMI users and non-users. The absolute risk of AP in MMI users was also calculated. Finally, a secondary analysis using a Self-Controlled Case Series (SCCS) approach was carried out to evaluate the role of possible unmeasured confounding.

Results: A total of 23,087 users of MMI were identified. Among these, 13 hospitalizations for AP were recorded within the first trimester of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

treatment, for a total of 61 hospitalizations occurring within the first 18 months. The crude RR for AP in the first trimester of treatment was 270 per 100,000 person-year [95% CI 170-428] in MMI users and 60 per 100,000 person-year [95% CI 59-61] in the general population. Values of adjRRs according to trimesters of observation were 3.40 [95% IC 2.12-5.48] for the first, 2.40 [95% IC 1.36-4.23] for the second, 2.80 [95% IC 1.66-4.73] for the third, 1.20 [95% IC 0.54-2.68] for the forth, 1.60 [95% IC 0.80-3.21] for the fifth and 0.80 [95% IC 0.30-2.14] for the sixth trimester. The absolute risk of AP in MMI users during the first 18 months of treatment was less than 0.39% in all sex- and age-classes. Results of the SCCS were comparable with the main analysis.

Conclusions: Our results support the EMA warning, suggesting that AP is an uncommon adverse drug reaction in MMI users. The increase in risk seems to be limited to the first 9 months of treatment. Further studies are warranted to identify subgroups at higher risk of AP onset.

4524 | Utility of electronic medical record for detecting adverse drug reaction signals in pediatrics: Discussion based on drug prescription and laboratory data in pediatrics in a single institution

Saeko Hirota[1,2], Shi-Wei Chiu[1], Munenori Takata[3], Ryusuke Inoue[4], Masaharu Nakayama[4], Chiharu Ota[5], Noriko Sugawara[5], Saori Katayama[5], Dai Suzuki[5], Yu Abe[5] and Takuhiro Yamaguchi[1]

[1]Tohoku University Graduate School of Medicine, Sendai, Japan; [2]EPS Corporation, Tokyo, Japan; [3]Tohoku University Hospital, Sendai, Japan; [4]Tohoku University Hospital, Sendai, Japan; [5]Tohoku University Graduate School of Medicine, Sendai, Japan

Background: Electronic medical records (EMRs) are increasingly recognized as valuable data source for post-market pharmacovigilance. Laboratory test result recorded in the EMRs is one of the most objective data which reflect patient's condition, suggesting its potential utility for detecting adverse drug reaction (ADR) signals. Some researchers investigated comprehensive signal detection using laboratory data in EMRs in adults, however, its applicability and feasibility in pediatrics are not previously discussed.

Objectives: To characterize drug prescription and the timing of laboratory testing in pediatrics, and to discuss the potential utility of these data for detecting ADR signals in pediatric population.

Methods: This study was conducted using EMR of Tohoku University Hospital from 01 January, 2010 to 06 September, 2019. We selected two target laboratory results of platelet count and serum creatinine. Pediatric patients less than 18 years old with at least one drug prescription and one target laboratory result were included in the study. We summarized patient characteristics, therapeutic category of prescribed drugs, and the timing of laboratory testing using descriptive statistics. All analyses were conducted using SAS 9.4.

Results: This study included 9,676 pediatric patients, in which 2,036,845 prescriptions and 267,348 target laboratory tests (135,298 for platelet count and 132,050 for serum creatinine) were performed. Blood substitutes accounted for the largest amount of prescriptions (n=704,277, 35%), followed by antibiotic preparations (n=216,621, 11%). Among 2,036,845 prescriptions, 1,864,491 (92%) had platelet count data and 1,861,595 (91%) had serum creatinine data in both before and after the prescription.

Conclusions: Majority of pediatric patients with drug prescriptions had target laboratory test results in both before and after the prescription. This suggested the possible applicability of laboratory data recorded in the EMRs to the ADR signal detection in pediatric population by comparing pre- and post-prescription laboratory results.

4590 | Pharmacists' perception of educational material: A survey on practices and awareness by the drug commission of German pharmacists

André Said[1], Leonard Freudewald[1], Natalie Parrau[1], Matthias Ganso[1] and Martin Schulz[1,2]

[1]Drug Commission of German Pharmacists (AMK), Berlin, Germany; [2]Freie Universität Berlin, Berlin, Germany

Background: Educational material (EM) addresses particular safety information of medicinal products to healthcare professionals and/or patients and can vary in form and layout. Since 2016, EM approved by German national competent authorities is labelled with a symbol of a "blue hand". Data is scarce regarding the utility of EM as a safety communication tool in everyday pharmacy practice.

Objectives: To investigate pharmacists' awareness and perception of EM in the setting of community and hospital pharmacies in Germany

Methods: The Drug Commission of German Pharmacists (AMK) surveyed its two nationwide networks of reference pharmacies: 677 community and 51 hospital pharmacies. Using the Survey Monkey® online tool, participants were asked to answer 10 questions on EM, (i) in general, (ii) for health care professionals, and (iii) for patients. The survey launched on 1/16/20 and concluded on 2/10/20. Data were analyzed using Microsoft Excel® 2016.

Results: A total of 373 communitiy and 32 hospital pharmacies participated; response rates of 55.1% and 62.8%, respectively. Overall, 85.8% (n=320) of community and all hospital pharmacists confirmed to be aware of EM, which is mainly received via postal shipping, as 85.4% (n=316) of community and all hospital pharmacists responded. Regarding EM for healthcare professionals, community and hospital pharmacists fully (46.9%, n=172 and 28.1%, n=9) or rather (29.4%, n=108 and 31.3%, n=10) agreed that EM is suitable to reduce risks of medicinal products. Furthermore, most reference pharmacies fully agreed, that EM is not combined with advertising (54.3%, n=197 of community and 50.0%, n=16 of hospital pharmacies). Whilst 73.5% (n=269) of community pharmacists forward EM to the pharmaceutical staff (also in subsidiaries), 87.5% (n=28) of hospital pharmacists inform the concerned physicians or the respective hospital wards. Considering EM for patients, 64.9% (n=237) of community and 53.1% (n=17) of hospital pharmacists confirmed to counsel patients or inform (long-term) care facilities. Finally, asking pharmacists on their personal

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

perception of EM, the refinement of the readability (n=48) and accessibility/availability (n=60) was indicated, among others.

Conclusions: Addressing emerging risks via EM is crucial to minimise (potential) harm for patients. Indeed, the participating pharmacists responded to be aware of EM in everyday practice, especially in hospital pharmacies. However, from a pharmacist perspective, the utility of EM still needs further improvement.

4619 | Impact of European medicines agency regulatory action on hydroxyzine initiation, discontinuation and switching to other medicines in Scotland, England, Denmark and the Netherlands: An Interrupted time series regression analysis

Daniel R Morales[1,2], Tom MacDonald[1], Rob Flynn[1], Steve Morant[1], Isla Mackenzie[1], Alex Doney[1], Lyn Mitchell[1], Jesper Hallas[2], Anton Pottergard[2], Martin Ernst[2], Lisa Smits[3], Ron Herings[3], Jetty Overbeek[3], Marion Bennie[4], Chris Robertson[4], Li Wei[5], Lizzie Nicholson[6] and Tatiana Macfarlane[1]

[1]University of Dundee, Dundee, United Kingdom; [2]University of Southern Denmark, Odense, Denmark; [3]PHARMO Institute, Utrecht, Netherlands; [4]University of Strathclyde, Glasgow, United Kingdom; [5]University College London, London, United Kingdom; [6]National Services Scotland, Edinburgh, United Kingdom

Background: : Antihistamines such as hydroxyzine, are commonly prescribed across Europe for the management of skin disorders, sleep disorders and anxiety. In February 2015, a European Medicines Agency (EMA) safety review concluded that hydroxyzine was pro-arrhythmogenic and that new changes to the product information were required to be implemented and communicated across Europe via a direct healthcare professional communication (DHPC).

Objectives: The aim of the study was to evaluate the impact of the risk minimisation measures following the 2015 review to manage the pro-arrhythmogenic risks of hydroxyzine in Denmark, Netherlands, England and Scotland.

Methods: Drug utilisation studies assessing hydroxyzine prescribing or dispensing spanning the regulatory intervention date (February 2015). Quarterly time series analyses was performed measuring the rate of hydroxyzine initiation and discontinuation, and switching to other antihistamines, benzodiazepines and/or antidepressant medications (tricyclic antidepressants, mirtazapine, selective serotonin reuptake inhibitors) in patients who discontinued hydroxyzine. Statistical significance testing was performed using interrupted time series regression.

Results: The 2015 EMA regulatory action had no significant impact on overall hydroxyzine initiation in Denmark or the Netherlands. It was associated with a significant: immediate fall in hydroxyzine initiation per 100,000 in England (-12.05, 95%CI -18.47 to -5.63) and Scotland (19.01, 95%CI -26.99 to -11.02); and change to a negative trend in hydroxyzine initiation per 100,000/quarter in England (-1.72, 95%CI -2.69 to -0.75) and Scotland (-2.38, 95%CI -3.32 to -1.44). The EMA regulatory action was associated with a significant: immediate rise in hydroxyzine discontinuation per 100,000 in England (3850.0, 95%CI 440.0 to 7240.0). The regulatory action was associated with no significant switching to other antihistamines, benzodiazepines or other antidepressant medicines following hydroxyzine discontinuation.

Conclusions: The 2015 Europe-wide regulatory intervention was associated with heterogeneous impact, with significant reductions in overall hydroxyzine initiation observed in England and Scotland only. There was limited impact on discontinuation in all countries but no evidence to suggest unintended consequences of switching to other antihistamines, benzodiazepines or other antidepressant medicines overall.

4629 | Impact of European medicines agency regulatory action for hydroxyzine initiation in people with contraindications in Scotland, England, Denmark and the Netherlands: An interrupted time series regression analysis

Daniel Morales[1,2], Rob Flynn[1], Tom MacDonald[1], Steve Morant[1], Isla Mackenzie[1], Alex Doney[1], Lyn Mitchell[1], Jesper Hallas[2], Anton Pottergard[2], Martin Ernst[2], Lisa Smits[3], Ron Herings[3], Jetty Overbeek[3], Marion Bennie[4], Chris Robertson[4], Li Wei[5] and Tatiana Macfarlane[1]

[1]University of Dundee, Dundee, United Kingdom; [2]University of Southern Denmark, Odense, Denmark; [3]PHARMO Institute, Utrecht, Netherlands; [4]University of Strathclyde, Glasgow, United Kingdom; [5]National Services Scotland, Edinburgh, United Kingdom

Background: Hydroxyzine is widely used across Europe for the management of skin disorders, sleep disorders and anxiety. Due to pro-arrhythmogenic safety concerns, the European Medicines Agency (EMA) recommended contraindications and changes to the product information for hydroxyzine across Europe in 2015.

Objectives: To measure its impact of the regulatory action among contraindicated populations.

Methods: Quarterly interrupted time series regression analyses of hydroxyzine initiation among cohorts with contraindications consisting of 1) people with a history of cardiovascular disease (consisting of ischaemic heart disease, peripheral vascular disease, congestive cardiac failure and/or cerebrovascular disease) and 2) concomitant use of drugs known to prolong the QT interval) from Denmark, The Netherlands, England and Scotland.

Results: The 2015 EMA regulatory action was associated with significant immediate reductions in hydroxyzine initiation in people with cardiovascular disease per 100,000 in Scotland (-46.16, 95%CI -69.98 to -22.34) and England (-36.47, 95%CI -59.42 to -13.51) but not Denmark and the Netherlands. Significant negative changes in post-intention trend per 100,000/quarter were also observed in Scotland (-3.79, 95%CI -6.60 to -0.98) and England (-3.20, 95%CI -6.75 to -0.36) but not in Denmark and the Netherlands. For concomitant use of drugs known to prolong the QT interval, regulatory action was associated with significant immediate reductions per 100,000 in Scotland (-57.06, 95%CI -84.69 to -29.44) and England (-50.10, 95%CI -71.07 to -29.12), with significant negative change in post-intervention trend per 100,000/quarter in Scotland (-7.45, 95%CI

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

-9.92 to -4.98), England (-8.51, 95%CI -16.24 to -0.77) and Denmark (-1.69, 95%CI -3.36 to -0.02), but not in the Netherlands.

Conclusions: Although EMA regulatory action was associated with significant reductions in hydroxyzine initiation apart from in the Netherlands, some patients with contraindications continued to be prescribed hydroxyzine, the extent of which varied by country and target condition. Further research understanding reasons for such variation may help to guide the design or dissemination of future safety warnings.

4636 | Direct healthcare professional communication: A quantitative assessment study

Hajar Alsaleh[1,2] and Thamir Alshammari[1,3]

[1]Saudi food and drug authority, Riyadh, Saudi Arabia; [2]King Suad university, Riyadh, Saudi Arabia; [3]Medication Safety Research Chair, Riyadh, Saudi Arabia

Background: Direct healthcare professional communication (DHPC) is one of the post-authorization regulatory requirements and represent an important source of data that covering safety-related issues of medicinal products.

Objectives: To evaluate the DHPC letters that have been submitted to the Saudi Food and Drug Authority (SFDA) and how they were complied with the pharmacovigilance guidelines.

Methods: A total 163 DHPC letters were retrieved from SFDA website since first letter published in the website until September 2019. Two independents reviewers have been reviewed these letters. Then, the letters were evaluated based on DHCPs letter requirements approved in the European pharmacovigilance guidelines. During the assessment, several fields were reviewed including: date of letter issuing, marketing authorization holder (MAH) name, MAH's logo, letter's title, trade and generic name of the product of interest, reason of letter dissemination, number of DHPC letter pages, company's contact information, adverse event reporting information, agreement with SFDA statement, signature availability and by whom. The statistical analyses were conducting utilizing statistical analysis software (SAS® 9.4)

Results: Out of 163 DHCP letters, 107 letters (66 %) were present the information within two-page limit. Title and reason of dissemination were clearly stated in all the letters. Furthermore, the logo and the date of the letter were mentioned in 158 (97%) and 159 (97.5%) letters, respectively. Relatively high percent of DHCP letters (17 letters, 10%) did not mention the agreement statement with SFDA and 42 letters (26%) did not include the MAH contact information. While four letters (2.5%) did not mention the trade name, one letter (0.6%) did not mention the generic name of the medicinal product of interest. For the reporting statement, the majority of letters were mention the details of reporting information to both SFDA and MAH (133 letters (81.6%)). On the other hand, 27 letters (16.6%) mentioned the reporting method to SFDA alone and one letter (0.6%) did not mention any details about the reporting. Qualified person responsible for pharmacovigilance and medical directors signed the majority of these letters (almost 35% for each). Moreover, four letters (2.5%) were missing the MAH signature.

Conclusions: This study found that the DHCP letters have an acceptable level of compliance with the current guidelines. However, the letters need to be carefully assessed by the authority due to the lacking of some important information.

4662 | The role of the Portuguese patients' associations in the pharmacovigilance system

Margarida Nieto[1], Paula Sousa Ferreira[1,2], Ana Paula Martins[1,2] and Carla Torre[1,2]

[1]Faculty of Pharmacy, Universidade de Lisboa, Lisboa, Portugal; [2]Lisboa, Setúbal and Santarém Pharmacovigilance Centre, Lisboa, Portugal

Background: patients' associations play an important role in pharmacovigilance, and their contribution in the spontaneous reporting system of adverse drug reactions (ADR) has been recognized overtime.

Objectives: To investigate the level of knowledge of the Portuguese patients' associations about the national pharmacovigilance system and to identify strategies to increase their participation.

Methods: A descriptive cross-sectional study was performed. Data about patients' associations opinions, attitudes, knowledge and involvement in the national pharmacovigilance system was collected through an online pre-tested questionnaire. Data were collected between 24th July and 12th September 2019.

Results: Out of the 91 patients' associations that were registered in Portugal, 49 agreed to participate in this study. The surveyed associations represented citizens with hereditary/genetic diseases (18.37%), followed by locomotion (12.24%) and oncologic diseases (12.24%). The majority of patients' associations (89.80%) reported having knowledge that patients/consumers are allowed to report an ADR and 84.09% were aware about the changes introduced by the European Directive 2010/84/EU. However, 10.20% believed that patients cannot contribute in a significant manner to pharmacovigilance systems. More than a half (53.06%) admitted to have little or no knowledge regarding Risk Management Plans and only 34.69% reported an active role in conducting activities to raise awareness on pharmacovigilance matters. A total of 18 associations (36.73%) considered that there are still barriers that prevent the disclosure of the national pharmacovigilance system, being the main obstacles identified: lack of resources (66.67%) and insufficient budget (55.56%).

Conclusions: Portuguese patients' associations revealed interest in drug safety issues, although, the majority does not seem to have a solid plan to act on. Patients' organizations play an important role in encouraging patients to report their ADR. In order to increase ADR reporting and patient awareness on pharmacovigilance, it is essential that competent authorities close involve patients' organizations as part of their benefit-risk medicines assessment strategy in the post-marketing authorization phase and maintain them up to date.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4698 | Implementation of medication error reporting system in community pharmacy setting

Marappa Umesh
JSS College of Pharmacy, Mysuru, Mysuru, India

Background: Medication errors (ME) may occur at any stage of the medication utilization process and require intense monitoring. In the community medical centers, iatrogenesis is rarely sought.
Objectives: To establish a Medication Error Reporting system (MERs) in a community pharmacy setting and assess the nature and extent of MEs
Methods: A Prospective Observational study conducted in private community pharmacies.in and around Mysuru city. Prescriptions of study participants were reviewed on a daily basis, the identified MEs. were documented in the suitable documentation form and also a database for easy retrieval of data. The reporting system was implemented in the community pharmacies and encouraged to adopt the medication error reporting system in their community pharmacy. To continue the system of reporting MEs, the designed medication error (MER) forms were made available in their community pharmacies.
Results: Among 1416 identified MEs, prescription errors 1242 (87.71%) and procurement error 157 (11.09%) were the most occurring error. The majorly implicated drug classes were analgesics (39.94%) followed by, antibiotics (20.74%). The utmost frequently involved drug was paracetamol (26.35%) and aceclofenac (15.46%).. The foremost causes associated with medication errors were regular practice which attributes to physicians (73.81%), lack of time and workload on the pharmacist (20.00%). Majority (55.14%) of category C, errors reached the patient but did not cause any harm to the patient., 11.09% category A, errors did not reach the patient, and 0.78% of errors reached patient and needed monitoring belonging to category D. A total of 55 potentially serious drug-drug interactions were identified among drugs prescribed for 514 study participants. The occurrence of medication error in healthcare. the setting is the most alarming concept.
Conclusions: Most of the errors are clinically substantial and it can be prevented by working in a collaborative manner, as a healthcare team. The reporting system. was inculcated in the community settings in order to monitor and prevent the MEs. Training and education program. can be carried out to create awareness regarding monitoring and prevention of medication errors. and educate them to prevent MEs.

4699 | Proactive drug safety monitoring of adverse events in Saudi Arabia: 2019 experience

Hajar ALSaleh, Adel Alrwisan and Fawaz Alharbi
Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: This project was initiated to proactively monitor the safety of medicinal products registered in Saudi Food & Drug Authority (SFDA).
Objectives: To assess the potential safety signals (adverse events (AEs)) reported with medicinal products registered by SFDA with high efficiency.
Methods: We created a list include the chemical entities that recently registered in Saudi Arabia from 2014-2018 and the biosimilar products that registered in Saudi Arabia (despite their approval year). We gave priority to highly utilized medications, those with approaching renewals, and those with risk minimization measures. We retrieved the cases of AEs from VigiBase, the WHO global database of individual case safety reports linked to targeted medicinal products. Then we crosschecked these events with the product information using local, the American, and the European labeling to exclude known AEs. The full safety assessment report was restricted to unknown AEs that have ≥ 2 serious reports and have been reported from ≥ 2 different sources (such as study and spontaneous reporting). In our assessment, we included several evidence sources including AE reports, literature, or regulatory documents. Moreover, we used the WHO-UMC causality assessment system to evaluate the possible association between the targeted drug and AE. Based on the available evidences in the safety assessment report, appropriate regulatory recommendation is suggested.
Results: Out of 7485 medicinal products, 67 products met the inclusion criteria and have been assessed. The majority of these products were classified as antineoplastic (n=31), anti-infective (n=11), and antidiabetic (n=8) products. The evaluation process was performed from January 2019 to the December 2019. Of 67 medicinal products, 190 potential safety signals were intensively assessed. The majority of these events were infections (n=24), followed by cardiac events (n=20) and blood disorders (n= 15). After intensive assessment stage, we recommended that 67 of 190 safety signals had potential association with targeted medicinal products. Of these, 52 signals (almost 78%) were supported by evidence from the literature. While out of the 123 refuted signals, 62 signals (almost 50 %) have no available evidence in literature.
Conclusions: Pharmacovigilance systems are increasingly faced with a large number of safety information and inadequate resources. In this project, we identified several potential signals with relatively few number of products been reviewed. Safety signals that have been reported in the literature need to have more attention by the regulatory authority.

4705 | Pattern of adverse drug events reported with use of fluoroquinolone among children in Saudi Arabia

Eman Alghamdi and Fawaz Alharbi
Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Background: Fluoroquinolones (FQs) have received several warnings of their use due to serious adverse effects. Despite these toxicities, FQs have been used in children if the expected benefits outweigh the risk. However, limited information is available about their use and safety in children in Saudi Arabia

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To evaluate the pattern of adverse drug events (ADEs) linked with use of FQs (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) in children, reporting spontaneously to the National Pharmacovigilance Center (NPC) in Saudi Arabia

Methods: We performed a descriptive analysis of suspected ADEs reported to the NPC and linked to FQs in children in September 2010 and August 2017. The ADEs were sourced from the NPC in Saudi Arabia and reviewed to obtain the following information: patient's age, gender, and indication, suspected fluoroquinolone type, ADR type, seriousness, and type of reporter. The study included all children who were less than 17 years old. Eligible patients were categorized into 3 age groups: infants (0-≤2 years), children (2 years-≤ 12 years), and adolescents (12-≤17 years). The analyses were conducted using statistical analysis software (SAS®).

Results: During the study period, a total of 63 ADEs were reported spontaneously to the NPC, 60 % of cases were serious. Out of 63 reported ADEs, males represented 72 %, females represented 22%, and the unknown gender represented 6%. Patients were aged from 1 to 17 years, with a mean of 10.2 years. ADEs were reported more in the age group of adolescents (46 %). Reporting sources of ADEs were from hospitals (48%), manufacturers (41 %), while three cases had an unknown sources. The indication of FQs was not reported in most cases (95%), while pneumonia was reported in the rest of the cases (5%). Ciprofloxacin was reported as a suspected drug in most of the cases (79.5%), moxifloxacin in 17.5% of cases, and levofloxacin in 3% of cases. The most common reported ADEs reported by system organ class (SOC) were skin and subcutaneous tissue disorders (39; 62%) followed by the nervous system disorders (6; 9%). Cardiac disorders represented (4; 6.5 %) of all reported ADEs. Rash (17; 30 %), Pruritus (10; 16 %), erythema (8; 12.5 %), and palpitation (4; 6.5 %) were the most frequently reported specific ADEs

Conclusions: Underreporting is a major problem in Saudi Arabia and worldwide. Our study shows that efforts should be intensified to increase public awareness of ADE and to encourage reporting in Saudi Arabia. Such reporting should be encouraged to be completed in order to be useful in identifying preventable ADRs and augmenting the knowledge to deal with ADRs more efficiently

4730 | Spontaneous reporting of adverse drug reactions by patients: a comparative study between European countries

Ana Isabel Parreira[1], Paula Sousa Ferreira[1,2], Ana Paula Martins[1,2] and Carla Torre[1,2]

[1]*Faculty of Pharmacy, Universidade de Lisboa, Lisboa, Portugal;* [2]*Lisboa, Setúbal and Santarém Pharmacovigilance Centre, Lisboa, Portugal*

Background: The contribution of patients in pharmacovigilance systems has been relevant for the development and assessment of medicines. Although the concept of patient reporting schemes is not new (having been around for more than 50 years) only since 2012, the legislation placed an obligation on all European Union (EU) member countries' national competent authorities (NCA) and marketing holders to record and report suspected adverse drug reactions (ADR) received from patients (Directive 2010/84/EU).

Objectives: To perform a descriptive cross-country study comparison (2015-18) aiming to provide insight into patient reporting in EU member countries.

Methods: An online survey was sent to all EU member countries NCA on June 2019. Data collection covered: number of reports and its seriousness by notifier (*e.g.* patients, healthcare professionals), reported ADR terms classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and most reported medicines classified according to the Anatomical Therapeutic Chemical (ATC) system. All NCA websites were searched and a literature review was conducted to collect data for countries that did not answer the questionnaire or to complement information when not available.

Results: Among the 28 surveyed-countries, 22 (78.6 %) answered the questionnaire. Overall, patient reporting increased over the study period. However, countries where patients reporting schemes were a reality before 2012 had, on average, higher patients' reporting proportions than the remainder EU member states. In 2018, the highest patient reporting proportions were observed in Belgium (51.9%), Ireland (36.0%), followed by Slovakia (38.8%) and Germany (38.4%). The latter were countries where patients reporting schemes were in place only after July 2012. Portugal, Austria and Latvia were the countries with the lowest patient reporting participation in the pharmacovigilance systems (<5%). Antiinfectives for systemic use (J) was the ATC main group most reported either for patients or HCP. However, patients were more likely than HCP to report for genitourinary system/sex hormones (G). Patients reported more in gastrointestinal MedDRA SOC than HCP.

Conclusions: The increasing numbers of patient reports overtime indicates patients' high motivation to report ADR (especially those that affected their quality of life) suggesting that EU pharmacovigilance legislation made a positive impact. Collaboration between NCA and patient associations can boost patient reporting, especially in countries with lower levels of patients' participation.

4737 | Clinical pharmacist initiated home medication review (HMR) for geriatric patients in a developing country's city

Jehath Syed, Jaidev Kumar B. R., Joslin Mariya Jose and Francis Lalhmingliana

JSS College of Pharmacy, Mysuru, India

Background: Home Medication Review in a developing country scenario would not only help improving health outcomes but also promote rational use of medications and reduce unplanned hospital visits and associated cost.

Objectives: To identify Drug Related Problems (DRPs) and assess medication adherence among elder community dwellers through home medication review.

Methods: A clinical pharmacist initiated home-medication review based cross-sectional interventional study and was carried out for a

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

period of six months in a small city located in Southern India. Eligible & voluntarily consented elderly were reviewed at a teaching hospital and followed them at their dwellings. DRPs were identified, classified according to Hepler & Strand's classification, reported and intervened accordingly. Medication adherence was assessed using simplified medication adherence questionnaire. Data was assessed categorically.

Results: A total of 47 (78%, n = 60) patients consented to be followed-up with them at their dwellings. Of whom the majority were females [27 (60%)] and males [18 (40%)] from undivided families and 2 (4%) patients died. The average age of the study participants was 71 ∓ 8.1 years. Amongst these patients, hypertension [40 (88.88%)], type 2 diabetes mellitus [31 (68.88%)], and IHD [12 (26.66%)] were most common diseases and per patient there were 5.24 medicines on an average. A total of 104 DRPs were identified, of which drug interactions [47 (45.19%)] were most common followed by over-dosage [20 (19.23%)], improper drug selection [10 (9.61%)]. Polypharmacy and multiple comorbidities are found to be predictors for DRPs (OR: 1.1 CI: 95% P <0.05). Further, 26 (57.7%) patients were found to be non-adherent to medications, for whom pharmacist counselling was done appropriately.

Conclusions: There were 2.3 DRPs per patient and two patients died during the study. Early detection of DRPs could reduce the untoward health outcomes and clinical pharmacists can aid in identifying and managing the DRPs.

4739 | Drug-induced hearing disorders in children: A review using the WHO pharmacovigilance database

Cyrielle Gonzales, Vanessa Rousseau, Leila Chebane and Geneviève Durrieu
Faculty of Medicine, Toulouse, France

Background: Hearing loss has negative educational and social consequences. Drug-induced hearing disorders is one of the acquired causes of deafness, mainly by cochleotoxic effects. However, these adverse drug reactions have been poorly investigated in children.

Objectives: The first objective of our study was to describe drug-induced hearing disorders in a paediatric population. Secondary objective was to evaluate association between hearing disorders and the most frequently involved drugs

Methods: We extracted individual case safety reports (ICSRs) of "hearing disorders" (HGLT term according to MedDRA classification) in children from the World Health Organization global individual case safety report database (VigiBase®) until December 31, 2018. Reports involving vaccines were excluded. Characteristics of children (age, gender), characteristics of ototoxic adverse reactions (Lowest Level MedDRA terms, seriousness) and "suspected drugs" (ATC classification system 2nd and 5th levels) were analyzed. We calculated disproportionality for the most frequently involved drugs with a reporting odds ratio (ROR) and 95% confidence interval.

Results: A total of 1613 ICSRs were identified, involving adolescents (12-17 years, n = 612, 37.9 %), children (2-11 years, n = 714, 44.3 %), infants (28 days-23 months, n = 184, 11.4 %) and neonates (birth-27 days, n= 103, 6.4%). Overall, 758 notifications (47.0 %) involved girls. A total of 793 (49.1 %) were "serious". The most frequent hearing disorders (LLT term) were: deafness (n=627, 38.8%), hypoacusis (n=497, 30.8 %), hyperacusis (n= 149, 9.2 %), deafness neurosensory (n=120, 7.4 %), and deafness unilateral (n=57, 3.5 %). The most involved ATC 1nd levels were antiinfectives for systemic use (n =514, 31.9%), nervous system (n = 459, 28.5%) and antineoplasic agents (n = 330, 20.5 %). The 5 most frequent suspected drugs (ATC 5th level) were: cisplatin (n = 129, 8.0 %), gentamicin (n = 71, 4.4 %), isotretinoin (n = 55, 3.4 %), azithromycin (n = 53, 3.3 %) and carboplatin (n = 46, 2.9 %). An increased disproportionality was observed for these drugs: cisplatin (ROR: 33.1, 95% CI: 27.7-39.6), carboplatin (ROR: 14.6, 11.0-19.3), gentamicin (ROR: 8.9, 7.1-11.0), azithromycin (ROR: 2.9, 2.3-3.8) and isotretinoin (ROR: 2.6, 2.0-3.3).

Conclusions: This review shows that the most frequently suspected drugs associated to hearing disorders in children were antineoplastic (cisplatin, carboplatin) and antibacterial (amikacin, azithromycin) agents. Moreover, this study identified an increased risk of hearing disorders associated with isotretinoin. Attention should be paid to this drug.

4742 | Longitudinal medical insights from internet fora

Gregory Powell
GlaxoSmithKline, RTP, NC

Background: Several research projects have explored the utility of using social media to augment traditional safety surveillance, with varying degrees of success. Some of the limitations of social media include the number of characters that can be posted (Twitter) and the "what's on my mind at this moment in time" context in which people post.

Objectives: To evaluate if linking social media posts from the same individual in a longitudinal fashion would allow for a more holistic assessment of an individual's journey with a chronic disease.

Methods: We analyzed publicly available, de-identified social media posts (01 January 2015 to 01 November 2015) from the Scleroderma and Arthritis support communities on Inspire.com. Each author was given a unique, anonymous identifier so that posts from the same individual could be linked together longitudinally. Expert reviewers manually curated a random sample of 2,817 threads containing 21,313 individual posts from 3,601 unique authors. To help systematically identify which collection of posts offered the best medical insights we generated a complexity score, comprised of 28 indicators, for each author's collection of longitudinal posts. The group of posts with the 16 highest complexity scores were further evaluated for relevant medical insights.

Results: The top 16 groups contained 1,672 posts, an average of 104 posts (median 34, range 11-534) per author. Relevant medical

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

insights included: medical history 16/16 (100%), disease burden 15/16 (94%), use of non-medical treatments 15/16 (94%), lab results 14/16 (88%), treatment history 13/16 (81%), and concomitant medications 12/16 (75%). The above insights were seen across groups of postings rather than being on the same posting (only 1 post out of the 1,672 contained all 6 of the medical insights above). Additionally, these posts also included important data elements related to adverse events (time to onset, dose of medication, duration of exposure, outcome of the event, statements of attribution, and treatment of adverse event).

Conclusions: Linked social media posts can provide medical insights not apparent from individual posts and might be relevant for pharmacovigilance activities.

4769 | Proactive signal detection of serious medical events following antidepressant initiation using big healthcare data

Mia Aakjær[1], Marie Louise De Bruin[1], Murat Kulahci[2] and Morten Andersen[1]

[1]*University of Copenhagen, Copenhagen, Denmark;* [2]*Technical University of Denmark, Lyngby, Denmark*

Background: The current process for generating evidence in pharmacovigilance has several limitations leading to a lacking detection of signals and an inaccurate and often much delayed evaluation of drug-associated risks. Active surveillance systems based on existing healthcare data have been suggested as an answer to the shortcomings.

Objectives: To investigate if a sequential cumulative analysis approach using big healthcare data is able to detect signals and quantify the risk of serious adverse reactions occurring during SSRI and SNRI use.

Methods: Using historical Danish healthcare register data from 1996 to 2016, we conducted repeated cohort studies in one year intervals of new SSRI and SNRI users. Patients were followed for a maximum of six months from treatment initiation to the relevant event or censoring. We selected 13 outcomes from the European Medical Agency designated medical event list. We performed Cox regression analysis with citalopram as reference estimating crude hazard ratios (HR) and 95% CI followed by adjustment for age/sex and chronic comorbidities. Cumulative HR estimates were plotted.

Results: In total, 969,692 new users of SSRI and SNRI were followed for a total of 461,518 person years. Numbers of events were anaphylaxis (N=78), angioedema (N=173), dermatitis exfoliative (N=11), erythema multiforme (N=36), cardiac arrest (N=765), ventricular fibrillation (N=148), toxic liver disease (N=203), hepatic failure (N=403), acute kidney injury (N=797), haemolytic anaemia (N=127), aplastic anaemia (N=163), agranulocytosis (N=92), and acute pancreatitis (N=620). At the end of the study period, we identified 17 potential signals in the crude analysis. These were reduced to nine and three signals in the age/sex and fully adjusted analyses, respectively. Signals after full adjustment were associations between fluoxetine and acute pancreatitis, HR 1.5 (95% CI 1.1-2.1), fluoxetine and cardiac arrest, 0.43 (0.24-0.76) and between sertraline and acute kidney injury, 0.71 (0.56-0.90). The latter two results may indicate a possibly increased risk for citalopram. The overall incidence rate for signals was 1.3-1.7 per 1000 person years and for other events 0.02-0.4 per 1000 person years.

Conclusions: The study demonstrates the feasibility of performing epidemiological surveillance of serious adverse reactions in Danish big healthcare data using a sequential cumulative analysis. Three signals out of 17 remained after the fully adjusted cohort analysis and will be further assessed. Larger populations are needed to evaluate rare events and infrequently used antidepressants.

4900 | Use of proton pump inhibitors and renal function: ELSA-Brasil results

William Neves Oliveira[1], Sandhi Maria Barreto[2], Roberto Marini Ladeira[2], José Geraldo Mill[3] and Roberta Carvalho Figueiredo[1]

[1]*Universidade Federal de São João Del-Rei, Divinópolis, Brazil;*
[2]*Universidade Federal de Minas Gerais, Belo Horizonte, Brazil;*
[3]*Universidade Federal do Espírito Santo, Vitória, Brazil*

Background: Proton pump inhibitors (PPIs), previously recognized for their high efficacy and safety profile, have been associated with an increasing number of serious adverse events, including renal function (RF) decline.

Objectives: To investigate whether the use of PPI is associated with decreased renal function in a large sample of Brazilian adults.

Methods: This is a cross-sectional analysis involving 15097 baseline participants (2008-2010) of the Longitudinal Study of Adult Health (ELSA-Brasil), a prospective multicenter cohort study carried out with public servants, from higher education or research institutions located in six Brazilian capitals. Of the total of 15,105 study participants, 8 were excluded for not having valid information on renal function. All participants were asked about the use of PPI in the last two weeks prior to the interview. RF was assessed by estimated glomerular filtration rate (eGFR), which was calculated using the equations from the Chronic Kidney Disease Epidemiology consortium without correction for race. Values of eGFR below 60ml/min/1.73m² were considered decreased. The association between the use of PPI and RF was estimated by logistic regression after adjustments for confounding factors (age, sex, race, education, smoking, body mass index, use of statins, non-steroidal anti-inflammatory drugs and acetylsalicylic acid). Crude and adjusted Odds Ratios (OR) were their respective 95% confidence intervals (95% CI) were estimated.

Results: The average age of the participants was 52 years old (sd = 9), 54.4% were women and 52.7% had completed higher education. The prevalence of use of PPI was 8%. The frequency of use of PPI (14.8%) was about twice as high among participants who had decreased eGFR compared to those did not have decreased eGFR (p <0.001). In the univariate analysis, the use of PPI was significantly associated with decreased eGFR [OR = 2.09 (95% CI = 1.68-2.59), p

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

<0.001]. Even after adjusting for confounding factors, PPI users, compared to non-users, had 27% greater chance [OR = 1.27 (95% CI = 1.01; 1.61), p <0.05] to have decreased renal function (p <0.05).

Conclusions: This study innovates by showing that use of PPI is associated with decreased eGFR in a large sample of Brazilian adults. Causality cannot be determined in a cross-sectional study, then longitudinal analyzes of ELSA-Brasil may contribute to elucidate the association between the use of PPI and renal function.

4904 | patients' perspective on pharmacovigilance and adverse drug reactions reporting in Lithuania: Qualitative study

Agne Valinciute-Jankauskiene and Loreta Kubiliene
Lithuanian University of Health Sciences, Kaunas, Lithuania

Background: Spontaneous adverse drug reactions (ADRs) are a significant cause of morbidity and mortality. Every report of a suspected ADR by patient or healthcare professional has a substantial impact on signal detection of new, rear, or serious ADRs. The number of reports received by *EudraVigilance*, the European database for ADRs is growing yearly; however, it does not correspond to the number of used medicines. Under-reporting remains a major issue undermining the effectiveness of spontaneous reports.

Objectives: The current study aimed to determine the patients' awareness of ADRs, to identify the barriers and motives impacting consumers reporting of ADRs.

Methods: This qualitative study was based on three focus group discussions with 32 consumers, aged between 32 and 90 years old, performed in January 2020. A semi-structured interview guide was used. All group discussions were audio-taped, transcribed verbatim, and were then analyzed for thematic contents analysis.

Results: The analysis of the focus group discussions revealed three major themes: familiarity with the terminology of the pharmacovigilance system used by a competent authority in Lithuania, sources of information on adverse reactions, the role of patients, healthcare, and pharmaceutical professionals in pharmacovigilance system. The term "pharmacovigilance" was heard for the first time in this study by all participants. However, all consumers could describe ADR and at least once experienced it. Current research suggests that the primary barrier to ADR reporting is remaining significant knowledge gaps concerning ADR reporting procedure and its importance to medicine safety. The consumers have little knowledge about what happens with reports; therefore, they are afraid to report or do not think that their report could make any impact. Almost all the participants agreed that pharmacovigilance and ADR reporting training are necessary for healthcare and pharmaceutical professionals, and easier understandable information needs to be provided to patients.

Conclusions: The main reason for underreporting is limited pharmacovigilance knowledge of consumers. Most patients were not aware of reporting systems, and others were confused about reporting. This study is the first qualitative study on ADR with patients in Lithuania, and close follow-up by authorities could help better understand barriers to behavior change in reporting ADRs.

4977 | Drug reaction with eosinophilia and systemic symptoms: Analysis of the German registry over 15 years

Maja Mockenhaupt[1], Camilla Berger[1], Sylvia H Kardaun[2] and Maren Paulmann[1]
[1]*Medical Center - University of Freiburg, Freiburg, Germany;* [2]*Isala-Diaconessenhuis, Meppel, Netherlands*

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse reaction characterized by a widespread skin eruption, eosinophilia and organ involvement. The skin reaction often presents with an infiltrated maculopapular exanthema and mild mucosal lesions. Besides eosinophilia, atypical lymphocytes, lymphnode enlargement, elevation of liver and kidney parameters are frequent signs of organ involvement.

Objectives: For this analysis, demographic data and risk factors of DRESS-cases collected in Germany between 2003 and 2017 were investigated.

Methods: Since 2003 cases of DRESS are ascertained by the German Registry for severe skin reactions as part of the multinational RegiSCAR-study. All cases enrolled were clinically reviewed by an expert committee blinded for potential causes through strict application of the RegiSCAR validation score for DRESS. The index-day (day of onset) was determined for all validated cases and causality assessment was performed as described previously (Kardaun et al, 2013).

Results: In this period of 15 years, 104 potential DRESS-cases of all age groups were collected, 22 were validated as "definite" and 41 as "probable" (n=63). The average age was 48.9 yrs, 55.5% of the patients were female. Mortality during hospitalization was 4.8%. Risk factors for death were severe underlying diseases, male gender and higher age. All patients with a validated diagnosis of DRESS had a skin eruption, 56% also had mucosal involvement. In 95% of the cases at least one organ was affected, most frequently liver (78%) and kidney (37%). Fever was present in 92% of the patients. Eosinophilia was observed in 86%, palpable lymphnode enlargement in 41% of the patients. Atypical lymphocytes were detected in 25/35 patients investigated, HHV-6-reactivation was found in 6/23. In 85.2% of the cases medication well known to induce DRESS was taken in the relevant time window before reaction onset. In further 8.2% drugs to date not known as inducers of DRESS were used in the relevant time window. Most frequent inducing medications were carbamazepine (31.1%), allopurinol (18%), lamotrigine (8.2%) and vancomycin as well as sulfasalazine (each 6.6%).

Conclusions: Demographic characteristics and inducing drugs in this cohort from Germany are comparable with results of other RegiSCAR-partners in Europe and Taiwan. Nevertheless, the percentage of cases induced by carbamazepine is higher in Germany than has been reported in other populations.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5044 | Off-label use of intravitreal bevacizumab at a national hospital in Peru: An active pharmacovigilance experience

Yesenia Rodríguez, Denys Romero, Paola Fernández and Violeta Saromo
Institute of Health Technology Assessment and Research (IETSI) ESSALUD, Lima, Peru

Background: Although there is high quality evidence that supports the off-label use of bevacizumab for ophthalmic conditions worldwide, in some Latin American countries is still controversial. In 2017, cases of *endophthalmitis* possibly related to off-label use of bevacizumab were notified to Pharmacovigilance Center of EsSalud so that an active pharmacovigilance activities for this biologic were developed

Objectives: To characterize the safety profile of off-label use of intravitreal bevacizumab for any ophthalmic condition

Methods: A prospective active surveillance of patients receiving intravitreal bevacizumab for any ophthalmic condition was conducted. Patient demographics, indication and pharmacotherapy information were obtained by patient interviews and medical records. Active Pharmacovigilance was implemented in two stages: during the administration of intravitreal bevacizumab at the surgery room and when patient was discharged. Outpatients were followed-up for 5 weeks and contacted 7 times to obtain ADRs information using a survey. The assessment of ADRs causality was performed using Karch and Lasagna algorithm. ADRs were classified according to MedDra methodology. Logistic regression analyses were performed to identify characteristics associated to ADRs.

Results: During the follow-up period a total of 169 patients participated with a median age of 72 years, 53.8% were women. The most common comorbidities were hypertension (49.7%) and Type 2 diabetes mellitus (44.4%). The main indication for intravitreal bevacizumab was wet Age-related macular degeneration (47.3%). Ninety-three patients (55%) suffered at least a suspected ADRs. Ocular pain and subconjunctival hemorrhage were the most frequent ADRs accounting for 35% and 15%, respectively. Cephalea occurred in eight patients with a median time to onset of two days. The causality of ADRs detected were possible (95.4%) and probable (4.6%). The 64.5% of ADRs were classified as mild and none was severe. Female gender has been shown to have a 1.7 fold greater risk of developing an ADR. Malignant Neoplasm was a predictor of Subconjunctival hemorrhage (OR: 4.51; 95%CI 1.3-16). No cases of endophtalmitis were notified.

Conclusions: To our knowledge, this is the first active pharmacovigilance experience focused on off-label use of intravitreal bevacizumab in Latin America. The results have been used in EsSalud not only to ensure the safe use of this off-label biologic treatment for ophthalmic conditions but also to create awareness about the importance of ophthalmologists conducting pharmacovigilance on a regular basis.

5072 | Health outcomes coding trends in the US FDA's sentinel system during the ICD-9/10 transition: A review

Young Hee Nam, Aaron B. Mendelsohn, Judith C. Maro and Jeffrey S. Brown
Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: Accurate identification of health outcomes of interest (HOIs) is critical in analyses using health care claims data. The transition from International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to ICD-10-CM in the US in October 2015 created a serious analytic gap due to the scarcity of validated ICD-10 algorithms. Since the transition to ICD-10, the US Food and Drug Administration (FDA)'s Sentinel Initiative has conducted and publicly posted trend analyses based on standardized mappings from ICD-9-CM to ICD-10-CM using claims data; the reports include graphs of monthly incidence and prevalence rates of HOIs across the ICD-9 to ICD-10 eras.

Objectives: To evaluate and make suggestions for improving the utility of Sentinel's ICD-9-CM to ICD-10-CM mapping trend analyses for public health research and surveillance.

Methods: We analyzed all trend analyses published on the Sentinel website through November 30, 2019. We describe the trends in the incidence/prevalence of HOIs across the ICD-9/10 eras based on the mapping method and characterize consistency in the trends based on visual inspection of graphs.

Results: We identified 78 HOIs (22 acute, 32 chronic, and 24 acute or chronic) and 140 definitions across the HOIs. About 61.4% (n=86) of the 140 mappings showed consistent trends; the remaining mappings were divided between inconsistent (n=45; 32.1%) and uncertain (n=9; 6.4%) trends. Forward-backward mapping appeared to produce more consistent results in general than simple forward mapping. The reports provided limited information on the following: context of original studies for which HOIs were used, rationale/references for the choice of and validation statistics of ICD-9 algorithms, and information needed for further statistical evaluation of trends beyond visual inspection, including tables of monthly counts and rates in incidence and prevalence (vs. graphs only), and confidence intervals.

Conclusions: Sentinel's HOI coding trend analyses are an important public resource. The results suggest that standardized mappings alone may not always be appropriate and may need manual refinement. Inclusion of data tables in the reports, in addition to graphs, and rationale for selecting a set of codes for a phenotype, as well as algorithm validation statistics when available, will enhance the utility of Sentinel reports for HOI ascertainment, refinement of ICD-10-CM algorithms, monitoring incidence and prevalence of HOIs, and improving the quality of studies of effectiveness and safety of medical products and health policies utilizing administrative health care data.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5153 | Barriers to reporting of adverse drugs reactions: A cross sectional study among community pharmacists in Indian locality

Srikanth M S[1] and Ramesh Adepu[2]
[1]JSS College of Pharmacy, Mysuru, India; [2]VCPS, Suryapet, India

Background: Adverse drug reactions (ADRs) are one of the important health problem due to increased morbidity, mortality and health related cost. ADRs are major economic burden in the public in terms of hospitalizations and other forms of healthcare.
Objectives: To identify the barriers towards ADR reporting among community pharmacists practicing in Indian Locality.
Methods: A prospective cross sectional study was carried out by administering validated barrier assessment questionnaire towards ADR reporting was conducted during 10 months of period. Community pharmacists practicing in the Mysuru district, were approached for the participation in this study. Barrier Assessment Questionnaire (BAQ) was administered to assess the barriers if any in ADR reporting. At the end of the study, frequencies and percentages were used to measure demographic details of the participant and Chi-Square test were applied to identify covariate for the barriers to ADR reporting.
Results: 117 community pharmacists participated in the study, 94.05% were male and 5.95% female. The mean ± SD age for community pharmacists was 40.89 ± 7.65 years. The majority of participants in the (41-45) age group were 37.62%. About 48 % of the pharmacists were aware with the existing pharmacovigilance program of India, the study findings shows that 56.8% of participants have strongly disagreed with the statement I am not aware that I can report suspected adverse drug. Major barriers identified for under reporting were lack of time 81%, inadequate knowledge and skills 71%, and lack of time from patients 59%. About 47.6% participants have mentioned reporting of ADR will take their business time followed by unavailability of ADR reporting forms in their pharmacy.
Conclusions: The study findings conclude that Indian community pharmacists have inadequate knowledge about the importance of spontaneous ADR reporting system and Pharmacovigilance program of India

Pregnancy and Lactation

39 | "I Know My Body Better Than You": Patient focus groups to inform a shared decision aid on oral corticosteroid (OCS) use during pregnancy

Kristin Palmsten, Dani Bredesen, Meghan JaKa, Jeanette Zigenfuss and Elyse Kharbanda
HealthPartners Institute, Minneapolis, MN

Background: Improved dissemination of evidence based information on medication safety in pregnancy to patients is needed. OCS use during pregnancy has been associated with adverse perinatal outcomes.
Objectives: Inform the development of a shared decision making aid on OCS use in pregnancy with patient focus groups.
Methods: Using EHR data, we identified patients in our Midwestern (USA) health care system who had a recent live birth and a condition for which OCSs may be prescribed (i.e., asthma, other autoimmune disease). We recruited women in 2019 with invitation letters and phone calls to participate in 1 of 5 focus groups. Participants completed a survey on demographics and health and responded to open-ended discussion questions. We conducted a conventional content analysis with inductive coding on verbatim transcripts.
Results: Among the 30 participants, the average age was 33 years, 66% were White, 77% had at least a college degree, and 66% had ever taken an OCS. Women consulted a variety of sources of information on medication safety in pregnancy (e.g., internet, health care providers, family, pharmacists) and expressed frustration with conflicting information. Women voiced support for patient-provider discussions about medication use during pregnancy in which the provider shares risks and benefits and the patient makes her decision. Furthermore, women generally expressed support for a patient-centered handout about OCS use during pregnancy that the provider discusses with the patient. Obstetrician/midwives were the preferred provider type for advising on OCS use during pregnancy because women trusted them to know the information, believing it was their job, and because of convenience at routine prenatal visits. Women wanted their non-obstetric specialists to collaborate with obstetric providers on medication treatment in pregnancy. When trying to decide whether to take OCSs in pregnancy, women had concerns about: the medication's impact on their baby (e.g., miscarriage, development, birth defects), themselves (e.g., side effects including mood, sleep, weight gain), pregnancy complications (e.g., preterm birth, increased blood pressure), and lactation. Women wanted information on OCSs (e.g., indications, length of treatment, and cost), alternative treatments, and risks of not taking OCSs.
Conclusions: The need for a decision aid handout on OCS use during pregnancy that obstetric providers can discuss with their patients was confirmed. The handout should at a minimum contain risks/benefits of the medication to mother, baby, pregnancy complications, and lactation.

82 | Ssri/snri discontinuation in pregnancy and obstetrical outcomes: A nordic population register-based study

Carolyn E. Cesta[1], Óskar Ö. Hálfdánarson[2], Jacqueline M. Cohen[3], Kristjana Einarsdóttir[2], Kari Furu[3], Mika Gissler[4,5,1], Maarit Leinonen[4], Mette Nørgaard[6], Johan Reutfors[1], Randi Semler[3], Helga Zoega[2,7], Laura Pazzagli[1] and Helle Kieler[1]
[1]Karolinska Institutet, Stockholm, Sweden; [2]University of Iceland, Reykjavik, Iceland; [3]Norwegian Institute of Public Health, Olso, Norway; [4]Finnish Institute for Health and Welfare, Helsinki, Finland; [5]University of Turku, Turku, Finland; [6]Aarhus University, Aarhus, Denmark; [7]UNSW Sydney, Sydney, Australia

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: A significant proportion of reproductive aged women use selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) to treat mild-to-moderate depression or anxiety, yet the guidelines for use during pregnancy are inadequate. While use of most of SSRI/SNRIs during pregnancy are considered safe for the fetus, women often discontinue use during pregnancy.

Objectives: To test our hypothesis that women who discontinue SSRI/SNRI use during pregnancy have higher rates of obstetrical complications compared with women who continue use throughout pregnancy.

Methods: Using the Nordic population health registers, an observational cohort study was conducted including all pregnancies to women who dispensed an SSRI or SNRI in the 90 days before the start of pregnancy from 2006-2016 (Sweden), 2004-2017 (Iceland), and 2005-2017 (Norway). Pregnancies in women with a history of inpatient psychiatric care, outpatient diagnoses of psychiatric disorders other than depression or anxiety, or co-medication to treat psychiatric disorders other than depression or anxiety were excluded. To identify discontinuation, k-means longitudinal modeling was used to cluster individual trajectories of SSRI/SNRI use based on the number of days of medication coverage for nine 30-day periods beginning from the start of pregnancy. Pregnancies in the trajectory with the highest continuous use over time were classified as continuers, and all others were classified as discontinuers. Rates of obstetrical complications in pregnancies with SSRI/SNRI discontinuation and continuation were calculated.

Results: In total, 36,783 (3.3%) pregnancies were identified in Sweden, 3525 (5.9%) in Iceland, and 4391 (0.8%) in Norway. Discontinuation of SSRI/SNRIs occurred in 93.6%, 92.9%, and 91.4% of pregnancies, respectively. Preliminary results show no differences in the rates of delivery by caesarian section, placental abruption, preterm delivery (<37 gestational weeks), breech position anytime during pregnancy, delivery of a small-for-gestational-age infant, and perinatal death.

Conclusions: The large majority of women discontinued SSRI/SNRI use during pregnancy; however, rates of obstetrical complications were not different between continuers and discontinuers. Next steps are to include data from Finland and Denmark, to conduct multivariate regression model analyses, and to investigate short and long-term maternal psychiatric health outcomes.

85 | First trimester pregnancy exposure to modafinil and risk of congenital malformations

Anne Broe and Per Damkier
University Hospital Odense, Odense, Denmark

Background: Modafinil is a stimulant drug used in the treatment of excessive daytime sleepiness associated with narcolepsy, and, in Denmark, used off-label for fatigue in multiple sclerosis. In June 2019, healthcare professionals were notified that an interim analysis of post-marketing surveillance data found an increased risk of major malformations among children exposed to modafinil during pregnancy

Objectives: To determine the risk of major malformations after first trimester exposure to modafinil

Methods: Using the Danish national health registries, we identified all pregnancies from 2004 to 2017. We excluded women not residing in Denmark for at least 2 years before delivery; pregnancies shorter than 18 weeks (any pregnancy ≥ 18 weeks were included) or missing information on gestational age; pregnancies exposed to known teratogenic medication; and infants/fetuses with chromosomal malformations. Modafinil exposure was defined as any prescription overlapping with the first trimester, estimated by the amount prescribed. Use of methylphenidate was used as an active comparator. Methylphenidate another central nervous system stimulant, is not associated with congenital malformations. A second comparator group was pregnancies unexposed to either modafinil and methylphenidate one year prior to, and during, pregnancy. Major malformations were identified, during pregnancy, at delivery, or during the first year of life using the EUROCAT classification of malformations. The odds ratios (OR) were estimated using logistic regression, adjusting for diagnosis of diabetes and hypertension, concomitant use of psychotropic drugs, maternal age, year of delivery, smoking status and body mass index (BMI).

Results: We identified 49 (.006%) pregnancies exposed to modafinil and 963 (0.12%) to methylphenidate. There were 6 major congenital malformations in the modafinil exposed group (no multiple sclerosis patient received teriflunomide, a suspected teratogen), 43 in the methylphenidate exposed group, and 32466 in unexposed pregnancies, for absolute risks of 12% for modafinil, 4.5% for methylphenidate and 3.9% for unexposed. The adjusted ORs were 3.4 (95% CI, 1.2-9.7) comparing modafinil and methylphenidate and 2.7 (95% CI, 1.1-6.9) compared with unexposed.

Conclusions: In this nationwide study, first trimester in utero exposure to modafinil compared with methylphenidate or no medication was associated with a substantially increased risk of congenital malformations. Although further research is needed, women contemplating pregnancy should currently avoid or discontinue modafinil.

2387 | Fertility treatment and oral contraceptive discontinuation for identification of pregnancy planning in routinely collected health data: An application to analgesic and antibiotic utilisation

Sarah Hjorth[1], Mollie Wood[2,1], Fatima Tauqeer[1] and Hedvig Nordeng[1,3]
[1]*University of Oslo, Oslo, Norway;* [2]*Harvard University, Boston, MA;* [3]*Norwegian Institute of Public Health, Oslo, Norway*

Background: Women with unplanned pregnancies use folic acid less frequently, and more often smoke and use potentially teratogenic medications in the first trimester. Yet most perinatal pharmacoepidemiological studies based on routinely collected data lack information on pregnancy planning. Further, for pregnancies to

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

appear in routinely collected data, they need to proceed beyond a certain point, for example week 12, or end in live birth. If pregnancy intention could be identified, it would be possible to ascertain pregnancies prospectively from an earlier time.

Objectives: To evaluate fertility treatment or discontinuation of oral contraceptives (OC) as proxies for pregnancy planning in routinely collected data. We hypothesised that (1) women on fertility treatment, and women who discontinue OC before pregnancy, would be less likely to use prescription analgesics in the three months before pregnancy and in the first trimester than women who discontinue OC during pregnancy, and (2) there would be no difference in use of prescription antibiotics.

Methods: This registry-based cohort study used data on pregnancies in the Medical Birth Registry of Norway from 2006 to 2017 linked to data from the Norwegian Prescription Database. We included women with either filled prescriptions for clomiphene in the year before pregnancy, or OC dispensed that covered the date one year before pregnancy start. Participant characteristics and proportion of pregnancies with filled prescriptions for antibiotics and analgesics were displayed for women on fertility treatment, women who discontinued OC before pregnancy, and women who discontinued during pregnancy.

Results: Of 175 628 included pregnancies, fertility treatment was identified in 20 580, and OC discontinuation in 155 048. As hypothesised, women who discontinued OC during pregnancy were slightly more likely to fill prescriptions for analgesics before pregnancy (10.5%) than women who discontinued before pregnancy (9.4%); however, they also filled more prescriptions for antibiotics (13.7% compared to 11.9% in women who discontinued OC before pregnancy). In the first trimester, patterns were similar. Contrary to our hypothesis, women on fertility treatment had the highest proportion of analgesic prescription fills before pregnancy (11.5%).

Conclusions: Fertility treatment and OC discontinuation from routinely collected health data may be markers of pregnancy planning, but cannot stand alone in identifying unplanned pregnancies.

2389 | Prenatal exposure to non-steroidal anti-inflammatory drugs and risk of attention deficit hyperactivity disorder diagnosis and symptoms: A follow-up in the Norwegian mother, father and child cohort study

Sarah Hjorth[1], Angela Lupattelli[1], Marte Handal[2], Olav Spigset[3,4], Eivind Ystrom[5,1,2] and Hedvig Nordeng[1,6]

[1]*University of Oslo, Oslo, Norway;* [2]*Norwegian Institute of Public Health, Oslo, Norway;* [3]*St. Olav's University Hospital, Trondheim, Norway;* [4]*Norwegian University of Science and Technology, Trondheim, Norway;* [5]*University of Oslo, Oslo, Norway;* [6]*Norwegian Institute of Public Health, Oslo, Norway*

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are used in 5-15% of pregnancies despite that first and third trimester use is associated with risk of negative birth outcomes. Few studies have investigated neurodevelopment in children exposed to NSAIDs in utero and none have followed the children up to school age.

Objectives: To investigate the association between timing and duration of prenatal exposure to NSAIDs and risk of attention deficit hyperactivity disorder (ADHD) diagnosis and symptoms.

Methods: This study was based on the Norwegian Mother, Father and Child Cohort Study linked to the Medical Birth Registry of Norway. The study sample was restricted to women reporting indications for NSAID use (N=76 385). Prenatal NSAID exposure was identified by maternal report during pregnancy and post-partum. The primary outcome, child ADHD, was identified as an ICD-10 diagnosis from the Norwegian Patient Registry and/or ADHD medication fills from the Norwegian Prescription Database. The secondary outcome, child ADHD symptoms at age 5 years, was measured using Conners' Parent Rating Scale-Revised. To account for time-varying exposure and confounders, marginal structural models were fitted to estimate hazard ratios and mean difference in z-scores. Missing data were handled via multiple imputation. Several sensitivity analyses were done to investigate potential misclassification of exposure and outcome, residual confounding by disease severity, and model misspecifications.

Results: The analyses on ADHD diagnoses included 56 340 children. The average age at follow-up was 10 years. The analyses on ADHD symptoms included 34 961 children. There was no increased risk of ADHD diagnosis in children exposed to NSAIDs in utero regardless of timing of exposure (first trimester: HR 1.12 [95% CI 0.86;1.45], second trimester: HR 0.98 [0.69;1.38], third trimester: HR 0.68 [0.31; 1.46]). ADHD symptoms scores were also similar in exposed and unexposed (first trimester: mean difference 0.03 [95% CI -0.03;0.09], second trimester: mean difference 0.03 [-0.04;0.11], third trimester: mean difference 0.11 [-0.03; 0.25]). There was no duration-response relationship. The results were stable in sensitivity analyses.

Conclusions: The findings are reassuring and suggest no substantially increased risk of ADHD diagnosis or symptoms in children exposed to NSAIDs in utero, regardless of timing or duration, though non-differential misclassification of the exposure may have attenuated results.

2412 | In utero exposure to antiretroviral drugs and pregnancy outcomes: Secondary analysis of the ANRS pharmacovigilance database from the ANRS-promoted HIV research studies

Laura Saint-Lary[1], Alpha Diallo[2], Laure-Amélie de Monteynard[3], Christelle Paul[2], Lucie Marchand[3], Claire Rekacewicz[3], Ventzislava Petrov-Sanchez[3], Roland Tubiana[4], Josiane Warszawski[5], Laurent Mandelbrot[6], Albert Faye[7], Jeanne Sibiude[8], François Dabis[3], Valériane Leroy[1] and Agnès Sommet[9]

[1]*Inserm UMR 1027, Université Toulouse 3, Toulouse, France;* [2]*ANRS, Paris, France;* [3]*ANRS, Paris, France;* [4]*Hôpital Pitié Salpétrière And Université Pierre et Marie Curie Inserm UMR 943 Pierre Louis Institute of Epidemiology and Public Health, Paris, France;* [5]*CESP, Inserm U1018, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris Université Paris*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Sud, Kremlin Bicêtre, France; [6]Hôpital Louis Mourier, Hôpitaux Universitaires Paris Nord Val de Seine, Assistance Publique-Hôpitaux de Paris, Colombes, France; [7]Université Paris Diderot Infectious Diseases Department, Bichat-Claude Bernard, Hôpitaux Universitaires Paris Nord Val de Seine, Paris, France; [8]Cesp, Inserm U1018 Hôpital Bicêtre, Assistance PubliqueHôpitaux De Paris Université Paris Sud, Kremlin Bicêtre, France; [9]Inserm UMR 1027, Université Toulouse 3, Toulouse, France

Background: More than 1.5 million pregnant women lived with HIV in 2016 and were eligible to receive antiretroviral drugs, raising the question of whether this treatment affects perinatal outcomes. Some studies have reported increased risks of adverse pregnancy outcomes in case of prenatal exposure to antiretroviral drugs, depending on class used. In 2018, the WHO has warned of an increased number of neural tube defects related to pre-conceptional exposure to Dolutegravir.

Objectives: We assessed the adverse pregnancy outcomes associated with antiretroviral drugs exposure notified to the French ANRS.

Methods: A systematic review has been performed using the ANRS pharmacovigilance database implemented for each ANRS-promoted HIV research from 2004 to 2019 with a routine notification pregnancy and its outcome: abortion, ectopic pregnancy, stillbirth, prematurity (<37 weeks of gestation), low-birth weight (<2500g) and congenital abnormalities. Logistic regression was performed for each outcome separately (if occurrence >50). Odd ratios (OR) and corresponding 95% CIs have been computed to assess association between outcomes and prenatal exposure to antiretroviral combinations.

Results: Of 1 148 pregnancies identified, our systematic review included 924 pregnancies reported in 34 studies. There was no significant association between spontaneous abortion, prematurity and low-birth weight risks exposure to non-NNRTI combinations compared to non-nucleoside reverse transcriptase inhibitor (NNRTI) combinations. An increased risk of low-birth weight was reported in new-born exposed to exclusive nucleoside reverse transcriptase inhibitor (NRTI) combinations (N=4; OR 7.50 [1.49-37.83]).

Conclusions: We did not present adverse pregnancy outcomes in case of exposure to different antiretroviral classes compared to NNRTI-based combinations, which is reassuring although not statistically powered for that purpose. Exposure to NRTI combinations seems to be associated with an increased risk of low-birth weight, but this result should be interpreted with caution considering the small size group and indication bias to use of exclusive NRTI combinations.

2487 | Risk of pregnancy loss after in utero exposure to triptans

Caroline Hurault-Delarue[1], Christophe Dematteï[2], Christine Damase-Michel[1], Alexandra Benachi[3], Antoine Pariente[4], Jeanne Stadler[5], Pascale Tubert-Bitter[6], Emmanuelle Ripoche[7] and Isabelle Lacroix[1]

[1]Laboratoire de Pharmacologie Médicale et Clinique, UMR INSERM 1027, Faculté de Médecine de l'Université Paul-Sabatier et Centre Hospitalier Universitaire, Toulouse, France; [2]Laboratoire de Biostatistique, Epidémiologie Clinique, Santé Publique Innovation et Méthodologie (BESPIM), CHU Nîmes, Nîmes, France; [3]Hôpital Antoine Béclère, AP-HP, Université Paris Saclay, Clamart, France; [4]Inserm U1219 BPH Research Center, Université Bordeaux, Centre Régional de Pharmacovigilance de Bordeaux, CHU de Bordeaux, Plateforme Nationale DRUGS-SAFE, Toulouse, France; [5]Consultant Toxicologie, Tours, France; [6]Inserm U1181: Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases (B2PHI), Villejuif, France; [7]Direction de la Surveillance, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), Saint-Denis, France

Background: Triptans are serotoninergic agonists with vasoconstrictive properties, indicated in migraine and vascular facial algia. Data on the effects of triptans during pregnancy mainly concern sumatriptan and are reassuring concerning the teratogenic risk. However, we can wonder about the potential risks of these drugs on the course of pregnancy.

Objectives: The objective was to study risks of pregnancy loss after *in utero* exposure to triptans.

Methods: We performed a comparative study in EFEMERIS database, including 135,576 pregnant women who delivered between 2004 and 2017, in a French department. Exposure to triptans (ATC code N02CC: Selective serotonin (5-HT1) agonists) during pregnancy was described. The comparisons of pregnancy loss prevalences between exposed and non-exposed pregnant women were performed using logistic regressions.

Results: During the study period, 802 pregnant women received at least one prescription and dispensation of triptans (0.6%), mainly during the first trimester of pregnancy (78.2%). Zolmitriptan, sumatriptan and eletriptan were the most prescribed. Among exposed women, 10.6% of pregnancies ended in a pregnancy loss (spontaneous abortions and fetal deaths) against 4.9% in the comparison group. After adjustment for confounding factors, a slight increased risk was observed for the triptan-exposed group (adjusted OR=1.3 [1.1-1.7]). An additional analysis taking into account NSAID exposure confirmed the slight increased risk of pregnancy loss after triptan exposure (3.9% in women neither exposed to triptans nor to NSAIDs, 6.3% in women exposed to triptans and not exposed to NSAIDs, 13.6% in women not exposed to triptans and exposed to NSAIDs, 17.2% in women exposed to both triptans and NSAIDs).

Conclusions: This study showed a slightly significant association between dispensation of triptans during pregnancy and pregnancy loss. The results of this study should be interpreted with caution due to bias, particularly the frequent concomitant exposure to NSAIDs known to increase the risk of fetal death. Anyway, the role of triptans cannot be ruled out because of a plausible pharmacological mechanism. In conclusion, looking forward to further pharmacoepidemiological investigations, the use of triptans should

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

not be trivialized in pregnant women, and requires a careful benefit/risk evaluation.

2488 | Drug prescriptions in French pregnant women between 2015 and 2017, a study in the EGB database

Mélanie Araujo[1], Caroline Hurault-Delarue[1], Agnès Sommet[2], Christine Damase-Michel[1], Justine Benevent[1] and Isabelle Lacroix[1]
[1]Réseau REGARDS, Centre Hospitalier Universitaire, Laboratoire de Pharmacologie, Médicale et Clinique, Faculté de Médecine de l'Université Paul-Sabatier et UMR INSERM 1027, Toulouse, France; [2]Réseau REGARDS, Centre Hospitalier Universitaire, Laboratoire de Pharmacologie, Médicale et Clinique, CIC INSERM 1436, Faculté de Médecine de l'Université Paul-Sabatier et UMR INSERM 1027, Toulouse, France

Background: Studies performed in France before 2014, consistently showed that a large number of drugs was prescribed to pregnant women.
Objectives: The aim of this study was to describe French drug prescription practices in pregnant women between 2015 and 2017. The secondary objective was to identify teratogenic and fetotoxic drug prescriptions during pregnancy.
Methods: This study was carried out using data from a Permanent Beneficiaries Sample (*Echantillon Généraliste des Bénéficiaires* - EGB), a French national health database which includes 1/97th of the French population. Our study population included all pregnant women, aged 10 to 60, who were registered in the EGB and had a pregnancy outcome between 2015 and 2017. Drugs prescribed and dispensed to women during pregnancy and the 3 months before, were collected and described for each year and according to pregnancy trimesters. Prescriptions of major teratogen or fetotoxic drugs were described.
Results: We identified 27,596 pregnant women. Among them, 93% received drug prescriptions and dispensations during pregnancy with an average of 7.4±5.4 different drugs. "Alimentary tract and metabolism (75.3%)", "nervous system (63.9%)" and "blood and blood forming organs (58.9%)" classes were the most frequently prescribed to pregnant women. The 5 most frequently prescribed drugs were paracetamol (60.3%), iron (49.2%), folic acid (45.3%), phloroglucinol (43.7%) and colecalciferol (41.7%). The most commonly prescribed drugs included some that have not yet been well evaluated in pregnancy as tixocortol, sertaconazole, helicidine, metopimazine and domperidone. Prescriptions and dispensations of teratogenic or fetotoxic drugs, as Non-Steroidal Anti-Inflammatory Drugs after the 6th month of pregnancy and retinoids were observed. Valproic acid prescriptions to pregnant women have become extremely rare.
Conclusions: This descriptive study demonstrates that several drugs are prescribed and dispensed to pregnant women in France. These include drugs with a proven teratogenic or fetotoxic effect and many drugs that have not yet been well evaluated in pregnancy.

2502 | Comparing maternal and neonatal outcomes with use of different antihypertensive medications in pregnancy

Sascha Dublin[1,2], Mary Akosile[1], Lyndsay A Avalos[3], T. Craig Cheetham[4], Thomas R Easterling[5], Lu Chen[1], Nerissa Nance[3], Zoe Bider-Canfield[6], Victoria L Holt[2], Romain S Neugebauer[3], Kristi Reynolds[6], Sylvia E Badon[3] and Susan M. Shortreed[1,7]
[1]Kaiser Permanente Washington, Seattle, WA; [2]University of Washington, Seattle, WA; [3]Kaiser Permanente Northern California, Oakland, CA; [4]Chapman University, Irvine, CA; [5]University of Washington, Seattle, WA; [6]Kaiser Permanente Southern California, Pasadena, CA;[7]University of Washington, Seattle, WA

Background: Over 5% of women experience hypertension in pregnancy, and many require treatment. There are scant data comparing the safety and effectiveness of different antihypertensive medications in pregnancy.
Objectives: To compare maternal and neonatal outcomes with use of different antihypertensive medications in pregnancy.
Methods: This retrospective cohort study included women age 15-45 years with a singleton birth from 2005-2014 who were treated for hypertension in pregnancy within Kaiser Permanente, a large integrated healthcare delivery system in the US. From electronic health records and birth certificate data, we ascertained demographic characteristics, gestational age, diagnoses, medication dispensings, and vital signs including blood pressure. Medication exposure was defined based on the earliest dispensing after the first prenatal visit and before 36 weeks' gestation. Outcomes were pre-eclampsia, preterm delivery, small for gestational age (SGA), neonatal intensive care unit (NICU) and maternal ICU admissions, and stillbirth or termination at > 20 weeks (validated through chart review). We calculated weighted outcome prevalences and used logistic regression to generate adjusted odds ratios (aORs) and 95% confidence intervals, with inverse probability of treatment weighting used to control for confounding.
Results: Among 6346 eligible deliveries, 48% were exposed to labetalol, 29% to methyldopa, 17% to nifedipine and 6% to other β-blockers. The mean maternal age was 33.6 years, 33% were non-Hispanic white, and 61% were obese. For SGA defined as birthweight below the 10th percentile, the weighted prevalence was 13.6% in infants exposed to methyldopa vs. 16.6% for labetalol (aOR 0.77, 95% CI 0.63-0.92). For birthweight < 3rd percentile, the corresponding aOR was 0.57 (0.39-0.80). Compared with labetalol, preterm delivery risk was higher with nifedipine (28.5% vs. 26%; aOR 1.25 [1.06-1.46]) or other β-blockers (aOR 1.58 [1.07-2.23]). Risk of preterm delivery was not higher for methyldopa (26.5%; aOR 1.10 [0.95-1.27]). NICU admission was more common with nifedipine than labetalol (25.9% vs. 23.3%; aOR 1.21 [1.02-1.43]), but not higher with methyldopa (23.1%; aOR 1.04 [0.89-1.21]). Risks for pre-eclampsia, maternal ICU admission, and stillbirth did not differ by medication.
Conclusions: Risk of several outcomes differed by medication, with methyldopa conveying risks lower than or equivalent to labetalol for all outcomes. While the latest US guidelines favor labetalol above methyldopa, our findings suggest methyldopa could also be considered as first line therapy.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2544 | Prenatal opioid exposure and risk of asthma in childhood: A population-based study from Denmark, Norway, and Sweden

Ingvild Odsbu[1], Marte Handal[2], Vidar Hjellvik[2], Sonia Hernandez-Diaz[3], Helle Kieler[1], Mette Nørgaard[4], Svetlana Skurtveit[2], Buket Öztürk[4] and Milada Mahic[2]

[1]Karolinska Institutet, Stockholm, Sweden; [2]Norwegian Institute of Public Health, Oslo, Norway; [3]Harvard T. H. Chan School of Public Health, Boston, MA; [4]Aarhus University Hospital, Aarhus, Denmark

Background: Opioids may modulate the immune function in both mother and fetus through opioid receptors on immune cells. Long-term consequences of prenatal opioid exposure on immune reactions is unknown.

Objectives: To investigate whether opioid exposure during fetal life was associated with the risk of childhood asthma.

Methods: Cohort study using linked nationwide registers. Two cohorts of children were identified using information from the medical birth registers and prescription registers in Denmark (DK), Norway (NO), and Sweden (SE). Opioid analgesics cohort: children whose mothers had filled >= 3 prescriptions with >= 30 Defined Daily Doses (DDD) of opioid analgesics (N02A) 1-365 days before start of pregnancy (defined as the first day of the last menstrual period). Long-term exposed (>= 30 DDD in pregnancy) were compared with unexposed (0 DDD). Opioid maintenance therapy (OMT) cohort: children whose mothers had filled at least 1 prescription of methadone, buprenorphine, or buprenorphine-naloxone any time before pregnancy start or during pregnancy. OMT exposed (>= 1 OMT prescription in pregnancy) were compared with OMT unexposed (no prescriptions). In children 1 year of age or older, asthma was defined as >= 2 dispensations of antiasthmatic (R03BA, R03DC, R03AK) medication within 365 days or a diagnosis of asthma (ICD-10 J45 or J46) as recorded in the patient registers. Hazard ratios (HRs) were calculated using Cox proportional hazards regression with attained age as the time scale. Inverse probability of treatment weights based on propensity scores was applied to adjust for measured confounders. Individual level data from NO and SE were pooled, whereas individual level data from DK were analyzed separately due to Danish legislation.

Results: In NO (2005-2015) and SE (2006-2013), a total of 3861 children were long-term exposed to opioid analgesics and 3719 were unexposed. In DK (1996-2015) the numbers were 1229 and 2949, respectively. For the opioid analgesics cohort, no increased risk of asthma was observed in long-term exposed vs. unexposed (NO/SE: HR = 1.04 [95% CI 0.82-1.31], DK: HR = 0.94 [0.79-1.11]). The numbers of OMT exposed children were 522 in NO and SE, and 287 in DK, and 156 and 630 children were unexposed, respectively. No increased risk of asthma was observed in OMT exposed vs. OMT unexposed (NO/SE: HR = 1.21 [0.68-2.16], DK: HR = 1.25 [0.86-1.84]).

Conclusions: There was no meaningful association between prenatal exposure to opioids and risk of childhood asthma. Results were consistent across two different opioid exposure groups with different confounder distributions.

2551 | Hypertensive disorders of pregnancy and use of antihypertensive medications in the 2015 Pelotas birth cohort study

Lisiane F Leal[1], Sonia M Grandi[2], Vanessa IA Miranda[3], Tatiane da S. Dal Pizzol[4], Robert W Platt[1] and Andréa D Bertoldi[3]

[1]McGill University, Montreal, QC, Canada; [2]National Institutes of Health, Bethesda, WA; [3]Universidade Federal de Pelotas, Pelotas, Brazil[4]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Background: Hypertensive disorders of pregnancy (HDP) affect approximately 140,000 women in Brazil. Pharmacotherapies play an important role in reducing the occurrence of adverse outcomes. However, the patterns of use of antihypertensives among women with HDP living in Brazil is unclear.

Objectives: To describe the use of antihypertensive agents among women with HDP in the Pelotas Birth Cohort. To compare the patterns of use, by trimester, between women with and without HDP.

Methods: We used data from the 2015 Pelotas (Brazil) Birth Cohort, one of the largest birth cohorts of women living in low and middle-income countries. HDP was classified as (i) chronic hypertension; (ii) preeclampsia superimposed on chronic hypertension; (iii) gestational hypertension and (iv) preeclampsia-eclampsia. Antihypertensive medications were defined using the 4th level of the Anatomical Therapeutic Chemical Classification System and the substance name. Descriptive statistics were used to describe this population. Patterns of use of antihypertensive medications were presented by trimester of use.

Results: Of the 4,270 eligible women in the cohort, 4,262 were included. HDP was present in 1,336 (31.35%) of women in the cohort. The majority of women with HDP were white (66.47%), had between 9-11 years of education (38.25%), and were of lower-middle socioeconomic class (54.12%). Comorbidities were slightly higher in women with HDP, compared to women without an HDP and these women were more likely to be hospitalized (30.16%). Among women with HDP, 636 (47.60%) reported having gestational hypertension, 409 (30.61%) chronic hypertension, 191 (14.30%) pre-eclampsia, and 89 (6.66%) preeclampsia superimposed on chronic hypertension. Approximately 71% of women with HDP reported not using antihypertensive medication during pregnancy. Among all antihypertensives reported by women with HDP, methyldopa in monotherapy was the most frequent (16%), regardless of the type of HDP. Methyldopa uses increased from 11.10-18.79% over the course of pregnancy for women with HDP, while those without HDP were found to increase their use of 'Other lipid modifying agents' (1.03-4.27%).

Conclusions: In the Pelotas Birth Cohort, women with HDP were found to have higher rates of comorbidities and hospital admissions. Patterns of use of methyldopa were in-line with the Brazilian guidelines as the first-line therapy for HDP. However, a large number of women with HDP not using antihypertensive agents require further investigation.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2555 | Co-occurrence of birth defects among infants with neonatal abstinence syndrome, 2012-2016

Elizabeth Ailes[1], Pam Owens[2], Jason Salemi[3], Caitlin Green[1], Jan Cragan[1], Kristie Clarke[1], Margaret Honein[1] and Jennita Reefhuis[1]
[1]*NCBDDD/CDC, Atlanta, GA;* [2]*AHRQ, North Bethesda, MD;* [3]*College of Public Health, Morsani College of Medicine, University of South Florida, Tampa, FL*

Background: *Prenatal opioid use has been associated with neonatal abstinence syndrome (NAS) and certain birth defects, but few data exist on their co-occurrence.*
Objectives: *We compared the prevalence of birth defects among newborns with and without NAS.*
Methods: We used the 2012-2016 Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project's National Inpatient Sample, a nationally representative sample of de-identified hospital discharge records. Among the ≤ 30 diagnosis codes per discharge, we identified (1) *newborns* using *International Statistical Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes V30.XX-V39.XX (1/2012-9/2015 discharges) and ICD-10 code Z38.XX (10/2015-12/2016); NAS using ICD-9 code 779.5 (excluding potential iatrogenic NAS: 765.00-765.05, 770.7, 772.1X, 779.7, 777.5X, 777.6) and ICD-10 code P96.1; and birth defects using Salemi et al. (Birth Defects Research. 2019;111:1365-1379). We calculated the prevalence of specific birth defects (for those with >10 unweighted discharges) among newborns with and without NAS and corresponding prevalence ratios (PR) and 95% confidence intervals (CI), accounting for sample weights.
Results: *We identified 3,795,785 discharges representing over 18.9 million newborn hospitalizations during 2012-2016. NAS and/or a birth defect were diagnosed in 6.1 and 22.5 per 1,000 newborns, respectively. The prevalence of 11 of 14 specific birth defects with sufficient sample size was significantly higher among newborns with NAS than without NAS, with the strongest associations for pulmonary valve atresia/stenosis (PR=4.2, CI: 3.2-5.4), cleft palate (PR=4.5, CI: 3.5-5.9), and cloacal exstrophy (PR=4.6, CI: 3.3-6.4).*
Conclusions: While these increases in prevalence of birth defects among infants with NAS might be related to prenatal opioid exposure, they could also result from common underlying causes of NAS and birth defects or variations in birth defect ascertainment among infants with and without NAS using billing records and across ICD coding transitions.

2613 | A validation study on the natural history of miscarriages in an established pregnancy cohort using BIFAP database in Spain

Sara Sanchez Ortiz[1], Consuelo Huerta[2], Paloma Ortega[1], Paloma Astasio[1], LLorente-García Ana[2] and Lucia Cea Soriano[1]
[1]*Faculty of Medicine, Complutense University of Madrid, Madrid, Spain;* [2]*Spanish Agency for Medicines and Medical Devices (AEMPS), Madrid, Spain*

Background: Few studies have evaluated and validated the natural history of miscarriages in electronic medical records
Objectives: To quantify and validate the frequency of miscarriages as well as to determine the specific time window for miscarriage onset using an established pregnancy cohort, using data from BIFAP database
Methods: We identified all pregnancy losses, classifying as i) miscarriages, ii) terminations of pregnancy (TOP) and iii) unspecified pregnancy losses. A multistep validation exercise was performed including a manual review of medical records. Potential cases with positive predictive values (PPV) <85% were excluded. Kaplan Meier figures and incidence rates of miscarriage with 95% confidence intervals (CIs) expressed by 1000 person-weeks were calculated. Stratifying analysis by age, specific high-risk groups, and drug exposure within the pre-pregnancy period were performed restricted to women with recording last menstrual period (LMP)
Results: For women initially classified as miscarriage and TOP, corresponding PPV were >90% and >85%, respectively. Unspecified pregnancy losses showed PPVs <85%. Women with confirmed miscarriage (N=18070 (11.6%)), tended to be older, with higher frequency of comorbidities and drug utilization compared to completed pregnancies women. Restricting to women with LPM recorded, incidence rate of miscarriage was 10.89 (CI 95% 10.68-11.10) per 1000 women-weeks, with a median follow-up of 10 weeks (IQR: 8-12). The incidence rate according to age was: 2.71 (CI 95% 2.59-2.84) in those aged <30 years compared to 9.11 (CI 95% 8.55-9.70) in women aged 40 years or above. Women with metabolic antecedents, psychiatric conditions, and those receiving at least one pregnancy within the pre-pregnancy period presented higher incidence rates
Conclusions: The present study showed how BIFAP database can be used to identify women suffering from miscarriages. This validated cohort will serve to further study risk factors associated with miscarriages with special attention to drug utilization

2650 | Online information discrepancies in patient information regarding medicine use during pregnancy and lactation: A conception study

Agnes Kant[1], Ulrika Nörby[2], Benedikte-Noël Cuppers[1], Michael Steel[3], Monali Desai[4], Sashka Hristoskova[5], Linda Härmark[1] and Ludivine Douarin[6]
[1]*Pharmacovigilance Centre Lareb, ´s Hertogenbosch, Netherlands;* [2]*Region Stockholm, Stockholm, Sweden;* [3]*Novartis Pharma AG, Basel, Switzerland;* [4]*Abbvie, North Chicago, IL;* [5]*Novartis AG, Basel, Switzerland;* [6]*Sanofi, Chilly-Mazarin, France*

Background: Consistent, adequate information on the safety of medicines during pregnancy and lactation is important for women's therapeutic decision making. Discrepancies between information resources may cause confusion, resulting in non-adherence to therapy with risks for both the mother, fetus or breastfed child.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To analyze the frequency and nature of discrepancies between different online information sources for patients in four European languages.

Methods: The study was performed on internet data sources, primarily via Google, in Swedish, Dutch, French and English. The medicines analysed were ibuprofen, ondansetron, olanzapine, fingolimod, methylphenidate and adalimumab, i.e. medicines commonly used during pregnancy and/or for treating chronic diseases in reproductive age. The top search hits with considerable information that could be classified into these data source categories, were collected: i) regulatory sources, ii) scientific sources, e.g. Teratology Information Services (TIS), iii) blogs/forums/social media, iv) commercial websites for patients. The recommendation was categorized as a) Can be used, b) Individual benefit-risk assessment, c) Should not be used, d) Trimester specific, e) Not classifiable. Descriptive analysis was used to identify the discrepancies.

Results: Pregnancy recommendations for adalimumab and fingolimod were consistent in all data sources in 3 out of the 4 languages, those for olanzapine were consistent in 2 languages, and pregnancy recommendations were consistent in only 1 language for ibuprofen, methylphenidate and ondansetron. Lactation recommendations for ondansetron were consistent in all data sources in 2/4 languages, for fingolimod and methylphenidate in 1/4 languages. Recommendations for adalimumab, ibuprofen and olanzapine were inconsistent in all languages. TIS center recommendations between countries were discrepant in 7% (2/27) of the pregnancy and 32% (7/22) of the lactation statements.

Conclusions: Information discrepancies are frequent for medicine use during pregnancy/lactation, especially for lactation. All major inconsistencies are however important. Compared to other sources, different TIS centers offer improved consistency in recommendations, indicating improved consensus on a scientific level. More work is needed to harmonize information both within and between countries, to avoid conflicting messages.

2665 | Validation of an ICD-10-based algorithm to identify stillbirth in the sentinel system

Susan E. Andrade[1], Mayura Shinde[2], Tiffany Moore Simas[3], Steven Bird[4], Justin Bohn[2], Kevin Haynes[5], Lockwood Taylor[4], Julianne Lauring[3], Erin Longley[6], Cheryl McMahill-Walraven[7], Connie Trinacty[8], Cassandra Saphirak[1], Christopher Delude[1], Sandra DeLuccia[2], Tancy Zhang[2], David Cole[2], Nina DiNunzio[2], Autumn Gertz[2], Elnara Fazio-Eynullay[2] and Danijela Stojanovic[4]

[1]University of Massachusetts Medical School, Worcester, MA; [2]Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; [3]University of Massachusetts Medical School, Worcester, MA; [4]Food and Drug Administration, Silver Spring, MD; [5]HealthCore, Inc., Wilmington, DE; [6]Community Health Care, Lakewood, WA; [7]Healthagen (Aetna), part of CVS Health Family of Companies, Blue Bell, PA; [8]Kaiser Permanente Center for Integrated Health Care Research, Honolulu, HI

Background: Electronic healthcare databases are widely used to study the use and safety of medical therapies during pregnancy. No published studies have evaluated International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM)-based algorithms to identify stillbirth.

Objectives: To develop and validate an ICD-10-CM-based algorithm to identify cases of stillbirth using electronic healthcare data.

Methods: We conducted a retrospective study using claims data in the Sentinel Distributed Database from three Data Partners (two national insurers and one integrated healthcare system). An algorithm was developed using ICD-10-CM diagnosis codes for stillbirth or a combination of codes for intrauterine death or papyraceous fetus and a gestational age (GA) ≥ 20 weeks to identify potential stillbirths among females aged 12-55 years between July 2016 and June 2018. A random sample of medical charts (N=169) was identified for chart abstraction and adjudication. Two physician adjudicators reviewed potential cases to determine whether a stillbirth event was definite/probable, the date of the event, and the GA at delivery. The positive predictive value (PPV) was calculated for the algorithm. Among confirmed cases, agreement between the claims data and medical charts was determined for both the event date and GA at stillbirth.

Results: Of the 110 potential cases with medical chart data available, adjudicators determined that 54 were stillbirth events (overall PPV= 49.1%; 95% CI, 39.4%-58.8%). All 54 confirmed cases had an ICD-10-CM diagnosis code indicating a GA ≥ 20 weeks. The PPV was 83.7% (95% CI, 70.3%-92.7%) among women with a code indicating a GA ≥ 20 weeks for whom no other pregnancy outcome code (i.e. livebirth, spontaneous abortion, induced abortion) was recorded on the index date. Of the 56 potential cases not confirmed to be stillbirth events, physician adjudicators judged that 22 (39.3%) were spontaneous abortions (pregnancy loss < 20 weeks GA), 19 (33.9%) were liveborn infants or continuing pregnancies, 1 was a neonatal death shortly after birth (1.8%), and 11 (19.6%) were terminations of pregnancy, including labor inductions for pregnancy complications; for 3 cases not enough information was available in the chart to determine a diagnosis. We found ≥ 90% agreement within 7 days between the claims data and medical charts for both the outcome date and GA at stillbirth.

Conclusions: Electronic healthcare data may be useful for signal detection of medical product exposures potentially associated with stillbirth. Further work is planned to refine the algorithm to maximize the PPV and sensitivity.

2676 | Oral corticosteroids and risk of preterm birth in the California medicaid program

Kristin Palmsten[1,2], Gretchen Bandoli[2], Jim Watkins[3], Gabriela Vazquez-Benitez[1], Todd P. Gilmer[4] and Christina D. Chambers[2]

[1]HealthPartners Institute, Minneapolis, MN; [2]University of California, San Diego, La Jolla, CA; [3]California Department of Health Services, Sacramento, CA; [4]University of California, San Diego, La Jolla, CA

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: There is limited information regarding the impact of dose and gestational timing of oral corticosteroid (OCS) use on preterm birth (PTB), especially in women with asthma.

Objectives: To evaluate the impact of OCS dose and timing of use on PTB in women with asthma and, as a comparison, systemic lupus erythematosus (SLE).

Methods: We used health care utilization data from California Medicaid program enrollees linked to birth certificate data (2007-2013), identifying women with asthma (n=22,084) and SLE (n=1,174). We used pharmacy dispensing data to define exposure and gestational age at delivery<37 weeks from birth certificates to define PTB. We estimated risk ratios (RR) for PTB modeling OCS cumulative dose trajectories (prednisone equivalent dose) and other disease-related medication (ie, for asthma: inhaled corticosteroids, long acting beta agonists, leukotriene modifier, other asthma medications; for SLE: Disease Modifying Antirheumatic Drugs (DMARDs)) before gestational day 140 and hazard ratios (HR) for PTB modeling time-varying exposures after day 139. We adjusted associations for demographics, parity, multiple gestations, pre-pregnancy body mass index, smoking, comorbidities, co-medication, health care utilization, and proxies of disease severity.

Results: Among women with asthma, PTB risk was 14.0% for no OCS exposure and 14.3%, 16.8%, 20.5%, and 32.7% in low, medium, medium-high, and high OCS cumulative dose trajectory groups during the first 139 days. After adjusting for covariates, only the high dose trajectory group remained moderately associated with PTB (adjusted (a)RR: 1.46 (95% CI: 1.00, 2.15). OCS dose after day 139 was not clearly associated with PTB, nor were asthma controller medications. For SLE, PTB risk for no OCS exposure was 24.9% and it was 39.1% in low and 61.2% in high dose trajectory groups during the first 139 days. aRRs were 1.80 (95% CI: 1.34, 2.40) for high and 1.24 (95% CI: 0.97, 1.58) for low dose trajectory groups. aHRs were 2.54, (95% CI: 1.60, 4.03) for OCS exposure to >20 mg/day of prednisone equivalent dose after day 139, 1.37 (95% CI: 0.80, 2.36) for 10 to 20 mg/day, and 1.15 (95% CI: 0.68, 1.95) for <10mg/day. DMARDs were not associated with PTB.

Conclusions: For asthma, higher OCS doses early in pregnancy, but not later, were associated with increased PTB. For SLE, higher doses early and later in pregnancy were associated with PTB. Other disease-related medications were not associated with PTB. Although the positive associations may reflect residual confounding by disease activity, results are reassuring for women who can manage asthma and SLE with non-OCS medications or lower OCS doses.

2682 | Personal history of febrile seizure increases risk of measles-mumps-rubella vaccine attributable seizure

Shirley V. Wang[1], Lily Bessette[1], Kristina Stefanini[1], Bruce Fireman[2], Ned Lewis[2], Jonathan Duffy[3], Michael McNeill[3], Seanna Vine[1], Krista Huybrechts[1] and Martin Kulldorff[1]

[1]*Brigham and Women's Hospital, Harvard Medical School, Boston, MA;* [2]*Kaiser Permanente Division of Research, Oakland, CA;* [3]*Centers for Disease Control, Atlanta, GA*

Background: The finding of a small increased risk of febrile seizure in the 7-10 days following measles-mumps-rubella (MMR) vaccination in children 11-22 months of age has been replicated in multiple studies using different data sources (attributable risk ~3-4 per 10,000 vaccinated children). The benefit of protection from measles, mumps, and rubella outweighs the potential harm from a febrile seizure. Nevertheless, there may be subgroups of children for whom the risk of MMR-attributable seizure is not small. Heterogeneity in the risk of vaccine-attributable seizures has not been deeply investigated.

Objectives: To evaluate the risk of vaccine-attributable seizure in children with and without a personal history of febrile seizure prior to vaccination.

Methods: We used a self-controlled risk-interval study design with data from two administrative healthcare insurance claims-based data sources, the IBM MarketScan Research Database (Jan 2003-Sep 2015) and Medicaid Analytic eXtracts (MAX) (Jan 2000-Dec 2014). We estimated the risk of seizure in the vaccine attributable risk window 7-10 days post vaccination compared to a reference window 14-17 days post vaccination. We evaluated whether the vaccine effect on seizure risk was modified by prior history of seizure. In children with and without a history of seizure, we estimated the relative risk of vaccine attributable seizure as well as the number needed to harm (NNH), standardized for age, gender, preterm birth and being born small for gestational age.

Results: There were 2,768,979 MMR vaccinated children, of whom 0.8% had history of seizure prior to vaccination. The overall NNH was 1,835. In children with and without a history of seizure, the standardized NNH was 77 and 2,036 respectively. In children with a seizure history, the risk of seizure was 4.8 (95% CI 2.2, 10.6) times higher on days 7-10 after vaccination than on days 14-17. In children without a history of seizure, the risk ratio was 3.6 (95% CI 1.7, 7.5). Test for multiplicative interaction, p = 0.07.

Conclusions: While the NNH for children with a personal history of seizure was small, a provider would need to administer MMR to 9,500 children, on average, before the occurrence of 1 excess seizure in a child with a prior history of seizure. Nevertheless, the variation in risk of MMR vaccine-attributable seizure observed in this study could be useful for informing clinical strategies to prevent febrile seizure after vaccination in high-risk children.

2684 | Treescan for active surveillance of the safety of medications used in pregnancy

Krista F. Huybrechts[1], Martin Kulldorff[1], Sonia Hernandez-Diaz[2], Brian T. Bateman[1], Yanmin Zhu[1], Helen Mogun[1] and Shirley V. Wang[1]

[1]*Brigham and Women's Hospital, Harvard Medical School, Boston, MA;* [2]*Harvard School of Public Health, Boston, MA*

Background: When new drugs enter the market, there is little to no information about safety during pregnancy. Most post-market studies of drug safety in pregnancy focus on a single or selected outcomes. However, to make informed treatment decisions, pregnant women

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

must balance the benefit of treatment against all possible adverse effects.

Objectives: To develop and evaluate tree-based scan statistic (TreeScan) methods as a safety surveillance approach that allows simultaneous evaluation of a comprehensive range of adverse pregnancy outcomes, while accounting for multiple testing and preserving the overall false positive rate.

Methods: We evaluated TreeScan with a cohort design and adjustment via propensity score matching and fine-stratification. We used two positive control test cases of drugs known to be associated with specific adverse pregnancy outcomes: 1) prescription opioids late in pregnancy and neonatal abstinence syndrome, and 2) valproate early in pregnancy and congenital malformations. These test cases were implemented in linked mother-infant pregnancy cohorts from the Medicaid Analytic eXtract (2000-2014; N=1,943,652) and the IBM MarketScan Research Database (2003-2015; N=1,251,451). We scanned across incident outcomes defined by hierarchical groupings of clinically related International Classification of Disease 9th version codes. Statistical alerts were defined by a threshold of p<0.05. However, because adverse pregnancy outcomes tend to be rare, and multiplicity adjustment decreases power, outcomes with large magnitude of effect were also interpreted from a clinical and methodologic perspective.

Results: In both test cases, we identified known safety concerns without generating numerous false positives. For opioids, out of >8,000 outcomes evaluated, there was only 1 statistical alert, which was for the known adverse event of drug withdrawal in the newborn. For valproate, there were statistical alerts for several known associations, including spina bifida, several cardiac malformations, hypospadias, and polydactyly after scanning close to 700 hierarchically defined malformation outcomes. The alert threshold of p<0.05 was not reached for oral clefts, but a relative risk of 2 was observed. There were no alerts for other safety concerns.

Conclusions: This evaluation shows the promise of TreeScan based approaches for systematic drug safety monitoring in pregnancy. Such a targeted screening approach followed by deeper investigation to refine understanding of potential signals will ensure pregnant women and their physicians have access to the best available evidence to inform treatment decisions.

3704 | Exploratory analyses of modafinil utilization during pregnancy and diagnoses of malformations in the offspring

Anna Julia Witzleb[1], Nadine Wentzell[1], Tania Schink[1] and Ulrike Haug[1,2]

[1]Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany; [2]Faculty of Human and Health Sciences, University of Bremen, Bremen, Germany

Background: Modafinil is indicated for excessive sleepiness in patients with narcolepsy. Based on data from pregnancy registries and case reports, modafinil is suspected to cause severe congenital malformations in the child when used during pregnancy. It is therefore contraindicated in pregnant women which has been stressed in 2019 by a warning that was issued by the manufacturer.

Objectives: To do exploratory analyses on the utilization of modafinil during pregnancy and diagnoses of malformations in the offspring based on German claims data.

Methods: Using the German Pharmacoepidemiological Research Database (GePaRD; health claims data covering 17% of the German population), we selected pregnancies ending between 2006 and 2016 (overall ~1.5 million pregnancies) and with at least one modafinil dispensation during pregnancy. For live births, the mother's and baby's data were linked and in- and outpatient diagnosis codes indicating a malformation in the child were explored.

Results: We identified 28 pregnancies in 24 women with at least one modafinil dispensation during pregnancy. Of these women, 71% had at least one diagnosis code of narcolepsy. In 26 pregnancies there was at least one modafinil dispensation during the first trimester, in seven during the second and in four during the third trimester. Overall, 71% of the 28 pregnancies ended in a live birth and 25% in induced abortions. Out of 20 live born children, 18 could be linked to their mothers' data. Four of these 18 children had diagnosis codes indicating a severe malformation (atrial septum defect: n=1; plagiocephaly: n=2, asymmetric face: n=1).

Conclusions: In our study period, we observed 28 pregnancies with at least one modafinil dispensation. In the majority, this dispensation was in the first trimester. Although the sample size is low, the high proportion of induced abortions is striking and also the proportion of children with diagnosis codes for malformations support the safety concerns regarding modafinil exposure during pregnancy. An important next step would be the pooling of data from several databases to allow risk quantification.

3705 | Fetotoxicity of RAAS-inhibitors

Tania Schink[1], Marlies Onken[2], Nadine Wentzell[1], Katarina Dathe[2] and Ulrike Haug[1]

[1]Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany[2]Charité – Universitätsmedizin Berlin, Berlin, Germany

Background: Treatment with inhibitors of the renin-angiotensin-aldosterone system (RAAS-I) during pregnancy can result in severe fetotoxic effects including oligohydramnios, renal damage and lung hypoplasia. Thus, RAAS-I (sartans, ACE inhibitors, renin inhibitors) are contraindicated during the 2nd and 3rd trimester of pregnancy, especially after gestational week (GW) 20.

Objectives: To quantify the risk of fetotoxic effects after exposure to RAAS-I compared to antihypertensive drugs of choice (metoprolol, methyldopa) overall and separately for different RAAS-I types.

Methods: We included all pregnancies in the German Pharmacoepidemiological Research database (GePaRD) between 2006 and 2016 in women between 12 and 50 years that continued for ≥20 GW. Newborns were linked to the pregnancy based on a published algorithm. Outcomes of interest were ICD-10 codes indicative for

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

fetotoxic effects, i.e. renal failure, pulmonary hypoplasia and thrombosis of vena cava inferior in the first 180 days after birth. Age, severity of hypertension, diabetes, and use of diuretics were assessed as potential confounders. In the main analysis, we compared pregnancies exposed to RAAS-I between day 140 (≥20 GW) and the end of pregnancy (critical period) with pregnancies exposed to metoprolol or methyldopa in the critical period. To asses potential confounding by indication, we compared in a sensitivity analysis pregnancies exposed to RAAS-I in the critical period with those exposed to RAAS-I only in the control period (90 days before to 90 days after start of pregnancy).

Results: We identified 21769 exposed pregnancies ending in a linked livebirth (98 to ACE inhibitors, 45 to sartans, 1 to a renin inhibitor, 6870 to metoprolol, 14755 to methyldopa). In the main analysis, an increased risk of renal failure was observed for sartans, ACE inhibitors and RAAS-I overall (relative risk 49.7/7.6/20.7, 95% confidence interval 15.7-157.3/1.1-55.3/7.3-58.2), of pulmonary hypoplasia for sartans and RAAS-I overall (213.6, 68.2-688.4/66.7, 20.8-214.3) and of thrombosis of vena cava inferior for sartans and RAAS-I overall (80.1, 9.8-651.9/25.0, 3.0-206.6). No cases of pulmonary hypoplasia and thrombosis of vena cava inferior were observed for ACE inhibitors. The results of sensitivity analyses showed patterns similar to the main analyses

Conclusions: Our study suggests that fetal exposure to RAAS-I after GW 20 is associated with a considerably increased risk of renal failure, pulmonary hypoplasia and thrombosis of vena cava inferior. Among RAAS-I, the highest risk was observed for sartans. Results of sensitivity analyses indicate that these results cannot be fully explained by confounding by indication.

3724 | Preconception antibiotic use and spontaneous abortion: A prospective study

Holly M. Crowe[1], Lauren A. Wise[1], Amelia K. Wesselink[1], Charles R. Horsburgh[1], Ellen M. Mikkelsen[2] and Elizabeth E. Hatch[1]

[1]Boston University, Boston, MA; [2]Aarhus University, Aarhus, Denmark

Background: Antibiotic use may increase the risk of spontaneous abortion (SAB) through increased oxidative stress or disruption of the reproductive tract microbiome.

Objectives: To examine the association between antibiotic use and SAB risk in a North American preconception cohort study.

Methods: From 2013 through 2019, we enrolled 10,921 female pregnancy planners; 5,793 conceived during 12 months of follow-up and 1,084 (19%) experienced SAB. At baseline, we collected data on antibiotic use in the past 4 weeks, including type and indication for use. Pregnancy losses at <20 gestational weeks were reported on follow-up questionnaires completed preconceptionally and in early and late pregnancy. We used Cox regression models, with gestational weeks as the time scale, to estimate hazard ratios (HR) and 95% CIs, adjusting for demographics, lifestyle, and reproductive history.

Results: Overall, 458 women (8%) reported using antibiotics in the four weeks before baseline, most commonly penicillins (24%) and macrolides (9%). Respiratory infections (31%) and urinary tract infections (UTI) (27%) were the most common indications for antibiotic use. Overall, preconception antibiotic use showed little association with SAB (HR=1.05, CI: 0.85-1.30). Use of penicillins (HR=1.01, CI: 0.65-1.55), macrolides (HR=0.87, CI: 0.41-1.82), or nitrofurantoin (HR=1.11, CI: 0.53-2.34) was not appreciably associated with SAB, while use of cephalosporins was associated with increased risk (HR=1.63, CI: 0.87-3.06), although estimates were imprecise. Antibiotic use was associated with a slightly increased risk of SAB when used for UTI (HR=1.27, CI: 0.87-1.84) or pelvic/vaginal infections (HR=1.58, CI: 0.96-2.61), but not for respiratory infections (HR=0.94, CI: 0.64-1.37), indicating potential confounding by indication.

Conclusions: Overall, our findings provide little support for the hypothesis that preconception antibiotic use is associated with SAB.

3747 | Association between antipsychotics use in pregnancy and the risk of gestational diabetes: Population-based cohort studies from the United Kingdom and Hong Kong

Zixuan Wang[1], Kenneth KC Man[1,2], Tiantian Ma[1], Louise M Howard[3], Li Wei[1], Ian CK Wong[1,2] and Ruth Brauer[1]

[1]UCL School of Pharmacy, London, United Kingdom; [2]The University of Hong Kong, Hong Kong, China; [3]King's College London, London, United Kingdom

Background: Previous studies suggested that the use of antipsychotic medications during pregnancy is associated with an increased risk of gestational diabetes mellitus (GDM) in mothers. However, the evidence is still insufficient, especially for specific antipsychotic classes.

Objectives: To investigate whether exposure to antipsychotic medications during pregnancy is associated with GDM.

Methods: Two population-based cohort studies were conducted using data from the United Kingdom The Health Improvement Network (THIN) and Hong Kong Clinical Data Analysis and Reporting System (CDARS). Nondiabetic women who received any type of antipsychotic before their first pregnancy were included in our study cohorts. The exposed group comprised women who continued using antipsychotics from the start of pregnancy to delivery, while the comparison group included women who used antipsychotics before the start of pregnancy but no longer used any antipsychotics during pregnancy. GDM was identified using maternal clinician reported GDM and/or GDM diagnosis. Odds ratios (ORs) with a 95% confidence interval (CI) were evaluated separately in THIN and CDARS to access the association between antipsychotic use during pregnancy and GDM using Propensity Score fine stratification weighting.

Results: 3,114 first pregnancies (2,351 in THIN and 763 in CDARS) were included in the two cohorts. 1,197 women (38.44%) continued their use of antipsychotics in pregnancy and 91 developed GDM. No association was found between the continued use of antipsychotics in pregnancy and GDM in both databases. The adjusted OR (aOR) of GDM in the exposure group was 0.73 (95% CI: 0.43-1.25) in THIN and 1.30 (95% CI: 0.85-1.97) in CDARS compared with the comparator group. Additionally, stratified results showed there is no robust evidence to demonstrate the association between the risk of GDM

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and prenatal continued use of typical antipsychotics (THIN: aOR 0.57, 95% CI 0.20-1.65; CDARS: aOR 1.32, 95% CI 0.81-2.15) or atypical antipsychotics (THIN: aOR 0.98, 95% CI: 0.51-1.88; CDARS: aOR 1.25, 95% CI: 0.72-2.19).

Conclusions: Our results suggest no evidence of an increased risk of GDM in women who continue using antipsychotics during pregnancy compared to women who stop. Women should not stop their regular antipsychotics prescriptions in pregnancy due to the fear of GDM.

3791 | Automated large-scale signal detection in pregnant women from medico-administrative databases and scientific literature

Romain Demailly, Sylvie Escolano, Pascale Tubert-Bitter and Ismaïl Ahmed
INSERM, Paris, France

Background: There is a lack of information on adverse drug reactions during pregnancy. In this context, medico-administrative databases are particularly valuable resources for pharmacovigilance purposes. We recently proposed a new signal detection method based on the disease risk score, the p-value relative decrease (p-RD), and showed its interest in prematurity drug inducer identification. Furthermore, the scientific literature is a promising tool for the annotation of generated signals.

Objectives: (i) To explore large scale potential of p-RD method applied to 20 pathologies (ii) To annotate generated signals by automated quantification of scientific literature knowledge

Methods: Using the French national health insurance database permanent sample, we included all pregnancies identified by ICD-10 codes in the hospitalization database between 01/01/2009 and 31/12/2016. Thirteen pregnancy specific and 7 general pathologies were identified by ICD-10 codes. Drug exposures were divided into trimesters. The disease risk score was estimated by machine learning with boosting on a subset of variables selected with the Bross formula. The threshold for the p-RD was 0.20. Concerning the automatic analysis of the scientific literature from MEDLINE, we used MeSH keywords to build queries targeting drug induced pathologies. The number of articles to define a positive annotation was determined according to a criterion based on the binomial distribution with a threshold of 0.20.

Results: Depending on the pathologies considered, up to 596 drugs and 58 525 pregnancies were investigated. The p-RD generated between 0 (for oligohydramnios) and 12 signals (for prematurity) for a total of 69. Most of the signals referred to exposures during the trimester preceding the end of pregnancy. The relevance of the generated signals depended on several factors such as : (i) the prevalence of the pathology (ii) the frequency of drug exposure (iii) the quality of the disease risk score and (iv) the specificity of the ICD-10 codes to qualify the pathology. Concerning the annotation of signals by the automated MeSH keyword extraction method, 42 % of the signals were supported by the literature.

Conclusions: Combining p-RD with automated scientific literature mining is a promising tool to perform signal detection for pregnancy on medico-administrative data. Resulting annotation can help prioritize and document generated signals in the evaluation process.

3844 | Utilization patterns of valproate in women with epilepsy before and during pregnancy

Nadine Wentzell[1], Tania Schink[1], Anna Julia Witzleb[1] and Ulrike Haug[1,2]
[1]*Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany*; [2]*Faculty of Human and Health Sciences, University of Bremen, Bremen, Germany*

Background: Valproate is very effective in the treatment of epilepsy, but especially during the first trimester of pregnancy it increases the risk for congenital malformations and developmental disorders in the child. Due to the teratogenic effect, the European Medicines Agency strengthened the warnings in 2014. Considering the potential of (unplanned) pregnancy, valproate should no longer be prescribed to women of childbearing age unless other treatments were ineffective or not tolerated. Despite the warnings, women may be treated with valproate before or during pregnancy.

Objectives: To examine the patterns regarding utilization of valproate and other antiepileptic drugs in women with epilepsy before and during pregnancy.

Methods: Based on data from the German Pharmacoepidemiological Research Database (GePaRD; health claims data covering 17% of the German population), we selected pregnancies i) beginning between 2014 and 2016, ii) in women with at least one epilepsy diagnosis in the year before the beginning of pregnancy, iii) at least one valproate dispensation any time before or during pregnancy, and iv) at least three years of observation before the beginning of pregnancy.

Results: We identified 454 pregnancies (89% live births, 8% induced abortions) in 430 women with epilepsy beginning between 2014 and 2016. In 357 (79%) pregnancies, valproate was only dispensed before pregnancy and the last valproate dispensation was in median 1414 days before pregnancy. Of these, 208 (58%) had at least one dispensation of another AED during pregnancy. In 97 pregnancies there was at least one valproate dispensation during pregnancy, in 77% in the first trimester (89% live births, 11% induced abortions) and in 81% after the first pregnancy-related visit (=when the pregnancy was assumed to be known to the woman and the prescribing physician). In 45% of pregnancies with valproate dispensation there was no dispensation of another AED within ≥3 years before pregnancy.

Conclusions: In the majority of our cohort (pregnant women with epilepsy and ≥1 valproate dispensation any time before or during pregnancy), valproate was only dispensed well before pregnancy. However, there was still a relevant number where valproate was dispensed during pregnancy and in particular, during the first trimester and after the pregnancy was diagnosed. In nearly half of these pregnancies other antiepileptic drugs had not been used within at least 3 years before pregnancy.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3851 | Ciprofloxacin in first trimester and adverse pregnancy outcomes: A danish nationwide cohort study

Mia Nørgaard[1] and Jon Trærup Andersen[1,2]
[1]Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark; [2]University of Copenhagen, Copenhagen, Denmark

Background: Ciprofloxacin is a highly effective broad-spectrum antibiotic belonging to the quinolones. It is listed on the World Health Organization (WHO) List of Essential Medicines and is among the most used antibiotics. Toxicological animal studies exposed to quinolones have shown possible teratogenic and postnatal adverse effects. However, regarding human pregnancy studies, the evidence is still sparse and not conclusive. Therefore, avoiding exposure during pregnancy are recommended, until safety has been further elucidated.
Objectives: To investigate the risk of spontaneous abortion and major congenital malformations during first trimester exposure.
Methods: A nationwide register-based cohort study in the period between 1997-2016 was conducted. Data on registered pregnancies were obtained from the Medical Birth Registry and the National Hospital Registry. All pregnancies exposed to ciprofloxacin in first trimester were identified by the Danish National Prescription Registry. We used Cox regression to estimate the hazard of spontaneous abortion and logistic regression to estimate the risk of major congenital malformation.
Results: We identified a total of 1,650,649 pregnancies. Of these, 2,050 pregnancies were exposed to ciprofloxacin. The hazard ratio of spontaneous abortion was 0.82 (95% CI: 0.69-0.97). As for the risk of major congenital malformation the odds ratio was 1.00 (95% CI: 0.74-1.40). In addition, no significant increased risks were observed in the subanalyses of the specific subgroups of major congenital malformation.
Conclusions: This is by far the largest cohort study ever published. Based on this comprehensive investigation we concluded that there was no increased risk of either spontaneous abortion or major congenital malformation. Consequently, in situations where ciprofloxacin treatment is required, sub-optimal therapy and treatment failure in pregnancy can be avoided.

3882 | A prospective study of pregravid injectable contraceptive use and spontaneous abortion

Jennifer J. Yland[1], Elizabeth E. Hatch[1], Kenneth J. Rothman[2,1] and Lauren A. Wise[1]
[1]Boston University School of Public Health, Boston, MA; [2]Research Triangle Institute, Research Triangle Park, NC

Background: Injectable contraceptives contain substantially higher dosages of progestin compared with other contraceptive methods, and pregravid use of injectables has been associated with preterm birth. However, little is known about the association of injectable contraceptive use with other perinatal outcomes.
Objectives: To evaluate the association between pregravid use of injectable contraceptives and spontaneous abortion (SAB).
Methods: We conducted a prospective cohort study of 5,879 pregnant women participating in the Pregnancy Online Study (PRESTO) during 2013-2019. PRESTO is a preconception cohort of North American couples aged 21-45 years. At baseline, participants reported the contraceptive method they most recently used. Among couples who conceived, we identified SAB using data from follow-up questionnaires. We fit Cox proportional hazards models using gestational weeks as the time scale. We compared use of injectables with 1) all other forms of contraception and 2) barrier methods only. We then stratified our analyses by time from discontinuation to conception. Models were adjusted for potential confounders.
Results: Only 96 (1.6%) women reported using injectables as their last form of contraception. Women who used injectable contraceptives were more likely to smoke at baseline; to have lower education and household income; to report higher intakes of alcohol, caffeine, and sugar-sweetened beverages; to be parous; and to have diagnoses of endometriosis or polycystic ovarian syndrome (PCOS). The incidence rate of SAB was 1.53-fold higher among users of injectable contraceptives compared with users of barrier methods, after adjusting for demographic factors, lifestyle characteristics, and medical history (95% confidence interval (CI): 0.98, 2.39). We observed an adjusted incidence rate ratio (aIRR) of 1.48 when comparing users of injectable contraceptives with users of all other contraceptive methods (CI: 0.98, 2.26). Among women who discontinued contraception ≤ 6 months before conception, the aIRR was 3.55 (CI: 1.74, 7.26) comparing injectable users with all others. However, among women who discontinued contraception > 6 months before conception, the aIRR was 1.09 (CI: 0.65, 1.84) comparing injectable users with all others.
Conclusions: Women who used injectable contraceptives had a higher rate of SAB compared with those who used barrier methods, although our findings were imprecise. These findings, though preliminary, raise concerns about possible adverse effects of injectable contraceptives on reproductive and perinatal health.

3901 | Pregnancy research within a global distributed network of health systems: A feasibility study

Jeffrey S. Brown[1], Megan Hiley[1], Kimberly Barrett[1], Jennifer Stacey[2] and Mayura Shinde[1]
[1]Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; [2]TriNetX, Cambridge, MA

Background: Data on the safety of medications use during pregnancy is often dependent on post-market research using patient registries, administrative claims data or electronic health records (EHR). Unfortunately, many studies fail to achieve the sample size needed to generate robust information for patients and decision-makers.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: Study the feasibility of using a global network of EHR data sources to conduct post-market surveillance of medical product use and safety in pregnancy.

Methods: We investigated data availability and completeness, and query capabilities to support medical product exposure during pregnancy research within the TriNetX (TNX) platform. The TNX Live Network has 70+ healthcare organizations with real-time EHR data available for aggregated querying via the TNX platform; most sites have both inpatient and outpatient EHR data. For this pilot we investigated the number of 1) live births identified via diagnosis codes, 2) possible pregnancies identified with a broad set of terms indicative of a pregnancy (e.g., amniocentesis), and 3) pregnancies identified through positive laboratory results (human chorionic gonadotropin level over 25 U/L). We identified patients with selected conditions (multiple sclerosis (MS), Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriasis, and irritable bowel disease, Crohn's disease and ulcerative colitis (IBD-C-UC)) in the year before live birth as well as those who used of selected drug classes (antihypertensive, antidepressants, and antihyperlipidemic agents) in the 40 weeks before live birth.

Results: We queried the TNX network on February 10, 2020, identifying over 1.5 million live births, including ~162k live births in the last year and 16k in the three months before the query date. Over 3.8 million possible pregnancies (versus live births) were found. 620k women had a positive pregnancy test result. About 2/3 of patients with live births had 2+ years of observation time available, and about 1/2 had 3 + years of observation time. Among all live births we identified approximately 1,800 MS, 3,700 SLE, 2,500 RA, 2,200 psoriasis, and 10,400 IBD-C-UC patients. Among live births in the last year, 5.4% had evidence of antidepressant use, 4.3% with antihypertensive use, and 0.2% with antihyperlipidemic use.

Conclusions: The TNX network quickly and efficiently identified live births, possible pregnancies, and positive pregnancy test results, along with assessment of clinical conditions and use of medications. Future work should assess data completeness and availability, especially for sites with both inpatient and outpatient EHRs.

3909 | Breastfeeding, postpartum timing, and indicators of difficult insertion among women with intrauterine devices

Mary Anthony[1], Darios Getahun[2], Mary Anne Armstrong[3], Jennifer Gatz[4], Alex Asiimwe[5], Catherine Saltus[6], Susan Reed[7], Jiaxiao Shi[2], Amy Alabaster[3], Michael Fassett[2], Jeffrey Peipert[8], Juliane Schoendorf[9], Shannon Hunter[1], Jinyi Wang[1], Giulia Chillemi[3] and Mary E. Ritchey[1]

[1]RTI Health Solutions, Research Triangle Park, NC; [2]Kaiser Permanente Southern California, Pasadena, CA; [3]Kaiser Permanente Northern California, Oakland, CA; [4]Regenstrief Institute, Indianapolis, IN; [5]Bayer AG, Berlin, Germany; [6]RTI Health Solutions, Waltham, MA; [7]Kaiser Permanente Washington, University of Washington, Seattle, Seattle, WA; [8]Indiana University School of Medicine, Indianapolis, IN; [9]Bayer OY, Espoo, Finland

Background: United States obstetrical and gynecology professional organizations recommend that women consider use of intrauterine devices (IUDs) beginning in the immediate postpartum (PP) time period to prevent unintended pregnancy. However, little has been published about the potential for difficult IUD insertion at different times PP with or without breastfeeding.

Objectives: To estimate the prevalence of indicators of difficult IUD insertion across three PP categories and among women who were and were not breastfeeding at the time of IUD insertion.

Methods: Women receiving IUDs were identified at four sites (three Kaiser Permanente sites—Northern California, Southern California, and Washington—and Regenstrief Institute, Indiana). Structured data (National Drug Codes, ICD-9/10 diagnosis and procedure codes, Current Procedural Terminology codes) and unstructured data (clinical notes) were used to identify breastfeeding and PP status as well as five indicators of potentially difficult insertion (cervical dilation, ultrasound guidance, paracervical block, misoprostol, and provider note for "difficult insertion"). The proportion of women with these indicators was assessed by breastfeeding status (yes/no) and time PP (≤ 6 weeks, 6 to ≤ 14 weeks, 14 to ≤ 52 weeks) at IUD insertion.

Results: Among 97,824 women with IUD insertions who delivered in the past year, 20.5% were ≤ 6 weeks PP, 57.3% were 6 to ≤ 14 weeks, and 22.2% were 14 to ≤ 52 weeks; 65.6% were breastfeeding, 31.3% were not, and 3.1% had unknown breastfeeding status. The proportion of women with an indicator of difficult IUD insertion was 2.6% among those breastfeeding and 3.5% among those not breastfeeding. The proportion of these indicators differed by time PP (≤ 6 weeks: 2.9%, 6 to ≤ 14 weeks: 2.2%, and 14 to ≤ 52 weeks: 5.3%). The most common difficult insertion indicator was paracervical block (4.5% of insertions). Women in the 14 to ≤ 52 weeks PP category had the highest proportion of all five difficult insertion indicators relative to the two earlier PP categories. Women who were not breastfeeding at IUD insertion had a higher proportion of all five indicators compared with those who were breastfeeding.

Conclusions: The prevalence of indicators of difficult insertions was lower for women with IUDs inserted at earlier PP time periods and among women who were breastfeeding. Thus, IUD insertions in earlier PP time periods and while women are breastfeeding do not appear to be more difficult insertions. Concomitant procedures may be performed with later PP insertions and should be assessed in future research.

3938 | Trajectories of prescription opioid utilization during pregnancy among pre-pregnancy chronic users and risk of neonatal abstinence syndrome

Loreen Straub[1], Krista F. Huybrechts[1], Sonia Hernandez-Diaz[2], Yanmin Zhu[1], Seanna Vine[1], Rishi J. Desai[1], Kathryn J. Gray[3] and Brian T. Bateman[1,4]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Harvard T.H. Chan School of Public Health, Boston, MA; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Neonatal abstinence syndrome (NAS) is a serious complication experienced by the newborn after prenatal exposure to psychotropic substances, mainly opioids, yet little is known about the impact of dose, duration and timing of exposure on the risk of NAS.

Objectives: To characterize patterns of prescription opioid use during pregnancy among chronic opioid users prior to pregnancy using group-based trajectory models, and to evaluate the association between individual trajectory groups and the risk of NAS.

Methods: Data for this study were derived from a cohort of pregnant women and their liveborn infants nested in the 2000-2014 nationwide Medicaid Analytic eXtract. The cohort was restricted to women with >=1 opioid dispensing in each of the 3 months prior to pregnancy (chronic opioid users), with >= 1 dispensing during pregnancy. We assessed dosage of prescription opioid exposure (measured in morphine milligram equivalents (MME)) within bi-weekly gestational age intervals and created group-based trajectory models to identify distinct opioid use patterns during pregnancy. Risk of NAS was assessed for each individual trajectory.

Results: We identified 435 cases of NAS among the 18,454 included pregnancies, corresponding to an absolute risk of 23.6 per 1,000 deliveries (95% confidence interval 21.4 - 25.8). Women were grouped into 6 distinct trajectories based on their opioid use patterns during pregnancy. The 6 identified groups corresponded to: (1) use at very low doses (mean MME across 2 week-intervals (mMME)=27.8; N=7,005 pregnancies), (2) use at low doses (mMME=151.0; N=4,555), (3) initially low doses which decreased to very low doses by the second half of pregnancy (mMME in first 12 weeks=295.0 vs. mMME in last 12 weeks=9.1; N=2,944), (4) use at moderate doses (mMME=420,2; N=2,373), (5) initially high doses which decreased to low doses in late pregnancy (mMME in first 12 weeks=684.5 vs. mMME in last 12 weeks=66.3; N=947), and (6) use at very high doses (mean MME=839.0; N=630). Absolute risk of NAS per 1,000 pregnancies was 7.0 (5.0 - 8.9) for those in group 1, 23.3 (18.9 - 27.7) in group 2, 14.3 (10.0 - 18.6) in group 3, 54.4 (45.2 - 63.5) in group 4, 41.2 (28.5 - 53.9) in group 5, and 111.1 (86.5 - 135.7) in group 6.

Conclusions: Trajectory models can be useful to understand distinct patterns of prescription opioid use during pregnancy and seem to track well with expected risk of NAS as higher and more recent exposure is associated with higher risk of NAS. This appears to be a promising approach in creating relevant groupings for evaluating the risk of opioid exposure in pregnancy.

3963 | Pregnancy pharmacoepidemiology: How often are key methodological data elements reported in publications?

Andrea V. Margulis[1], Alison T. Kawai[2], Mary Anthony[3] and Elena Rivero-Ferrer[1]

[1]RTI Health Solutions, Barcelona, Spain; [2]RTI Health Solutions, Waltham, MA; [3]RTI Health Solutions, Research Triangle Park, NC

Background: Key pieces of information that are needed to fully understand studies on drug utilization and safety in pregnancy are sometimes omitted from publications—e.g., the decision to include multiple pregnancies in the study population, which can impact the prevalence of some outcomes.

Objectives: To identify key methodological data elements necessary for understanding observational pharmacoepidemiological research in pregnancy and quantify the proportion of studies that report these key data elements in a sample of published studies.

Methods: Key methodological data elements were identified from the pregnancy pharmacoepidemiology draft guidelines from the Food and Drug Administration (2019) and European Medicines Agency (2020), relevant literature, and subject matter knowledge: pregnancy start (date, clinical entity, source of information); mother-infant, birth certificate, and other linkages (process, success rate); unit of analysis; and whether non-live births and fetuses with various anomalies were included in the study population.

We searched PubMed for observational studies on drug utilization or safety during pregnancy published in 2015-2018. After screening of titles and abstracts, full-text screening was conducted. For quality control, extracted data were confirmed against the publication. We estimated the prevalence of reporting of key data elements across studies.

Results: The PubMed search retrieved 1,981 entries; data were extracted from a convenience sample of 50 eligible papers. Of these, 6% were published in epidemiology or pharmacoepidemiology journals; 16% were drug utilization studies, and 84% were safety studies. The mean study size was 109,060 subjects. Thirty-three percent of studies reported the method for determining pregnancy start; 59% reported whether the study population included multiple pregnancies; 44%, more than 1 pregnancy per woman; 60%, fetuses with major congenital malformations; 15%, fetuses with chromosomal abnormalities; and 85%, non-live births. Of the 5 studies that sought mother-infant linkage, 40% described the process, reported the linkage success rate, and specified which outcomes had been ascertained from maternal or infant files. Among the studies with more than one pregnancy/offspring per woman, 27% reported methods to address sibling correlation.

Conclusions: In this sample of pregnancy pharmacoepidemiology studies, completeness of methods reporting can be improved. A pregnancy-specific checklist would help to increase transparency in the dissemination of study results.

3977 | Periconceptional prescription opioid and alcohol or tobacco use and birth defect risk

Kayla N. Anderson, Elizabeth C. Ailes, Cheryl S. Broussard, Clark H. Denny and Jennita Reefhuis

National Center on Birth Defects and Developmental Disabilities, U.S. Centers for Disease Control and Prevention, Atlanta, GA

Background: Data examining the effect of periconceptional prescription opioid and alcohol and/or tobacco use on risks for birth defects are limited.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To examine associations between periconceptional prescription opioid medication use concomitantly with alcohol and/or tobacco and specific birth defects.

Methods: We used data from the National Birth Defects Prevention Study, a U.S. multicenter, population-based case-control study (1997-2011). Cases were from active birth defects surveillance systems; controls were liveborn infants without major defects. Using multivariable logistic regression to examine associations between prescription opioid medication use and birth defects with ≥4 exposed cases, we calculated adjusted odds ratios (aORs) and 95% confidence intervals (CIs) to compare women who were exposed periconceptionally (month before conception through the third pregnancy month) to (a) opioids (but not alcohol or tobacco) (n=297 case, 91 control), relative to women who did not use opioids, alcohol, and tobacco three months before or during pregnancy; (b) opioids and alcohol only (n=193 case, 53 control), relative to periconceptional opioid-only exposed women; (c) opioids and tobacco only (n=156 case, 44 control), relative to periconceptional opioid-only exposed women; (d) opioids, alcohol, and tobacco (n=167 case, 48 control), relative to periconceptional opioid-only exposed women. Opioid, alcohol, and tobacco use was defined as any use. Models were, as needed, adjusted for maternal age, race, education, obesity, previous livebirths, and folic acid use. Given small samples for some defects, we considered aORs ≥2.0 with a 95% CI lower bound ≥0.8 as meaningfully elevated.

Results: Compared to women not using prescription opioids, alcohol, or tobacco, periconceptional prescription opioid use was associated with 5 of 28 examined defects. Periconceptional opioid and alcohol use was associated with cleft lip with or without (w/wo) cleft palate (aOR: 2.2, 95% CI: 1.0-4.9), anorectal atresia/stenosis (aOR: 2.1, 95% CI: 0.8-6.0), and gastroschisis (aOR: 2.8, 95% CI: 1.0-7.9). Periconceptional opioid and tobacco use was associated with cleft palate (aOR: 2.6, 95% CI: 1.0-6.7) and cleft lip w/wo cleft palate (aOR: 2.7, 95% CI: 1.3-5.8); opioid, alcohol, and tobacco use was associated with cleft palate (aOR: 3.0, 95% CI: 1.2-7.8), cleft lip w/wo cleft palate (aOR: 3.1, 95% CI: 1.4-6.6), diaphragmatic hernia (aOR: 3.0, 95% CI: 0.8-11.5), and gastroschisis (aOR: 2.1; 95% CI: 0.8-5.4).

Conclusions: Alcohol and/or tobacco use, beyond opioid use only, was associated with increased risk for some birth defects.

4000 | Antiemetic medication use during pregnancy: A drug utilization study among 777,991 pregnancies in Norway

Marleen van Gelder[1] and Hedvig Nordeng[2]

[1]Radboud University Medical Center, Nijmegen, Netherlands; [2]University of Oslo, Oslo, Norway

Background: Nausea and vomiting of pregnancy (NVP) is very common, affecting up to 70% of pregnant women. Although NVP is not associated with adverse pregnancy outcomes, it has a major impact on daily life functioning and quality of life. Given the recent recommendation from the European Medicines Agency to avoid use of ondansetron during the first trimester, insight into how NVP is pharmacologically managed is necessary.

Objectives: To determine treatment patterns and management of antiemetic medications during pregnancy in Norway, with special focus on the use of ondansetron.

Methods: We conducted a population-based registry study based on data from the Norwegian Prescription Database (NorPD) linked to the Medical Birth Registry of Norway (MBRN) for 777,991 pregnancies from 2005 to 2017. Antiemetic medication use was defined as prescription fills of medications used for NVP according to the Norwegian clinical guidelines during pregnancy. Descriptive analytics and *k*-means clustering were used to determine drug utilization patterns.

Results: Prescription fill rates for any antiemetic medication during pregnancy steadily increased over the study period from 5.3% (95% confidence interval [CI] 5.2-5.5) in 2005 to 10.4% (95% CI 10.1-10.6) in 2017. Among pregnancies with antiemetic medication prescription fills, 61.9% was dispensed metoclopramide, 27.9% meclizine, and 17.4% promethazine; in 16.1%, prescriptions for multiple different antiemetic medications were filled. Prescriptions for ondansetron were filled in 0.3% of pregnancies, increasing from 0.05% in 2004 to 1.0% in 2017, with 77% being filled in the first trimester. Antiemetic medication use during pregnancy was associated with multiparity, non-smoking, and multiple pregnancy, with generally stronger associations observed for pregnancies with ondansetron prescription fills.

Conclusions: We observed a strong increase in the prevalence of prescription fills for antiemetic medication in Norway over the study years. In the overwhelming majority of pregnancies with antiemetic medication fills, NVP was managed with metoclopramide and/or antihistamines, in sharp contrast to the current treatment regimen in the United States.

4162 | Off-label use of domperidone among postpartum women: A multi-database study

Carolina Moriello[1], J. Michael Paterson[2], Pauline Reynier[1], Matthew Dahl[3], Wusiman Aibibula[1], Anat Fisher[4], John-Michael Gamble[5], I Fan Kuo[3], Paul E Ronksley[6], Brandce Winquist[7], Kristian B Filion[8] and the CNODES Investigators[9]

[1]Jewish General Hospital, Montreal, QC, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]University of Manitoba, Winnipeg, MB, Canada; [4]University of British Columbia, Vancouver, BC, Canada; [5]University of Waterloo, Kitchener, ON, Canada; [6]University of Calgary, Calgary, AB, Canada; [7]University of Saskatchewan, Saskatoon, SK, Canada; [8]McGill University, Montreal, QC, Canada; [9]Canadian Network for Observational Drug Effect Studies (CNODES), Montreal, QC, Canada

Background: Domperidone is frequently used off-label to promote lactation among postpartum women. However, trends in use in this population remain poorly understood. Furthermore, the impact of the Health Canada advisories regarding ventricular tachyarrhythmia (VT) and sudden cardiac death (SCD) on its use among postpartum

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

women remains unknown, and limited safety data are available in this population.

Objectives: To describe domperidone use among postpartum women in Canada, to evaluate the impact of the Health Canada advisories on prescribing patterns, and to describe the association between domperidone use and SCD/VT among postpartum women.

Methods: On behalf of the Canadian Network for Observational Drug Effect Studies (CNODES), we conducted a multi-database cohort study of pregnant women with live births between 2004 and 2017 using the administrative health databases from five Canadian provinces (British Columbia [BC], Alberta, Manitoba, Saskatchewan, and Ontario). We described domperidone use in the six months postpartum and assessed the impact of the 2012 and 2015 Health Canada advisories on prescribing practices via interrupted time series analysis. We also estimated crude rates of VT/SCD.

Results: We included 1,190,987 pregnancies that resulted in live births from 801,959 distinct women. Postpartum domperidone use increased substantially over time, increasing from 7% in 2003-05 to 12% in 2015-17. Variations in domperidone use existed across provinces, ranging from 2% in Saskatchewan to 10% in BC in 2003-05 and 6% in Manitoba to 14% in BC in 2015-18. The 2012 advisory was followed by decreased prescribing overall (an immediate drop of 11.5 initiators/100,000 person-days at the time of the advisory and a post-advisory reduction in the slope of 0.8 initiators/100,000 person-days per quarter). Similar trends were observed for prescriptions of doses >30mg/day and of durations >14 days. The 2015 advisory had a more modest impact on prescribing practices overall, with no immediate drop and a smaller change in slope observed (-1.0 initiators/100,000 person-days per quarter). Crude analysis suggests that domperidone may be associated with an increased rate of VT/SCD (rate ratio: 2.01; 95% CI: 0.47, 8.60; rate difference per 10,000 person-years: 0.37; 95% CI: -0.67, 1.41).

Conclusions: Domperidone use among postpartum women increased substantially between 2004 and 2017, though prescribing trends were attenuated following Health Canada advisories. The absolute rate of VT/SCD is very low in this population, suggesting that any increased risk is likely to have a minimal impact at the population level.

4211 | New-generation antiepileptic drugs during pregnancy and the risk of attention-deficit hyperactivity disorder

Christine Vaccaro[1], Emily Czaplinski[1], Ahmad Shakeri[2] and Sherif Eltonsy[1]

[1]University of Manitoba, Winnipeg, MB, Canada; [2]University of Toronto, Toronto, ON, Canada

Background: Maternal antiepileptic drug (AED) use during pregnancy is associated with increased risk of cognitive adverse effects among the offspring. As new-generation AEDs continue to enter the market, evidence on the safety of these newer AEDs during pregnancy is scarce. To date, there are no published reviews summarizing the evidence of new-generation AED exposure in utero and the development of attention deficit-hyperactivity disorder (ADHD) in the offspring.

Objectives: The objective of this scoping review was to summarize the available evidence on the risk of ADHD after maternal exposure to new-generation AEDs during pregnancy.

Methods: Using PRISMA Guidelines for scoping reviews we searched electronic databases (EMBASE and MEDLINE) for articles published between January 1, 1988, and July 22, 2019. New-generation AEDs were defined as any AED marketed after 1988. ADHD was defined as attention-deficit hyperactivity disorder, hyperkinetic disorder, hyperkinesis, or conduct disorder.

Results: Out of 805 screened articles, a total of 8 publications met the inclusion criteria (7 cohort studies and 1 systematic review). Across the studies, the sample size of pregnant women exposed to AEDs ranged from 1 to 1383. AED monotherapy was examined in 6 studies (mostly lamotrigine), while only 2 studies examined AED polytherapy. The included studies reported a range of adjusted relative risks, from 0.84 [0.59-1.19] to 1.63 [0.41-6.06].

Conclusions: Lamotrigine monotherapy holds the largest body of evidence among new-generation AEDs, with most studies concluding no significant risk of ADHD among the offspring. However, the current available evidence is scarce, with several methodological limitations in the published studies. Disentangling the effect of AEDs from epilepsy itself and examining polytherapy's that include new and old generation AEDs are challenges that merit additional investigations. Further comparative safety studies with longer follow-up periods and large sample sizes are needed to accurately quantify the true impact of new-generation AEDs exposure during pregnancy and ADHD.

4218 | Identification of pregnancies and pregnancy outcomes using real-world healthcare data

Clara Weil[1], Ran Rotem[1,2], Anushua Sinha[3], Gabriel Chodick[1,4], Wei Wang[3], Shawna Calhoun[3], Efraim Bilavsky[5,4] and Morgan A Marks[3]

[1]Maccabi Healthcare Services, Tel Aviv, Israel; [2]Harvard T.H. Chan School of Public Health, Cambridge, MA; [3]Merck & Co., Inc., Kenilworth, NJ; [4]Tel Aviv University, Tel Aviv, Israel; [5]Schneider Children's Medical Center, Petah Tikva, Israel

Background: Administrative healthcare data are increasingly being used to identify pregnancies in pharmacoepidemiology research. Ascertainment of the timing of conception, gestation duration, and birth outcomes remain key methodological challenges.

Objectives: To identify pregnancies and pregnancy outcomes and estimate pregnancy rates using real-world healthcare data in Israel.

Methods: A retrospective closed cohort study was performed using electronic healthcare data collected from Maccabi Healthcare Services, a 2.3-million-member healthcare provider in Israel. Women 18-44 years old on July 1st, 2013, with no indication of pregnancy in the prior six months, were followed through 31/12/2018 for their first pregnancy event (PE; pregnancy occurrence and outcome). PEs were identified using diagnostic, procedural, laboratory and pharmacy

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

data, documented last menstrual cycle, and linked gestational age data (Israeli Ministry of Health). Birth outcome was assessed through linkage of maternal and infant data and identification of relevant diagnostic and procedural codes, and was defined as linked live births (LLB), non-linked live births (NLB), stillbirths (SB) and abortions (Ab; spontaneous/elective/unspecified). The incidence rate (per 1000 person-year) of first PE, 12/24-month cumulative % of first PE, and frequency of PE outcomes were calculated.

Results: The cohort included 298,903 women (median age=32y; IQR=24-39y). There were 82,683 PEs identified, with an incidence rate of 76.8 (95% CI:76.3-77.3) per 1000 person-year. Among women aged 18-24y, 25-34y and 35-44y, rates were 71.1 (70.1-72.0), 170.5 (168.9-172.0) and 30.4 (30.0-30.9), respectively. Estimated % PE at 12 and 24 months was 9.7% and 16.9%. Twelve-month cumulative incidence of PE was 6.2%, 18.7% and 5.3% among women aged 18-24y, 25-34y and 35-44y, respectively. Women with 1 or ≥4 prior children had a higher incidence of PE as compared to women with no children (P<0.05). LLB, NLB, SB and Ab accounted for 81.9%, 1.4%, 0.02% and 9.5% of PE outcomes, with 7.2% of PEs having uncertain outcome.

Conclusions: Using electronic healthcare data collected from a large Israeli healthcare system, the estimated incidence of pregnancy events was consistent with national reports of LB and Ab, and most pregnancy outcomes were ascertained. While further investigation into the impact of early pregnancy loss on these estimates is needed in this cohort, databases such as this represent important resources for pregnancy-related pharmacoepidemiologic investigations.

4248 | Maternal use of antidepressant medication in pregnancy and risk of gestational diabetes mellitus

Angela Lupattelli[1], Francesco Barone-Adesi[2] and Hedvig Nordeng[1]
[1]*University of Oslo, Oslo, Norway;* [2]*University of Eastern Piedmont, Novara, Italy*

Background: Data about the safety of prenatal antidepressant exposure on maternal risk of gestational diabetes mellitus (GDM) is limited.

Objectives: This study sought to examine whether antidepressant exposure during early-mid pregnancy is associated with increased risks of GDM in women, according to antidepressant affinity to the histamine-1 (H1) receptor.

Methods: Data originate from the nation-wide, prospective Norwegian Mother and Child Cohort Study (MoBa) conducted in 1999-2008, linked to the national Medical Birth Registry. The study included women with depressive/anxiety disorders during and/or six months prior to pregnancy. Women medicated with antidepressants with low affinity to the H_1-receptor (group 1, including all selective-serotonin reuptake inhibitors, venlafaxine, duloxetine and clomipramine) or high affinity (group 2, including amitriptyline, trimipramine, maprotiline, nortriptyline, mianserin, mirtazapine, doxepin and nefazodone) were compared to non-medicated in pregnancy. We fit crude and weighted modified Poisson regression models using inverse probability of treatment weighting (IPTW) to control for confounding. In a secondary analysis, we modelled exposure as continuous variable, based on antidepressant-specific binding affinity for the H_1-receptor.

Results: We included 6647 pregnancies, whereof 84 (1.3%) were diagnosed with GDM. Overall, 12.3% and 1.2% of the pregnancies were within women taking antidepressants of group 1 or 2, respectively. The risk of GDM was greater in group 2 antidepressant-exposed women (3.9%, 95% Confidence Interval (CI): 1.2-11.7%), relative to non-medicated (1.3%, 95% CI: 1.0-1.6%) or group 1 antidepressant-exposed women (1.1%, 95% CI: 0.6-2.1%), although the CI were overlapping between the three groups. In the analysis using IPTW to control for confounding, there was no evidence for an association between antidepressant group 1 exposure in early-mid pregnancy and risk of GDM (Relative Risk (RR): 0.91, 95% (CI): 0.41-2.02). There was a weak evidence for an association between GDM and antidepressant group 2 exposure (RR: 3.60, 95% CI: 1.90-11.94), albeit the CI was wide and based on three cases among exposed.

Conclusions: Gestational use of antidepressants with low H_1-receptor affinity does not pose a substantial risk of GDM in women with depressive/anxiety disorders in pregnancy, compared to no-use. Although the role chance and unmeasured confounding cannot be ruled out, this maternal risk seems heightened following exposure to high H_1-receptor affinity antidepressants specifically.

4250 | Treatment of preterm labor with ritodrine in Taiwan, 2002-2016

Chih-Wan Lin[1,2], K. Arnold Chan[3], Yi-Yung Chen[4], Wei-I Huang[1], Pi-Hui Chao[1], Wen-Wen Chen[1] and Fei-Yuan Hsiao[2,5,6]
[1]*Taiwan Drug Relief Foundation, Taipei, Taiwan;* [2]*Graduate Institute of Clinical Pharmacy, National Taiwan University, Taipei, Taiwan;* [3]*Health Data Research Center, National Taiwan University, Taipei, Taiwan;* [4]*Division of High-risk Pregnancy, Department of Obstetrics & Gynecology, Mackay Memorial Hospital, Taipei, Taiwan;* [5]*School of Pharmacy, National Taiwan University, Taipei, Taiwan;* [6]*Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan*

Background: Many countries have imposed different restrictions on the use of ritodrine for managing preterm labor due to its risk of adverse maternal cardiovascular events. Some countries withdrawal all forms of ritodrine while others only kept intravenous form of ritodrine for emergency use. In Taiwan, the Food and Drug Administration has issued a safety regulation (label revision to add precautions to adverse maternal cardiovascular events) in 2014 for all forms of ritodrine instead.

Objectives: We aimed to examine the usage patterns of ritodrine and to explore whether the label revisions issued by Taiwan Food and Drug Administration in 2014 affected the use of ritodrine.

Methods: By linking Taiwan's National Birth Certificate Application Database with National Health Insurance Research Database, pregnancies greater than 20 weeks were included as study population. The proportion of pregnant women receiving ritodrine and the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

number of ritodrine prescriptions were assessed annually, and the characteristics of pregnant women and their prescribers were explored. Stratified analyses were further conducted to those who used oral or intravenous form of ritodrine.

Results: From 2002 through 2016, 2,721,420 pregnancies were identified, and a significant shift toward older maternal age was found (≥35 years: 7.5% in 2002 vs. 23.1% in 2016). Prevalence of pregnant women using ritodrine increased from 16.1% in 2002 to 30.6% in 2016. Increased use of oral ritodrine contributed to this upward trend (pregnant women only using oral therapy: 11.0% in 2002 vs. 25.6% in 2016). Cumulative number of oral prescriptions during individual pregnancy also slightly increased (women receiving 1, 2, or ≥ 3 prescriptions during pregnancy: 68.2%, 19.1%, and 12.7% in 2002 vs. 60.2%, 21.0%, and 18.8% in 2016). Among 107,853 oral prescriptions in 2016, 85.8% were from the outpatient settings. In contrast, prevalence of pregnant women ever receiving ritodrine injections was highest in 2010 (6.3%) and decreased thereafter (5.0% in 2016). Cumulative days of intravenous ritodrine therapy during pregnancy remained stable (median: 3 days), with 27.3% of women receiving ≥7 days in 2016.

Conclusions: The use of oral ritodrine in Taiwan increased over time, even after the label revision, and these prescriptions were mainly from outpatient clinics where regular monitoring of cardiopulmonary function is challenging. On the contrary, the use of injectable ritodrine in Taiwan declined in recent years, but a considerable proportion of pregnant women still received treatment longer than recommended (≥ 2-3 days). Reinforcing safety regulations and communications may be warranted.

4251 | Use of beta-adrenergic agonist ritodrine in tocolysis and risk of maternal cardiovascular events: A nationwide nested case-control study

Chih-Wan Lin[1,2], K. Arnold Chan[3], Yi-Yung Chen[4], Wei-I Huang[1], Pi-Hui Chao[1], Wen-Wen Chen[1] and Fei-Yuan Hsiao[2,5,6]

[1]Taiwan Drug Relief Foundation, Taipei, Taiwan; [2]Graduate Institute of Clinical Pharmacy, National Taiwan University, Taipei, Taiwan; [3]Health Data Research Center, National Taiwan University, Taipei, Taiwan; [4]Division of High-risk Pregnancy, Department of Obstetrics & Gynecology, Mackay Memorial Hospital, Taipei, Taiwan; [5]School of Pharmacy, National Taiwan University, Taipei, Taiwan; [6]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

Background: Accumulating evidence from the US and Europe has revealed the risk of life-threatening maternal cardiovascular events associated with the use of beta-adrenergic agonists for managing preterm labor. However, real-world data on this topic in Asian population were scarce, especially on the risk of different cardiovascular events related to different routes of beta-adrenergic agonists administration.

Objectives: We aimed to examine the risk of maternal cardiovascular events associated with ritodrine, the predominant beta-adrenergic agonist used among pregnant women in Taiwan.

Methods: By linking Taiwan's National Birth Certificate Application Database with National Health Insurance Research Database, pregnancies over 20 weeks of gestation between 2002 and 2015 were identified as study cohort. Three separate nested case-control analyses were conducted to evaluate the risk of pulmonary edema, heart failure, and arrhythmia associated with prior drug use. Cases were defined by inpatient diagnoses of cardiovascular events plus prescriptions of specific medications, and controls were identified using incidence density sampling (1:10 matched by gestation day, age, year of delivery, and multiplicity). Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression models adjusted for comorbidities and concomitant tocolytic agents.

Results: Among 2,536,527 pregnancies, 256 cases of pulmonary edema, 272 cases of heart failure, and 333 cases of arrhythmia were identified. Compared with no exposure during pregnancy, exposure to ritodrine were associated with increased risks of pulmonary edema (aOR 2.99 [95% CI 2.13-4.18]), arrhythmia (aOR 1.77 [1.34-2.34]), and heart failure (aOR 1.37 [0.98-1.91]). When classifying exposure by administration route, exposure only to oral ritodrine shows modest risk of pulmonary edema (aOR 1.59 [1.05-2.42]), arrhythmia (aOR 1.63 [1.21-2.19]), and heart failure (aOR 1.04 [0.71-1.51]), whereas exposure to injectable ritodrine shows greater risk (corresponding aORs: 11.41 [7.01-18.58], 2.97 [1.72-5.13], 3.69 [2.11-6.48]). Sensitivity analyses varying the identification periods of study cohort and the definition of cardiovascular events yielded similar results.

Conclusions: Pregnant women receiving intravenous ritodrine therapy are at pronounced cardiovascular risks and should be intensively monitored. Nevertheless, healthcare professionals should still be aware of the lower but considerable cardiovascular risks during oral ritodrine therapy.

4257 | Anti-thyroid drug use during the first trimester of pregnancy and the risk of birth defects in offspring: Systematic review and meta-analysis of observational studies with methodological considerations

Daniel R. Morales[1,2], Lionel Fonkwen[1] and Hedvig Nordeng[3]

[1]University of Dundee, Dundee, United Kingdom; [2]University of Southern Denmark, Odense, Denmark; [3]University of Oslo, Oslo, Norway

Background: Maternal anti-thyroid drug (ATD) use during the first trimester of pregnancy has been associated with an increased risk of birth defects in offspring. Uncertainty remains on the size of this risk and how it compares to untreated hyperthyroidism. Furthermore limitations of previous studies exist that have meta-analysed data from observational studies as if they had come from randomized controlled trials.

Objectives: 1) To quantify the association between first trimester ATD use and birth defects, 2) to assess the association between untreated hyperthyroidism and birth defects and 3) examine the impact of correctly meta-analyzing data from observational studies.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: A systematic reivew of Medline and Embase were conducted to identify all observational studies examining exposure to ATD during the first trimester of pregnancy and risk of birth defects. Data were extracted on study characteristics, confounders, adjusted effect estimates and different comparator groups examined. Effect estimates were pooled using a random-effects generic inverse variance method of analysis and reported incidence used to calculate absolute risk.

Results: Seven cohort studies and one case-control study (involving 6212322 pregnancies and 388976 birth defects) were identified. Compared to unexposed women, the association between ATD use during the first trimester of pregnancy and birth defects in offspring was: adjusted risk ratio [aRR] 1.16 95% CI 1.08-1.25 for propylthyoruacil (PTU); aRR 1.28 95% CI 1.06-1.54 for methimazole/carbimazole (MMI/CMZ); and aRR 1.51, 95% CI 1.16-1.97 for both MMI/CMZ and PTU; and aRR 1.15 95%CI 1.02-1.29 for untreated hyperthyroidism. The risk of major birth defects per 1000 live births was: 9.6 for PTU; 16.8 for MMI/CMZ; 30.6 for both MMI/CMZ and PTU; and 9.0 for untreated hyperthyroidism.

Conclusions: When appropriately analysed the risk of birth defects associated with ATD use in the first trimester of pregnancy is attenuated. Although still elevated, the risk of birth defects is smallest with PTU compared to use of MMI/CMZ and may be similar to that of untreated hyperthyroidism. Meta-analyzing observational studies as if data come from RCTs results in residual confounding, and should be avoided.

4260 | Association between antidepressant treatment during pregnancy and postnatal self-harm ideation: A cross-sectional, multinational study using the Edinburgh postnatal depression scale

Jennifer Vallee, Yih Wong, Eline Mannino and Angela Lupattelli
University of Oslo, Oslo, Norway

Background: Self-harm ideation, that is having thoughts of inflicting injuries on oneself without fatal intent, is not uncommon in perinatal women with psychiatric disorders. Currently, there is limited evidence on the effectiveness of antidepressant medication in pregnancy, or as a preventive treatment of postnatal mental illness, including self-harm ideation.

Objectives: To provide a preliminary estimate of the association between antidepressant use during pregnancy and self-harm ideation in the postnatal period.

Methods: We used data from the Multinational Medication Use in Pregnancy Study, a web-based study collecting data on more than 8000 pregnancies in 12 European countries via an electronic questionnaire. The sample included 187 postnatal women who had reported a psychiatric disorder during pregnancy. Our outcome measure was frequency of self-harm ideation ('often/sometimes', 'hardly ever', 'never'), as measured by the Edinburgh Postnatal Depression Scale item 10. Antidepressant medication use in pregnancy was our exposure variable, as self-reported by women. We fit logistic models with a composite weight comprised of an inverse probability of treatment weighting (IPTW) multiplied by the sampling weight. The IPTW was generated using a propensity score.

Results: Overall, 52% women were medicated with an antidepressant during pregnancy and 34% reported self-harm ideation as often/sometimes or hardly ever. Women medicated with antidepressants in pregnancy had a lower odds of reporting hardly ever self-harm ideation than the non-medicated counterpart (weighted Odds Ratio (OR): 0.39, 95% Confidence Interval (CI): 0.13, 1.14). This treatment did not seem to have a preventive effect on reporting sometimes/often self-harm ideation (weighted OR: 1.96, 95% CI: 0.61, 6.25).

Conclusions: Although longitudinal studies are needed to confirm or refute this association, women treated with antidepressant medication during pregnancy were less likely to report occasional postnatal self-harm ideation. This association is not evident for more frequent self-harm ideation. This analysis is only a first step in providing evidence to inform psychiatric disorder treatment decisions for pregnant women in relation to their mental health during the entire perinatal period.

4261 | Antihypertensive treatment during pregnancy: An evaluation of the German embryotox database

Maria Hoeltzenbein, Evelin Beck, Anne-Katrin Fietz, Marjann Schäfer, Katarina Dathe and Christof Schaefer
Charité – Universitätsmedizin Berlin, Berlin, Germany

Background: There are essential differences in treatment of chronic hypertension between non-pregnant and pregnant women. RAS (renin-angiotensin-system) inhibitors should be avoided in pregnancy because of well-known fetotoxicity. In addition, there is an ongoing debate about possible teratogenic effects after treatment with antihypertensive (AH) drugs during the first trimester leading to uncertainties in treatment of hypertension in early pregnancy.

Objectives: As 40% of pregnancies are unplanned, the aim of the study was to assess and characterize use of AH drugs at conception and to evaluate treatment changes during pregnancy.

Methods: This observational study includes 3175 requests to Embryotox from 2000-2017 related to use of AH drugs in prospectively ascertained pregnancies. We analyzed treatment pattern including discontinuation or switching of AHs during pregnancy and number of concomitant AHs in the subgroup of 1152 pregnancies with chronic hypertension and completed follow-up.

Results: The most frequently used AHs at conception in prospective pregnancies (n=3175) were beta-blockers (64%), followed by RAS inhibitors (29%) and diuretics (14%). In 51% of pregnancies AHs were used in monotherapy, in 29% two AHs and in 20% 3 or more AHs were used concomitantly. 73% of woman taking AH drugs at conception had chronic hypertension. In the subgroup of pregnancies with chronic hypertension and completed follow-up (n= 1152), nearly 40 %

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of women used RAS-inhibitors at conception. For these, the number of concomitant antihypertensive drugs was higher than for women without RAS-inhibitors. In general, changes in AH treatment during pregnancy resulted in a reduction of the number of AH used concomitantly and a shift towards the drugs of choice like methyldopa and metoprolol. Most changes were reported in the first and early second trimester. However, continued exposure with RAS-inhibitors occurred mostly when pregnancy was not recognized.

Conclusions: Treatment changes from non-recommended to recommended AH during first trimester reflect the proportion of unplanned pregnancies. In patients on fetotoxic medication it is of utmost importance to recognize pregnancy early enough for switching to safe treatment. In contrast to administrative databases, our data enable detailed assessment of exposure to AH drugs and treatment changes during pregnancy as a prerequisite for analysis of adverse pregnancy outcomes possibly related to drug exposure.

This work was performed with financial support from the German Ministry of Health (BMG) and the German Federal Institute for Drugs and Medical Devices (BfArM).

4324 | perinatal use of triptans and other migraine medications: A nationwide drug utilisation study

Fatima Tauqeer[1], Mollie Wood[2,1], Sarah Hjorth[1], Angela Lupattelli[1] and Hedvig Nordeng[1,3]

[1]University of Oslo, Oslo, Norway; [2]T.H. Chan School of Public Health, Boston, MA; [3]Norwegian Institute of Public Health, Oslo, Norway

Background: Around 25% of women with migraine continue to experience migraine in pregnancy, and maybe in need of migraine medications. Women on preventive migraine therapy are in most cases recommended to stop this treatment and to rely on acute migraine medications such as triptans when needed in pregnancy. Knowledge about drug utilization patterns among women with migraine remains limited. Such studies could potentially enhance our understanding of migraine and co-morbidities management in pregnancy.

Objectives: To investigate utilisation patterns of triptans alongside analgesics, antinauseants and migraine preventive drugs before, during and after pregnancy in a population of women using triptans prior to pregnancy.

Methods: Data were obtained by linking the Medical Birth Registry of Norway to the Norwegian Prescription Database from 2006 to 2017. We included women with at least one filled prescription of a triptan in the year before pregnancy, as a proxy for migraine. Women were classified as continuers if they filled at least one triptan prescription from last menstrual period date to delivery, and discontinuers if no prescription was filled during pregnancy. Participant characteristics and extent of concomitant filled prescriptions of analgesics, antinauseants and preventive drugs were examined in continuers and discontinuers. Further, cumulative daily defined doses, number of prescriptions filled, and proportion of days covered were studied. Overuse of migraine medications in pregnancy was investigated using Lorenz curves and calculating the 1% top users (Gini coefficients).

Results: Of 21478 included triptan users, 21.7% were continuers while 78.3% were discontinuers. The continuers were slightly older, more often primiparous, had more obstetric comorbidities, and more often smoked before pregnancy. The use of analgesics (41.6% vs. 18.4%), antinauseants (40.0% vs. 30.0%) and preventive drugs (antidepressants, 17.2% vs. 9.0%, beta-blockers, 7.7% vs 4.0%, antiepileptics, 3.6% vs 1.6%) was higher among the continuers than discontinuers. Of the continuers, 2.3% had triptan overuse during pregnancy. In this sample, 21.0% were on preventive treatments before pregnancy. Triptan overuse occurred more commonly among these women than those without prior preventive therapy (4.8% vs. 1.6%).

Conclusions: Triptan continuers in pregnancy have higher comorbidity and a higher degree of co-medication with prescribed analgesics and antinauseants than discontinuers. Overuse of triptan occurs in pregnancy. These results indicate that there is room for improvement of migraine management in pregnancy.

4401 | Chronic prescription opioid use in pregnancy in the United States

Loreen Straub[1], Krista F Huybrechts[1], Sonia Hernandez-Diaz[2], Yanmin Zhu[1], Seanna Vine[1], Rishi J. Desai[1], Kathryn J. Gray[3] and Brian T. Bateman[1,4]

[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard T.H. Chan School of Public Health, Boston, MA; [3]Brigham and Women's Hospital, Boston, MA; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background: Given the risks for both mother and child associated with prolonged prenatal opioid exposure, understanding chronic opioid utilization in pregnancy is important for informing clinical guidelines, health services, and research needed to address this issue.

Objectives: To evaluate patterns of chronic opioid use during pregnancy using nationwide data from Medicaid and commercial insurance beneficiaries.

Methods: Pregnancy cohorts were identified using data from the Medicaid Analytical eXtract 2008-2014, which includes Medicaid beneficiaries, and the IBM Health MarketScan Research Database 2008-2015, which contains commercial insurance beneficiaries. Dispensing of opioids was evaluated using claims from filled prescriptions. Two different definitions of chronic opioid use were employed: ≥ 90 days' supply of prescription opioids during pregnancy and ≥ 180 days' supply. Patient characteristics including medical and obstetric conditions of women on chronic opioid therapy during pregnancy were assessed. Variations in the prevalence of chronic opioid therapy were described by geographic region and over time.

Results: The cohorts consisted of 975,169 pregnancies in Medicaid-insured women and 1,037,599 in commercially insured women. Among

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

these, 1.50% of Medicaid beneficiaries and 0.32% of commercial insurance beneficiaries filled prescriptions for ≥90 days' supply; 0.78% of Medicaid beneficiaries and 0.17% of commercial insurance beneficiaries filled prescriptions for ≥180 days' supply. The prevalence of chronic opioid therapy approximately doubled in Medicaid beneficiaries from 2008 to 2014, while it remained relatively stable for commercial insurance beneficiaries. For both populations, the most commonly prescribed opioid for chronic opioid therapy was hydrocodone, followed by oxycodone and tramadol. Opioid indications commonly associated with chronic opioid use were back/neck pain (recorded in >60% of chronic users in both cohorts), abdominal/pelvic pain, musculoskeletal pain and migraine (each with a prevalence of ≥25% among chronic users). Substantial regional variation was observed, with chronic opioid use more common in the South and several states reporting a frequency in excess of 30 per 1000 pregnancies in Medicaid-insured patients.

Conclusions: Chronic opioid therapy in pregnancy is prevalent, with a marked disparity between Medicaid and commercially insured patients. These findings call for the development of guidelines on safe chronic pain management during pregnancy, including the utilization of non-opioid analgesics and non-pharmacologic approaches that are tailored for pregnancy.

4403 | Multi-stakeholder consortium on the safety of asthma medications during pregnancy and lactation

Christina D. Chambers[1], Jerry A. Krishnan[2] and Michael Schatz[3]
[1]*University of California San Diego, La Jolla, CA;* [2]*University of Illinois at Chicago, Chicago, IL;* [3]*Kaiser Permanente Southern California, San Diego, CA*

Background: Asthma is the most common potentially serious medical problem to occur during pregnancy and lactation. The revised U.S. Food and Drug Administration (FDA) Prescribing Information highlights a critical need for high quality human safety data to inform the use of asthma medications during pregnancy and lactation.

Objectives: A group of key stakeholders across multiple relevant disciplines were invited to take part in an effort to prioritize, strategize and mobilize action steps to fill important gaps in knowledge regarding asthma medication safety in pregnancy and lactation. The objectives of this effort were to 1) review existing evidence, 2) understand the role of randomized clinical trials and real-world evidence from observational studies in formulating clinical guideline recommendations, 3) discuss studies underway to fill evidence gaps, and 4) define steps needed to address stakeholder-defined evidence gaps.

Methods: On November 8, 2019, key stakeholder representatives convened for a one-day conference at FDA. Stakeholder representatives included academic researchers, obstetric/maternal-fetal medicine specialists, regulatory and other federal agencies, and others representing the pharmaceutical industry, clinicians, patient advocacy groups, and patients.

Results: The stakeholders identified substantial gaps in the literature on the safety of asthma medications used during pregnancy and lactation and prioritized strategies to fill those gaps. Short-term action steps included linking data from existing complementary study designs (U.S. and international claims data, single drug pregnancy registries, case-control studies, and coordinated systematic data systems). Long-term action steps included creating an asthma disease registry, incorporating the disease registry into electronic health record systems, and coordinating care across disciplines. The stakeholders also prioritized establishing new infrastructures/collaborations to perform research in pregnant and lactating women and to include patient perspectives throughout the process.

Conclusions: As a result of this conference, a multi-stakeholder consortium has been developed. In order to address the evidence gaps, and aid in populating product labels with data that informs clinical decision making, the consortium has developed a plan to systematically obtain necessary data in the most efficient and timely manner. As a future goal, the design and activities of this consortium can serve as a model for addressing similar gaps in knowledge about pregnancy and lactation medication safety in other therapeutic areas.

4406 | Validation of claims-based algorithms to identify specific major congenital malformations

Loreen Straub[1], Krista F. Huybrechts[1], Sonia Hernandez-Diaz[2], Yanmin Zhu[1], Kathryn J. Gray[3] and Brian T. Bateman[1,4]
[1]*Brigham and Women's Hospital, Boston, MA;* [2]*Harvard T.H. Chan School of Public Health, Boston, MA;* [3]*Brigham and Women's Hospital, Boston, MA;* [4]*Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Background: While healthcare utilization databases are increasingly used to evaluate drug safety in pregnancy, the validity of such research relies heavily on the quality of recorded diagnostic information.

Objectives: The aim of this study was to validate claims-based algorithms for identifying selected congenital malformations using hospital medical records.

Methods: This validation was conducted as part of a study on the impact of prenatal opioid exposure on major congenital malformations, including Ventricular Septal Defects (VSD), Secundum Atrial Septal Defects/Patent Foramen Ovale (ASD/PFO), Neural Tube Defects (NTD), Club Foot, and Oral Clefts. Using the Partners Research Patient Data Registry - a centralized clinical data warehouse of patients receiving care at affiliated hospitals in the Boston area - we identified infants born between 2008 and 2014 who had a malformation of interest based on algorithms using ICD-9 and CPT diagnostic and procedural codes. To avoid inclusion of rule-out diagnosis or coding errors, a malformation was considered present if a diagnosis was recorded on ≥ 2 different dates, or if only recorded on 1 date,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

associated with a specific therapeutic procedure or surgery code or infant death shortly after birth. Since we cannot distinguish ASD from prematurity-related PFO based on ICD-9 codes, we excluded ASD/PFO diagnoses in preterm infants and required diagnostic codes to persist for ≥ 6 weeks. Medical charts of algorithm-identified cases were independently reviewed by two physicians to assess the presence of the outcome. Reviewer pairs were asked to reevaluate cases together whenever there was disagreement. Positive predictive values (PPVs) and 95% confidence intervals (CIs) were calculated, using medical charts as the gold standard.

Results: 50 randomly sampled cases were considered for each outcome, except for NTD for which all 24 cases identified in the database were reviewed. Medical charts were missing for 1 case of VSD, 1 case of NTD and 1 case of Oral Cleft. All 49 retrievable VSDs were classified as true positives (PPV=100%; 95% CI=91%, 100%). All 50 ASD/PFO cases were either true ASDs (N=18) or PFOs (N=32), resulting in a PPV of 100% (91%, 100%). PPVs were 74% (51%, 89%) for NTD, 98% (88%, 100%) for Club Foot and 96% (85%, 99%) for Oral Cleft.

Conclusions: With PPVs ranging between 74% and 100%, claims-based algorithms with stringent identification criteria can accurately classify the selected malformations in infants, suggesting that healthcare utilization data can be used for epidemiologic research on such outcomes.

4414 | Validity of claims-based algorithms to identify developmental disorders in children

Loreen Straub[1], Sonia Hernandez-Diaz[2], Brian T. Bateman[1,3], Yanmin Zhu[1], Kathryn J. Gray[4] and Krista F. Huybrechts[1]

[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard T.H. Chan School of Public Health, Boston, MA; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [4]Brigham and Women's Hospital, Boston, MA

Background: While prospective cohort studies are well-suited to document subtle manifestations of neurodevelopmental disorders (NDD) in children, they frequently lack power to evaluate the risk of less common but more clinically consequential conditions, such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and specific developmental delays, following *in utero* exposure to medications. To study these more severe conditions, large cohorts with long-term follow-up are needed. Healthcare utilization databases are increasingly being used for this purpose, yet the validity of NDD diagnoses based on medical claims is unclear.

Objectives: To validate claim-based algorithms for identifying NDDs using hospital records as the reference.

Methods: We developed claims-based algorithms for ASD, ADHD, behavioral disorder, speech/language disorder, intellectual disability (ID), learning disability (LD) and developmental coordination disorder (DCD). To avoid inclusion of rule-out diagnoses or coding errors, ICD-9 CM diagnoses were required to be recorded on ≥2 distinct days, at an age when the disorder of interest is expected to present itself. 50 algorithm-derived cases for each outcome were randomly sampled from a clinical data registry of patients receiving care at hospitals in Boston and their medical records were independently reviewed by two physicians to adjudicate the diagnosis. Reviewer pairs reevaluated cases for which there was initial disagreement. Positive predictive values (PPVs) and 95% confidence intervals (CIs) were calculated.

Results: The PPV was 0.94 (95% CI: 0.83 - 0.99) for ASD, 0.88 (0.76 - 0.95) for ADHD, 0.92 (0.81 - 0.98) for behavioral disorder, 0.98 (0.89 - 1.00) for speech/language disorder, 0.82 (0.69 - 0.91) for ID, and 0.98 (0.89 - 1.00) for LD. Nineteen algorithm-based cases of DCD were identified as severe coordination disorders with functional impairment, with a PPV of 0.38 (0.25 - 0.53). When expanding the definition to include visual-motor integration deficits and coordination deficits that did not persist throughout childhood (14 additional cases), the PPV increased to 0.66 (0.51 - 0.78). Of the remaining 17 cases, 12 were in children with coordination issues due to an underlying medical condition (e.g., cerebral palsy and visual impairment) and 5 in children with no DCD but ≥1 other severe NDD.

Conclusions: For most outcomes considered, PPVs were high, ranging between 0.82 and 0.98, suggesting that claims-based algorithms can validly be used to study NDDs in children. Further restriction criteria are needed to improve identification of true DCD cases.

4428 | Epidemiology of prenatal opioid use and associated maternal characteristics in Ontario, Canada

Andi Camden[1,2,3], Teresa To[1,4,3], Joel G Ray[1,5], Tara Gomes[1,5], Li Bai[3], Kinwah Fung[3] and Astrid Guttmann[1,2,3]

[1]University of Toronto, Toronto, ON, Canada; [2]Hospital for Sick Children, Toronto, ON, Canada; [3]ICES, Toronto, ON, Canada; [4]Hospital for Sick Children, Toronto, ON, Canada; [5]St. Michael's Hospital, Toronto, ON, Canada

Background: Confounding by indication is a critical threat to validity in research designed to understand the health effects of prenatal opioid exposure; however, there is a lack of knowledge of the epidemiology of maternal opioid use and influence of specific maternal characteristics associated with type of opioid therapy.

Objectives: 1) To estimate the rate of any opioid use and type of opioid use during pregnancy among in Ontario from 2014-2017; 2) To describe concurrent maternal factors by type of opioid therapy used in pregnancy.

Methods: Population-based cohort study of all hospital live and still births from 2014-2017 in Ontario, Canada. Multiple linked population-based health administrative databases were used to identify maternal opioid use (prescription and health care visits) and maternal demographic, social, pharmacologic and medical characteristics. We estimated the rate of maternal opioid use among all births

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and examined maternal characteristics by opioid therapy during pregnancy.

Results: The rate of opioid use during pregnancy was 56 per 1000 births. Decreasing opioid analgesic use influenced the trend in overall prescription opioid rate; however, other indicators of opioid use (i.e. neonatal abstinence syndrome (NAS), opioid-related health care) remained stable. Maternal characteristics varied by opioid type and duration. There was a dose-response trend in vulnerability among women with 90+ days of analgesic use during pregnancy contrasted with 30+ days and intermittent use, with respective rates of 48%, 39%, 23% for social assistance, 21%, 15%, 10% for 3+ previous live births and 74%, 71%, 53% for high medical comorbidities. Similar social vulnerabilities were noted between women with chronic analgesic use and buprenorphine with respective rates of 48% vs. 47% for social assistance, 21% vs. 28% for 3+ previous live births and 4% vs. 6% for being a victim of violence.

Conclusions: We provide the first population-based estimates of type of opioid use in pregnancy in Canada across multiple opioid therapies in a single study. Findings suggest heterogeneity within and between opioid therapy and identify high-risk groups and important confounders, which can inform studies on the impact of multiple maternal risk factors and opioid use on perinatal and child health outcomes.

4432 | Factors associated with losses to follow-up in pregnancy exposure registries

Deborah Covington, Kristin Veley, Rebecca Buus and Paige Churchill
Evidera, Wilmington, NC

Background: To provide quality data and robust results, pregnancy registries must obtain outcome data by reducing losses to follow-up (LTFU). Numerous factors can affect LTFU including enrollment and data collection processes, number of follow-ups, and length of follow-up.

Objectives: To review LTFU rates and associated factors in prospective pregnancy registries.

Methods: We searched PubMed using the term "pregnancy registry" to identify pregnancy registry publications. We reviewed the abstracts of all 284 identified publications, excluded 166 that did not report data for prospective pregnancy registries (e.g., retrospective studies, case reports, review), yielding a total of 118 publications for 34 registries (80.5% had multiple publications). From the most recent publication for each registry, we extracted data, including registry start year, LTFU rate, number of follow-ups, length of follow-up, enrollment and data collection methods. Six registries did not report LTFU data.

Results: For registries with LTFU data, the mean LTFU rate was 16.4% (median: 12.1%; range: 0-43.7%). Registry enrollment and data collection methods differed between registries: for 11 registries, only healthcare providers (HCPs) enrolled women and provided data; for 17 registries, women self-enrolled and provided data in addition to HCPs. For registries with enrollment and data collection by HCPs only, the mean LTFU rate was 28.3% (median: 31.7%; range: 2.0-43.7%). For 90.9% of these registries, HCPs reported de-identified, anonymous data at pregnancy outcome with no infant follow-up. For registries in which women self-enrolled and provided data that was supplemented by multiple HCPs (prescriber, Ob, Pediatrician) or medical records, the mean LTFU rate was 8.7% (median: 5.3%; range: 0-36.1%), and 88.2% of these registries had multiple follow-ups until the infant was 12 months old. The median start year was 1996 (range: 1984-2006) for HCP-only registries and 2004 (range 1982-2010) for registries in which women self-enrolled.

Conclusions: Registries in which HCPs enrolled women and provided data tended to start earlier and had higher LTFU rates than registries in which women self-enrolled and provided data. Paradoxically, HCP-only registries had fewer follow-ups and shorter lengths of follow-up. However, they primarily collected de-identified data, likely accounting for the higher LTFU rates. Registries in which women self-enrolled and directly participated had more reporters and follow-ups and longer lengths of follow-up. Results suggest a key to reducing LTFU could be direct engagement of women in the enrollment and data collection process.

4446 | Opioid use after vaginal birth and the risk of serious opioid-related events: Is there a safe dose?

Andrew D. Wiese[1], Sarah S. Osmundson[1], Ed Mitchel, Jr.[1], Margaret Adgent[1], Sharon Phillips[2], Stephen W. Patrick[3], Marie Griffin[1] and Carlos G. Grijalva[1]
[1]VUMC, Nashville, TN;[2]VUMC, Nashville, TN;[3]VUMC, Nashville, TN

Background: In the US, postpartum opioid use is common among opioid naïve women with uncomplicated vaginal birth. Studies suggest that such use may increase risk of serious opioid-related events, yet it is unclear whether there is a safe opioid dose for prescribing post-discharge after vaginal birth.

Objectives: To examine the association between dose of the first prescribed opioid after discharge for a vaginal birth and the risk of serious opioid-related events.

Methods: We identified opioid naïve women enrolled in Tennessee Medicaid with a vaginal birth (2007-2015). Pharmacy prescription fill data characterized opioids filled within 5 days after discharge. Mothers were followed from day 5 post-discharge to the earliest of end of follow-up (365 d), enrollment loss, non-opioid-related death, or a serious opioid-related event (persistent opioid use, methadone/buprenorphine fill, opioid use disorder (OUD) diagnosis, overdose or opioid-related death). We modeled adjusted hazard ratios (aHRs) and 95% confidence intervals (CI) for the outcome according to the dose [morphine milligram equivalents (MME)] of the first opioid prescription accounting for delivery complications, multiple deliveries, and comorbidities and medication use during pregnancy. Secondary analyses examined the risk of serious opioid-related events excluding persistent opioid use.

Results: Over half of women (53%) with a vaginal birth (n=162259) filled an opioid prescription within 5 days of discharge. Serious-opioid related event rates were higher for women that filled an opioid prescription at any dose [range of four categories: 2.8-3.4 per 100 person-years (py)] compared to women that did not fill a prescription (1.4

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

per 100 py). We observed an elevated risk for serious opioid-related events among women filling a post-discharge opioid prescription across all dose categories, compared to filling none [<100 MME aHR: 1.5 (CI: 1.4-1.7); 100-149 MME aHR: 1.4 (CI: 1.3-1.6); 150-199 MME aHR: 1.4 (CI: 1.3-1.6) and >=200 MME aHR: 1.6 (CI: 1.5-1.8)]. When opioid dose was modeled as a continuous variable, a significant risk of serious-opioid related events was observed at any opioid dose >0 MME. In secondary analyses excluding persistent use (62% of events), women filling an initial postpartum opioid prescription >=200 MME had a significantly higher risk of a methadone/buprenorphine fill, OUD, overdose or opioid-related death [aHR: 1.3 (95% CI: 1.1-1.5)].

Conclusions: Filling an initial opioid prescription following vaginal birth was associated with an increased risk of serious opioid-related events among opioid naïve women, regardless of dose.

4471 | Prevalence of outcomes in pregnancy registries versus general population

Kristin Veley, Deborah Covington, Ronna Chan and Paige Churchill
PPD/Evidera, Wilmington, NC

Background: Recent regulatory guidance suggests that pregnancy registries should assess multiple pregnancy and infant outcomes, including major congenital malformation (MCM), spontaneous abortion (SAB), stillbirth, elective termination, small for gestational age (SGA), preterm birth, and postnatal growth deficiency.

Objectives: To compare the prevalence rates of outcomes observed in prospective pregnancy registries to those observed in the general population.

Methods: Registries were identified from multiple sources: FDA website, ENCePP, clinicaltrials.gov, PubMed. The search identified 34 pregnancy registries with published results, 31 (91%) of which collected data in the US and were included in analyses. Of these, 14 (45%) also collected data in other countries. US general population data were available from CDC Metropolitan Atlanta Congenital Defects Program, US National Vital Statistics System, and CDC Abortion Surveillance System. The most recent published data were extracted and analyzed descriptively. The mean year of publication was 2012 (range: 1992-2019) for pregnancy registries and 2016 (range: 2007-2019) for population data.

Results: Registry-observed rates of MCM (mean: 5.14%; median: 4.63%; range: 2.27-10.4%) and preterm birth (mean: 11.5%; median: 9.63%; range: 3.26-35.7%) were slightly higher than population rates (2.78% and 8.24%, respectively). Registry-observed rates of stillbirth (mean: 0.464%; median: 0.382%; range: 0-2.02%) and postnatal growth deficiency (mean: 10.8%; median: 13.6%; range: 4.65-14.3%) were similar to population rates (0.596% and 10%, respectively). Registry-observed rates of SAB (mean: 8.65%; median 7.80%; range: 1.34-30.1%) and SGA (mean: 6.98%; median: 7.34%; range: 0.362-16.1%) were slightly lower than population rates (13.4% and 10%, respectively); and the registry-observed rate of elective termination (mean: 4.07%; median: 2.54%; range: 0-21.4%) was substantially lower than the population rate of 18.6%.

Conclusions: These findings suggest that prevalence rates of outcomes observed in pregnancy registries differ from those observed in the US general population. Lower registry-observed rates of SAB and elective termination could be attributed the nature, timing, and ascertainment of these outcomes. Women who intend to terminate their pregnancies are not likely to enroll in pregnancy registries; and women who enroll may do so after the risk of early fetal loss has passed. Elevated rates of other outcomes (e.g., MCM and preterm birth) could be attributed to the exposure or disease being studied.

4476 | Sample size calculations for pregnancy registries: Improving accuracy

Kristin Veley, Deborah Covington, Rebecca Buus, Ronna Chan and Paige Churchill
PPD/Evidera, Wilmington, NC

Background: The primary objective of most pregnancy registries is to estimate the risk of major congenital malformation (MCM). To achieve this objective, a sufficient number of pregnant women must be enrolled in the registry. The prevalence of MCM in the general population, which is reported among live births, is used to inform sample size calculations. To extrapolate from live births to pregnant women for enrollment targets, it is necessary to make assumptions regarding live birth rate.

Objectives: To compare the live birth rate observed in prospective pregnancy registries to that of the US general population. To explore the potential effects of using registry-observed live birth rate rather than general population live birth rate to estimate enrollment targets.

Methods: Thirty-four pregnancy registries with published results were identified from multiple sources: FDA website, ENCePP, clinicaltrials.gov, PubMed. Of these, 100% reported data on live births, 91% collected data in the US, and 41% collected data in the US as well as other countries. Live birth rate data in the US general population were available from CDC National Vital Statistics System. The most recent published data were extracted from each data source and analyzed descriptively.

Results: The live birth rate observed in these registries (mean: 87.3%; median: 88.6%; range: 65.9-98.9%) was substantially higher than the general population rate of 64.6%. If a registry aimed to detect a 3-fold increased risk of MCM between internal registry cohorts, approximately 600 live births (300 in each cohort) would be needed. Assuming a live birth rate equivalent to the general population (64.6%), approximately 930 pregnant women would need to be enrolled in the registry to produce 600 live births. Assuming a live birth rate of 87.3% (mean registry-observed rate), only 690 pregnant women would need to be enrolled (difference: 240 enrolled women).

Conclusions: The live birth rate observed in pregnancy registries is substantially higher than the rate observed in the general population. This finding could be due to several factors. Women who intend to terminate their pregnancies are not likely to enroll in pregnancy registries; and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

women who enroll may do so after the risk of early fetal loss has passed. When designing a pregnancy registry, the use of registry-observed (rather than general population) live birth rate should be considered to improve the accuracy of enrollment targets. Use of the registry-observed rate will yield lower enrollment targets and, in turn, shorten the enrollment period, reduce costs, and allow for earlier dissemination of study results.

4481 | Neural tube defect risk among infants exposed to opioids during early pregnancy

Denise M. Boudreau[1], Jennifer F. Bobb[1], Gaia Pocobelli[1], T. Craig Cheetham[2], Sascha Dublin[1], Susan Andrade[3], Ladia Albertson-Junkans[4], Marie Griffin[5], De-Kun Lee[6], Marsha A. Raebel[7], Rulin Hechter[2], David H Smith[8], Pam A. Pawloski[9], Darren Toh[10], Darren Toh[10], Lockwood Taylor[11], Wei Hua[12], David Graham[12], Rita Ouellet-Hellstrom[12], Pamela Horn[12], Miriam Dinatale[12], Carrie Ceresa[12], Mat Soukup[12], Yong Ma[12] and James P. Trinidad[12]

[1]Kaiser Permanente Washington, Seattle, WA; [2]Kaiser Permanente Southern California, Pasadena, CA; [3]Meyers Primary Care Institute, Worcester, MA; [4]Kaiser Permanente Washington Health Research Institute, Seattle, WA; [5]Vanderbilt University, Nashville, TN; [6]Kaiser Permanente Northern California, Oakland, CA; [7]Kaiser Permanente Colorado, Denver, CO; [8]Kaiser Permanente Northwest, Portland, OR; [9]Health Partners Institute, Minneapolis, MN; [10]Harvard Pilgrim Healthcare Institute, Boston, MA; [11]IQVIA, Austin, TX;[12]US Food and Drug Administration, Rockville, MD

Background: Opioids cross the placenta, and it is hypothesized that exposure during early pregnancy is a risk factor for neural tube defects (NTDs). Previous studies are limited.

Objectives: To evaluate the risk of NTDs among infants exposed to opioids during early pregnancy.

Methods: We conducted a retrospective cohort study across 9 health systems participating in the Medication Exposure in Pregnancy Risk Evaluation Program. The study population included liveborn singletons 2001-2014 with linked mother-infant electronic healthcare data and birth certificate records. We studied new use of opioids, excluding women with an opioid dispensing from 90 days before their last menstrual period (LMP) to 17 days after. Exposure was defined as an opioid dispensed 18-56 days after LMP. Unexposed births (matched 3:1 on maternal age and site) had no maternal opioids dispensed 90 days before to 56 days after LMP. The main outcome was primary NTDs (i.e., anencephaly, myelomeningocele). The secondary outcome was primary NTDs and post-neurulation defects (e.g. encephalocele). Potential NTDs were validated by medical record review. To estimate risk of NTDs between exposure groups, we applied logistic regression models with propensity score (PS) weighting to control for potential confounders. We conducted sensitivity analyses comparing births exposed during only the 2nd and/or 3rd trimester ("negative control" time window where no causal relation is expected) to those never exposed (no dispensing 90 days before LMP to end of pregnancy).

Results: There were 19,069 opioid-exposed and 57,208 unexposed live births. The number of confirmed primary NTDs and post-neurulation defects was lower than expected - 5 and 3 in the exposed and 6 and 6 in the unexposed. After PS weighting, the covariate distribution was well balanced. The odds ratio (OR) associated with exposure to opioids during 18-56 days LMP was OR=3.0 (95% CI: 0.7-12.7) for primary NTDs and OR=2.3 (0.8-6.7) for primary and postneurulation NTDs. The ORs for both outcomes were also increased for opioid exposure during the 2nd and/or 3rd trimester only (OR=2.4 (0.8-7.6) for primary NTDs and OR=1.6 (0.6-4.4) for primary and post-neurulation defects).

Conclusions: The study results do not support an increased risk of NTDs associated with opioid exposure in early pregnancy. Although the numerically increased odds ratios are in the same magnitude as previous studies, the study is underpowered and there is suggestion of unmeasured confounding. Future studies that are sufficiently powered and consider well-defined methods to assess potential unmeasured confounding are warranted.

4482 | Gestational weight gain following use of antidepressant medication in pregnancy: Results from the Norwegian mother and child cohort study

Angela Lupattelli[1], Francesco Barone-Adesi[2] and Hedvig Nordeng[1]

[1]University of Oslo, Oslo, Norway; [2]University of Eastern Piedmont, Novara, Italy

Background: Excessive gestational weight gain is a major cause of morbidity for both mother and child. Nevertheless, its association to maternal use of antidepressants during pregnancy has been insufficiently studied.

Objectives: The aim of this study is to estimate the association of excessive gestational weight gain with use of antidepressants in pregnancy, according to drug affinity to the histamine-1 (H_1) receptor.

Methods: Data originate from the nation-wide, prospective Norwegian Mother and Child Cohort Study (MoBa) conducted in 1999-2008, linked to the national Medical Birth Registry. The study included women with depressive/anxiety disorders during and/or six months prior to pregnancy. Women medicated with antidepressants with low affinity to the H_1-receptor (group 1, including all selective-serotonin reuptake inhibitors, venlafaxine, duloxetine and clomipramine) or high affinity (group 2, including amitriptyline, trimipramine, maprotiline, nortriptyline, mianserin, mirtazapine, doxepin and nefazodone) were compared to non-medicated in pregnancy. We fit crude and weighted modified Poisson regression, as well as generalized linear models using inverse probability of treatment weighting to control for confounding. In a secondary analysis, we modelled exposure as continuous variable, based on antidepressant-specific binding affinity for the H_1-receptor.

Results: We included 5258 pregnancies with available outcome data. The mean gestational weight-gain in the population was 15.8 Kg (sd: 6.8). Based on maternal body mass index at conception, 2682 (51.0%) of the women were categorized as having gained excessive weight in gestation. Overall, 13.4% and 1.6% of the pregnancies were within women taking antidepressants of group 1 or 2 during pregnancy,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

respectively. Women medicated in pregnancy with antidepressants of either low (weighted Relative Risk (RR): 0.91, 95% Confidence Interval (CI): 0.82-1.01) or high (weighted RR: 0.76, 95% CI: 0.54-1.08) H_1-affinity presented lower risk of excessive weight-gain in pregnancy than non-medicated, albeit the evidence was weak. The difference in mean weight was in the range -2.1 to -0.3 Kg for low and high H_1-affinity antidepressant exposed, respectively, compared to non-medicated.

Conclusions: This study suggests that women with depressive/anxiety disorders who are medicated with antidepressants of either affinity level to the H_1-receptor, present lower risks of excessive weight-gain in pregnancy than the non-medicated, albeit the effect size seems negligible.

4509 | Prevalence of prescription opioid use during pregnancy in 8 U.S Health plans during 2001-2014

Gaia Pocobelli[1], Sascha Dublin[1], Jennifer F Bobb[1], Ladia Albertson-Junkans[1], Susan Andrade[2], T. Craig Cheetham[3], Gladys Salgado[1], Marie Griffin[4], Marsha A. Raebel[5], David Smith[6], De-Kun Li[7], Pamala A. Pawloski[8], Sengwee Toh[9], Lockwood Taylor[10], Wei Hua[10], Pamela Horn[10], James P. Trinidad[10] and Denise M. Boudreau[1]

[1]Kaiser Permanente Washington Health Research Institute, Seattle, WA; [2]Meyers Primary Care Institute, Worcester, MA; [3]Kaiser Permanente Research, Pasadena, CA; [4]Vanderbilt University Medical Center, Nashville, TN; [5]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO; [6]Kaiser Permanente Center for Health Research, Portland, OR; [7]Kaiser Foundation Research Institute, Oakland, CA; [8]Health Partners Institute, Bloomington, MN; [9]Harvard Pilgrim Health Care Institute, Boston, MA; [10]Food and Drug Administration, Washington, DC

Background: Chronic opioid use during pregnancy can lead to neonatal abstinence syndrome. Opioid use during pregnancy has also been associated with risk of congenital malformations. It is therefore important to understand prevalence of prescription opioid use during pregnancy. However, the most recently published data on U.S. prevalence of opioid use during pregnancy is from 2011.

Objectives: To estimate prevalence of prescription opioid use during pregnancy in 8 U.S. health plans during 2001-2014.

Methods: We conducted a cohort study of singleton live birth deliveries during 2001-2014 at 8 health plans (four Kaiser Permanente Health Plans [Washington, northwest U.S., Colorado, and Southern California], Harvard Pilgrim Health Care Institute [Massachusetts], HealthPartners Institute [Minnesota], Fallon Health [Massachusetts] and Tennessee's state Medicaid program). Maternal characteristics and gestational age were ascertained from health plan and/or birth certificate data. Opioid use during pregnancy was ascertained from health plan pharmacy dispensing records. Prevalence of opioid use during pregnancy was calculated for any opioid use, cumulative days of use, and number of dispensings. Results were reported separately for Tennessee Medicaid because the 7 other health plans were primarily commercially-insured populations (only 4% of deliveries in these 7 plans were to Medicaid-insured women).

Results: In the 7 health plans other than Tennessee Medicaid (n=587,093 deliveries), prevalence of prescription opioid use during pregnancy was relatively stable, varying between 9-11% throughout 2001-2014. In Tennessee Medicaid (n=256,724 deliveries), prevalence increased from 29% in 2001 to a peak of 36-37% in 2004-2010, and then declined to 28% in 2014. Use of opioids for ≥30 days during pregnancy was stable at 1% during 2001-2014 in the 7 health plans, and increased from 2% to 7% in Tennessee Medicaid. Receipt of ≥5 opioid dispensings during pregnancy increased in the 7 health plans (from 0.3% to 0.6%) and Tennessee Medicaid (from 3% to 5%) during 2001-2014. Receipt of 1 and 2-4 dispensings was relatively stable (7 health plans) or declined after peaking around 2005 (Tennessee Medicaid).

Conclusions: During 2001-2014, prescription opioid use during pregnancy was appreciably more common in Tennessee Medicaid compared to the 7 other health plans. Although a small percentage of women had opioid use during pregnancy for ≥30 days or ≥5 dispensings, they represent thousands of pregnant women during 2001-2014. Our findings may not be generalizable to other populations.

4526 | Comparing adolescent and adult risk factors for postpartum depression following first birth: A retrospective cohort study

Nakyung Jeon

Chonnam National University, Gwang-ju, Republic of Korea

Background: Risk factors that have been associated with postpartum depression (PPD) are often studied in adult dominant populations. However, some risk factors may have more or less pronounced associations with PPD during adolescence.

Objectives: To compare risk factors for PPD between adolescent and adult women having their first birth

Methods: *Study Setting and Design:* The present study is a retrospective cohort study utilizing electronic health records that is linked to Utah birth and fetal death records through Utah population database (UPDB). Study population includes Utah residents with a first live birth between 2005 and 2015 who received non-emergent care at least once prior to the first birth. *Outcome:* PPD was defined as having a diagnosis code of depression at an in- or outpatient visit occurred within one year after delivery. *Covariates:* Demographic variables included age at delivery, race, ethnicity, education, poverty, marital status; behavioral variables included lack of prenatal visit, tobacco use, recent use of long-acting reversible contraceptive (LARC) method; Clinical variables included gestational diabetes and hypertension, infection during pregnancy, depression or anxiety during pregnancy, cesarean section, no breastfeeding, and preterm birth. *Statistical Analysis:* We stratified the cohort by maternal age less than 20 and 20 or older. Multivariable logistic regression was used to evaluate associations between candidate risk factors and PPD in each stratum. An odds ratio (OR) along with 95% confidence interval (CIs) was calculated for each risk factor.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: Among 61,226 first-time mothers, 10.5% (N=6,435) were under 20 years of age and 89.5% (N=54.791) were adults. The overall PPD prevalence was 4.0% (N=2,475) where the prevalence is higher among adolescents compared to adult mothers (6.1% vs 3.8%). Several factors were more prevalent among adolescents. For example, higher proportions of adolescent mothers had PPD, delayed first prenatal care, tobacco use, infections, and no breastfeeding. In multivariable logistic regressions, we found age, insurance type, tobacco use, LARC use, and history of mood disorder were significant in both cohorts. However, gestational hypertension, cesarean delivery, and no breastfeeding at discharge were significant risk factors only for adult PPD.

Conclusions: The present study successfully identified similarities and dissimilarities in demographic, behavioral, and clinical epidemiology for PPD between adolescent and adult mothers.

4529 | Obstetrical complications and prescription opioid use during pregnancy: using a marginal structural model of time-dependent exposure

Shuang Wang[1], Kristina Ward[1], E Christine Brousseau[2], Egle Bavry[3] and Xuerong Wen[1]

[1]University of Rhode Island, Kingston, RI; [2]Warren Alpert Medical School of Brown University, Providence, RI; [3]University of Florida College of Medicine, Gainesville, FL

Background: Prescription opioids are frequently used for pain management in pregnancy; however, its association with maternal obstetrical complications has not been fully examined.

Objectives: To assess the effect of prescription opioid use during pregnancy on adverse obstetric complications.

Methods: A retrospective cohort study was designed to use the Rhode Island Medicaid claims data linked to vital statistics throughout 2008-2015. Pregnant women aged 12-55 years with a live birth were included. Women with opioid use disorder, chromosomal disorder, and cancer at baseline (within 6 months preceding pregnancy) or during pregnancy were excluded as were women exposed to teratogenic medications during pregnancy. The main outcomes included adverse pregnancy and obstetric complications throughout pregnancy or in the first 6 weeks after delivery. Marginal structural Cox Model with time-dependent exposure was applied to assess the association of adverse obstetrical outcomes with prescription opioids, controlling for baseline maternal demographic characteristics and chronic comorbidities, and time-dependent covariates (i.e., concomitant medications and pain indications). Sensitivity studies were conducted with varying opioid types and doses, and exposure trimesters.

Results: Of 11,042 mother-child pairs, 431 (3.9%) filled ≥1 prescription opioid merely during pregnancy, 320 (2.9%) filled ≥1 prescription opioid during baseline and pregnancy, and 999 (9.05%) filled ≥1 prescription opioid only at baseline. Compared to those without opioid exposure during pregnancies, opioid-exposed pregnancies were associated with an increased risk of caesarean section (aHR: 4.13; 95% CI: 2.62-6.79), assisted vaginal delivery (aHR: 4.15; 95% CI: 2.74-6.28), placental abruption (aHR: 4.37; 95% CI: 1.03-18.51), and postpartum hemorrhage (aHR: 5.91; 95% CI: 1.25-27.95). Opioid exposure both at baseline and during pregnancy was associated with a higher risk of preterm birth (aHR: 3.58; 95% CI: 1.06-12.14) and antepartum hemorrhage (aHR: 3.86; 95% CI: 1.11-13.43) in addition to assisted vaginal delivery (aHR: 3.80; 95% CI: 2.00-7.22) and forceps/vacuum delivery (aHR: 2.96; 95% CI: 1.25-6.98).

Conclusions: Prescription opioid use during pregnancy is associated with a significantly increased risk of obstetrical complications.

4532 | Discontinuation and reinitiation of antidepressants during pregnancy in South Korea, 2013-2017

Yunha Noh[1], Seung-Ah Choe[2] and Ju-Young Shin[1]

[1]Sungkyunkwan University (SKKU), Suwon, Republic of Korea; [2]CHA University, Gyeonggi-do, Republic of Korea

Background: Women tend to discontinue antidepressants (AD) during pregnancy, especially in its early phase, as they are anxious of the potential detrimental effects ADs may have on their fetus. However, AD discontinuation may instead result in poor health outcomes such as non-optimal fetal development and depression relapse.

Objectives: To assess the rate of AD discontinuation and reinitiation during pregnancy and factors associated with its discontinuation in the 1st trimester.

Methods: We used Korea's nationwide healthcare database from 2011 to 2017, having both in- and outpatient records. Our study cohort included 5,207 women who were aged 15-50 years, gave birth during 2013-2017, had ≥1 depression diagnosis, ≥2 AD prescriptions within 6-months of preconception, and prescribed ADs in the month before pregnancy. Pregnancy duration was defined as 245 days for women with preterm-related codes at delivery, and 273 days for all others. The ADs were classified as selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic ADs (TCA), and others. We estimated the rate of AD discontinuation (no refill within 30 days) and reinitiation during pregnancy or in the postpartum period (90-day period after delivery). To evaluate factors associated with AD discontinuation in the 1st trimester, the Cox proportional hazard model was used to estimate hazard ratios (HR) with 95% confidence intervals (CI), adjusting for demographic and clinical characteristics.

Results: During pregnancy, 4,952 (95.1%) women discontinued ADs, where 4,680 (89.9%), 219 (4.2%), and 53 (1.0%) discontinued them in the 1st, 2nd, and 3rd trimester, respectively. The mean duration to discontinuation was 32.7 days from pregnancy onset. Of the 4,952 women who discontinued ADs, 424 (9.1%) reinitiated them during pregnancy, whereas 702 (15.0%) reinitiated them in postpartum period. Although the rate of discontinuation was similar in all AD classes, women receiving SSRIs (HR 0.86, 95% CI 0.77-0.96) or SNRIs (0.83, 0.70-0.99) were less likely to discontinue them than those receiving TCAs. Moreover, discontinuation occurred less in women

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

with psychiatric comorbidities, such as epilepsy (0.71, 0.56-0.91) or schizophrenia (0.79, 0.67-0.94), and those receiving ADs >120 days (0.41, 0.38-0.44) or 61-120 days (0.68, 0.63-0.73) compared to ≤60 days, in the 6-month preconception period.

Conclusions: We found high rates of AD discontinuation and reinitiation of during pregnancy. Our results suggest a higher AD persistence during pregnancy when women received SSRIs or SNRIs, or had psychiatric comorbidities.

4543 | Postpartum opioid use and 1-year risk of death

Arlyn Horn, Sarah Osmundson, Andrew Wiese, Edward Mitchel, Sharon Phillips, Stephen Patrick, Margaret Adgent, Marie Griffin and Carlos Grijalva

Vanderbilt University Medical Center, Nashville, TN

Background: Postpartum opioid use is associated with serious opioid-related events, especially when filling >= 2 opioid prescriptions. However, few studies have specifically examined the association between postpartum opioid use and death.

Objectives: To examine the association between filling >=2 postpartum opioid prescriptions and the 1-year risk of all-cause death.

Methods: We identified women age 14-44 years enrolled in Tennessee Medicaid (TennCare), who experienced childbirth (2007-2014). Pregnancy, delivery and postpartum information was supplemented with birth certificate data. Postpartum opioid use was classified as <=1 or >=2 outpatient opioid fills during the 41 days post-childbirth. The outcome was all-cause death, confirmed through linkage with Tennessee death certificates. Patients were followed from day 42 postpartum to the date of death or 365 days of follow-up. Propensity scores were calculated to summarize and balance information from relevant covariates between exposure groups. Covariates assessed during pregnancy, delivery and postpartum included medication use (including opioid use during pregnancy), comorbidities, pregnancy and delivery complications, and opioid use disorder history. We computed stabilized inverse probability of treatment weights and used weighted Cox proportional hazard regression models to compare time to death between opioid exposure groups. Estimates were further stratified by mode of delivery.

Results: Among 264,135 women, 18% filled >=2 opioid prescriptions in 41 days postpartum period. Starting at 42 days post-childbirth, there were 182 deaths in the 365 days of follow-up. Most common causes of death included motor vehicle accidents (29%), violent deaths (19%), overdoses (17%) and others (35%). When the risk of death was compared between women with >=2 postpartum opioid prescriptions and women with <=1 prescription, the crude hazard ratio was 2.09 (1.52-2.85). All covariates were balanced after propensity score weighting (standardized mean differences <0.1). The adjusted hazard ratio [aHR] for all-cause death was 1.53 (1.06-2.22) comparing patients filling >=2 postpartum opioid prescriptions to those with <=1 fills. Results of subgroup analyses were consistent with results from the main analysis [aHR: 1.64 (1.01-2.68) and 1.35 (0.8-2.26) for vaginal and cesarean births, respectively].

Conclusions: Filling two or more opioid prescriptions during the postpartum period was associated with a significant increase in the 1-year risk of death.

4584 | The effect of a pharmacist consultation in early pregnancy on pregnant women's quality of life: An intervention study

Maria Bich-Thuy Truong[1], Elin Ngo[1], Hilde Ariansen[2], Ross T. Tsuyuki[3] and Hedvig Nordeng[1]

[1]University of Oslo, Oslo, Norway; [2]The Norwegian Pharmacy Association, Oslo, Norway; [3]University of Alberta, Alberta, AB, Canada

Background: Pharmacist consultations providing information about medication use have shown to be beneficial on medication adherence and disease control in several patient populations. Yet, no studies have investigated the effect of a pharmacist consultation on the quality of life among pregnant women.

Objectives: This study aims to investigate the impact of a pharmacist consultation in early pregnancy on women's quality of life (QOL), focusing on nausea and vomiting in pregnancy (NVP), and the patient satisfaction with the consultation.

Methods: Pregnant women in their first trimester were eligible for inclusion and were mainly recruited through social media. All women were assigned to either the intervention or the control group. The intervention was a pharmacist consultation in the first trimester tailored to each woman's information needs about medications and pregnancy-related ailments. Data were collected by online questionnaires at the time of recruitment (Q1, baseline) and 13 weeks after recruitment (Q2, second trimester). Women in the intervention group completed an additional 7-item satisfaction questionnaire after the consultation was completed. The primary outcome was the change in the quality of life from Q1 to Q2 and assessed by linear regressions. QOL was measured by the 16-item Quality of Life Scale (QOLS), ranging from 16-112, where a higher score indicates a higher QOL. Secondary analyses were performed to assess the effect modification by NVP severity as defined by the PUQE score (mild: ≤6 points, moderate: 7-12 points, or severe: ≥13 points). Results were presented as the crude and adjusted changes in QOLS (beta coefficients) with 95% confidence intervals.

Results: Of the 340 women included in this study, half were assigned to receive the consultation. The majority of women who completed the consultation reported it to be useful to a large/very large extent (78/96, 81%). The intervention had no overall effect on the QOLS change compared to standard care (adjusted β: 0.7, 95% CI: -2.1, 3.4). The effect of the intervention was higher in women with moderate/severe NVP compared to women with mild NVP (predicted mean QOLS change: 3.6 vs. -1.9, p=0.048).

Conclusions: The pharmacist consultation had little effect on pregnant women's change in QOL. Future studies should further explore the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

effect of a pharmacist consultation specifically for moderate to severe NVP and on other outcomes such as the utilization of health care services and medication use in pregnancy.

4615 | Use of antiseizure drugs in pregnancy and in women of childbearing age between 2014 and 2018 in Switzerland: A retrospective analysis of Swiss health care claims data

Julia Spoendlin[1], Eva Blozik[2], Sereina M. Graber[2], Marlene S. Rauch[1], Carole A. Marxer[1], Stephan Rueegg[3], Christoph R. Meier[1], Ursula Winterfeld[4] and Alice Panchaud[5,6]

[1]University of Basel & University Hospital Basel, Basel, Switzerland; [2]Helsana Insurance Group, Zurich, Switzerland; [3]University Hospital Basel, Basel, Switzerland; [4]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [5]Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [6], Institute for Pharmaceutical Sciences of Western Switzerland, Lausanne, Switzerland

Background: The prevalence of the use of antiseizure drugs during pregnancy and in women of childbearing age in Switzerland is not known.

Objectives: We aimed to study the use of antiseizure drugs, with a focus on valproate, during pregnancy and in women of childbearing age in Switzerland.

Methods: We conducted a retrospective descriptive study using the health care claims database of the Swiss health insurance Helsana (2014 - 2018). We established two separate study populations; 1) a cohort of pregnancies leading to a delivery, and 2) all women of childbearing age (15-45 years) who were insured with Helsana for at least 1 year during the study period. We identified dispensing of valproate, lamotrigine, carbamazepine, levetiracetam, topiramate, pregabalin, gabapentin, phenobarbital, and phenytoin 1) between delivery and 3 months prior to the estimated date of the last menstrual period and 2) by calendar year. We quantified exposure prevalence of each antiseizure drug as the number of women with ≥1 prescription fill per 10'000 1) pregnancies/2) women by calendar year. Results were weighted for the demographic distribution of the Helsana population relative to the Swiss population.

Results: We identified a weighted pregnancy population of 387'418 pregnancies, with a mean maternal age at delivery of 31.9 years (standard deviation 5.1 years). Lamotrigine was the most frequently dispensed antiseizure drug during pregnancy (20/10'000), followed by levetiracetam (11/10'000), and pregabalin (3.8/10'000). Valproate was dispensed to 1.9/10'000 women during pregnancy and to 1.3/10'000 women within 90 days prior to the last menstrual period but not during pregnancy. The weighted study population of women aged 15-45 years consisted of 2'781'151 women, of whom 74'080 (2.66%) were exposed to ≥1 of the evaluated antiseizure drugs. Pregabalin was the most frequently dispensed antiseizure drug (64/10'000), followed by lamotrigine (46/10'000), topiramate (32/10'000), and valproate (25/10'000). The use of valproate decreased from 28/10'000 women in 2014 to 21/10'000 women in 2018.

Conclusions: The prevalence of exposure to valproate during pregnancy was comparable to Denmark and lower than in other European countries. Despite decreasing exposure prevalence, the use of valproate in women of childbearing age seems higher than the actual clinical need.

4625 | Dispensing patterns among pregnant women of eight risky drug classes during pregnancy: A French nationwide population-based study

Pierre-Olivier Blotière[1], Alain Weill[2] and Géric Maura[1]

[1]French National Health Insurance (Caisse Nationale de l'Assurance Maladie - Cnam), Paris, France; [2]EPI-PHARE Epidemiology of Health Products. French National Agency for Medicines and Health Products Safety (ANSM) and French National Health Insurance (Cnam), Saint-Denis, France

Background: Utilization studies investigating the prescribing of risky drugs during pregnancy are critical for establishing priorities in pregnancy safety research with major public health implications.

Objectives: To investigate the dispensing patterns of the most risky drug classes during pregnancy in France based on nationwide reimbursement data.

Methods: Based on the most recent data available from the French national healthcare databases (67 million beneficiaries), a drug utilization study was performed including all pregnancies beginning in 2016-2017 and identified by their outcomes (live births, stillbirths, all types of abortions, ectopic pregnancies). Among the most risky drug classes during pregnancy, eight were selected according to the Australian ADEC classification, the Swedish FASS classification and data from the French medicine agency. Pregnant women were considered exposed if they were reimbursed at least once for any drugs of these eight classes, from the first up to the last estimated day of pregnancy: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), tetracycline antibiotics, vitamin K antagonist oral anticoagulants (VKA), retinoids, antineoplastic drugs (L01 ATC class only) and antiepileptic drugs (phenobarbital, primidone, phenytoin, carbamazepine, valproic acid and derivatives, vigabatrin and topiramate only).

Results: Among a total of 1,844,447 pregnancies [live births: 1,348,098], the prevalence of exposed pregnancies was 1.0‰ (N=1,921) for ACE inhibitors [live births: 0.9‰, 2nd or 3rd trimester: 0.2‰]; 0.9‰ (N=1,732) for ARBs [live births: 0.8‰, 2nd or 3rd trimester: 0.2‰]; 167.5‰ (N=308,877) for NSAIDs [live births: 115.4‰, 2nd or 3rd trimester: 49.0‰]; 9.0‰ (N=16,535) for tetracyclines [live births: 3.9‰, 2nd or 3rd trimester: 0.5‰]; 0.3‰ (N=640) for VKA [live births: 0.3‰]; 2.0‰ (N=3,695) for retinoids [live births: 1.9‰] including 0.4‰ (N=710) for retinoids for systemic use; 0.3‰ (N=484) for the antineoplastic drugs [live births: 0.2‰] and 1.0‰ (N=1,864) for the antiepileptic drugs considered [live births: 0.8‰].

Conclusions: Considering eight of the most risky drug classes, exposure during pregnancy is high in 2016-2017 in France, especially for

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

NSAIDs and retinoids. As exposure to these drug classes during pregnancy has been clearly linked to adverse birth outcomes, these results are a recall for clinicians to avoid prescribing these drugs to pregnant women as much as possible.

4627 | Prevalence and pharmacological treatment of gestational diabetes in Norway 2013-2018

Kari Furu[1,2], Lars J. Kjerpeseth[1], Vidar Hjellvik[1] and Hanne L. Gulseth[1]
[1]*Norwegian Institute of Public Health, Oslo, Norway*; [2]*Norwegian Institute of Public Health, Oslo, Norway*

Background: The prevalence of gestational diabetes (GDM) is increasing worldwide. There is a growing burden to the health care system due to that GDM is associated with short- and long-term complications for mother and infant. Historically, insulin has been the standard treatment for women with GDM who fail diet therapy/lifestyle changes. However, oral hypoglycemic agents such as metformin and glyburide have been acceptable alternatives in later years. In 2017, Norway implemented new diagnostic criteria and treatment guidelines for GDM

Objectives: To explore trends in GDM prevalence and treatment in Norway during 2013-2018

Methods: We linked data from Norwegian registries on primary care (Norway Control and Payment of Health Reimbursement Database; KUHR), secondary care (Norwegian Patient Registry; NPR), births (Medical Birth Registry of Norway; MBRN) and prescriptions (Norwegian prescription database; NorPD) from 2013-2018. We included all women with a live or stillbirth in MBRN after week 16 of pregnancy, except those with a diabetes diagnosis other than GDM in NPR or KUHR (ICD-10 codes: E10-14 or ICPC-2 codes T89/T90) during the 2 years before birth, or a diabetes drug prescription in NorPD (ATC code A10) from 2 years before birth to the start of pregnancy. GDM was identified by ICD-10 code O244 in NPR during pregnancy and a specific diabetes variable in MBRN. Second and third trimester use of insulin and metformin was defined as ≥ 1 prescription fill from 90 days after the last menstrual period to birth. We calculated the proportion of insulin/metformin users in the GDM population by birth year from 2013 to 2018.

Results: We included 346,593 deliveries. The overall prevalence of GDM was 4.5%, increasing from 3.2% in 2013 to 5.4% in 2016 and thereafter quite stable. In 2013 85.4% of those diagnosed with GDM were treated with lifestyle only, 4.2% with metformin only, 9.3% with insulin only and 1.2% with both metformin and insulin. The proportions in 2017 were 81.4, 6.5, 9.8, and 2.3%, and in 2018 65.9, 11.1, 18.5 and 4.5%, respectively.

Conclusions: The prevalence of GDM in Norway increased only until 2016. There has been an increase in the pharmacological treatment of GDM with insulin use doubled and metformin nearly tripled from 2013 to 2018. The changes in treatment were mainly from 2017 to 2018.

4632 | Determinants of the use of gonadotropin formulations in the treatment of female infertility in a central Italian region

Alessandro Cesare ROSA, 00142
Department of Epidemiology Asl Roma1 Lazio Region, Rome, Italy

Background: Gonadotropins (Gona) are commonly used for infertility treatment in women. They are available as urinary purified extracts (u-Gona) and recombinants (r-Gona).

Objectives: We investigated if socio-demographic characteristics of treated women, year of dispensation and type of prescriber may play a role in the choice of a treatment with respect to the other.

Methods: From administrative healthcare databases, we collected claims of Gona for women, aged 18-45, enrolled in the health care system in the year preceding the first prescription (years 2009-2018). Treatment cycles were defined as a 21-day mobile time window. We identified three groups: u-Gona, r-Gona and treatment with both formulations (m-Gona). To identify determinants, we linked women with the socio-economic position (SEP), a composite deprivation index, based on the 2011 Italian Census data, categorized in 4 levels (high, medium-high, medium-low, low). We associated prescriptions with the type of prescriber, distinguishing between specialists and general practitioners. We used polytomous logistic models to measure relationships between variables and treatment choice.

Results: We retrieved 38,598 Gona treatment cycles prescribed to 23,412 women and distributed between formulations as follows: r-Gona 47.4%, u-Gona 26.3% and m-Gona 26.3%. The median age was 38 years for r-Gona and u-Gona, 39 for m-Gona. Comparing the type of prescriber, specialists were more likely to prescribe u-Gona instead of r-Gona (OR: 2.14; 95%CI: 2.02-2.27) than general practitioners. Similar result for m-Gona vs r-Gona No relation was found between SEP and Gona formulations, except for patients with the highest level who were more likely to be prescribed with r-Gona instead of u-Gona (OR: 1.12; 95%CI: 1.03-1.21). Time trends showed that treatment choices changed over time, with a significantly higher probability of m-Gona in 2011- 2014, and r-Gona in 2014- 2016, with respect to u-Gona.

Conclusions: In the Lazio region, the choice of gonadotropin formulations varied over time and was found to be related to the prescriber and partly to socio-economic position. Further investigation and an analysis of outcomes related to different treatments is under way.

4660 | Exposure to mycophenolic acid products during pregnancy from 2010 to 2017 in France: A nationwide cohort study

Emmanuelle Dufour, Stéphanie Duret, Thien Le Tri and Rosemary Dray-Spira
EPI-PHARE, Epidemiology of Health Products (French National Agency for the Safety of Medicines and Health Products [ANSM], and French National Health Insurance [CNAM]), Saint-Denis, France

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Mycophenolic Acid (MPA) products, used as a first-line treatments for the prevention of organ transplant rejection, are also used off-label to treat autoimmune disorders. Due to its highly teratogenic nature, MPA use is contraindicated during pregnancy in Europe. In addition, the conditions for prescribing and dispensing MPA in women of childbearing age have been reinforced in France since 2016.

Objectives: The aim was to quantify and characterize exposure to MPA during pregnancy in France between 2010 and 2017, according to the pathological context of use (organ transplant or other).

Methods: The study was conducted using data of the French National Health Data System (SNDS). Any pregnancy with at least one dispensation of MPA in the 3 months prior to onset and/or during pregnancy was considered exposed. All MPA-exposed pregnancies initiated and completed between April 1, 2010 and December 31, 2017 were included. The analyses consisted in describing the MPA-exposed pregnancies (socio-demographic characteristics of the women, pathological context of use, period of exposure during pregnancy) and their outcomes.

Results: A total of 383 pregnancies exposed to MPA were identified: 175 (46%) for whom MPA was used in an organ transplant context and 208 (54%) in another context. The annual number of exposed pregnancies was approximately 50 pregnancies per year throughout the study period. The proportion of pregnancies exposed in a transplant context and in another context remained stable. The exposure period included the first trimester of pregnancy in the majority of cases (55%). 169 (44%) exposed pregnancies had an unfavorable outcome, mainly termination of pregnancy. Of the 214 pregnancies that resulted in live births, 164 newborns exposed in utero to MPA could be identified. A congenital malformation was diagnosed at birth for 19 of them (12%).

Conclusions: Nearly 400 pregnancies were exposed to MPA between 2010 and 2017 in France. The consequences on pregnancy outcomes and on the risk of birth defects in children exposed in utero are damaging.

4668 | Unmeasured confounding by maternal personality traits on the association between prenatal medication exposures and child developmental outcomes

Angela Lupattelli[1], Kristen Vamsæter[2], Eivind Ystrom[3] and Hedvig Nordeng[1]

[1]*University of Oslo, Oslo, Norway;* [2]*University of Oslo, Oslo, Norway;* [3]*Norwegian Institute of Public Health, Oslo, Norway*

Background: Maternal personality traits may confound the association between prenatal medication use and child developmental outcomes. Personality remains often unmeasured in observational studies, and its relationship to prenatal medication exposures is not fully elucidated. Estimating the strength of this association is necessary to assess the influence of such unmeasured confounder.

Objectives: To estimate the association between maternal personality and use of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, anxiolytics/z-hypnotics in pregnancy. To examine to what extent this unmeasured confounder can cancel out developmental child risks following prenatal medication exposures using the bounding factor.

Methods: We used data from the Multinational Medication Use in Pregnancy Study, a web-based study collecting data on more than 8000 pregnancies in 12 European countries. Women reporting use in pregnancy of antidepressants, opioid analgesics, anxiolytics and/or z-hypnotics, NSAIDs or acetaminophen were considered as exposed. Personality was assessed with the Big Five Inventory, capturing the dimensions of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Adjusted binomial regression analyses were conducted. We used the bounding factor by Ding and VanderWeele.

Results: The study population included 8,953 perinatal women. One-unit increase in neuroticism was associated with greater use of antidepressants (adjusted Odds Ratio (aOR): 1.18, 95% Confidence Interval (CI):1.15-1.21), anxiolytics/z-hypnotics (aOR: 1.16, 95% CI:1.12-1.20), and acetaminophen (aOR: 1.02, 95% CI:1.01-1.02) in pregnancy. Personality was not associated with use of NSAIDs. Given the observed association between high neuroticism and externalizing problems in children (aOR: 2.28; 95% CI:1.58-3.30) and our findings, prior relative risks equal or smaller than 1.20-1.29 for child externalizing problems after prenatal use of anxiolytics/z-hypnotics or antidepressant, could be cancelled out by maternal unmeasured neuroticism. Larger medication risks can only be reduced to true relative risks by unmeasured maternal neuroticism.

Conclusions: Maternal neurotic traits are associated with use of specific medications in pregnancy. Our point estimates can be used in bounding factor analyses to assess the influence of unmeasured maternal personality on the associations prenatal drug exposure - child development.

4687 | Antibiotic prescribing in the first eight weeks after childbirth

Holly C Smith[1], Sonia Saxena, Prof[2] and Irene Petersen[1]

[1]*University College London, London, United Kingdom;* [2]*Imperial College London, London, United Kingdom*

Background: Many women will receive antibiotics around the time of childbirth and delivery. However, in the United Kingdom, maternal care is transferred from secondary care to primary care shortly after birth and little is known about antibiotic treatments in women in the first few weeks after childbirth.

Objectives: To determine the rate of antibiotic prescribing in women in the first eight weeks after childbirth.

Methods: We conducted a cohort study using UK primary care electronic health records from The Health Improvement Network (THIN) database. Women aged 15-49 who gave birth between 1 January 2006 and 31 December 2016 were included. The primary outcome was antibiotic treatment in the first eight weeks after childbirth. We

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

estimated the prevalence rate ratio (PRR) of antibiotic use. The PRR was estimated by age, socio-economic deprivation, mode of delivery, parity and calendar time for antibiotic prescribing.

Results: Of 309,573 women included in the study, 68,485 (22.1%) had at least one antibiotic prescription in the first eight weeks after childbirth. Most antibiotics were prescribed between 5 and 15 days after childbirth and the number declined steadily thereafter. A total of 90,524 antibiotics were issued. Prevalence Rate Ratios of antibiotic prescribing were: 76% higher in those who had a caesarean compared to vaginal delivery (PRR: 1.76 95% CI: 1.72-1.80); 11% higher in women aged 40-45 years compared to those aged 15-19 (PRR: 1.11, 95% CI: 1.06-1.17); 9% higher in the least deprived women compared to most (PRR: 1.09, 95% CI: 1.06-1.11); and 7% higher in first time mothers compared to those who had their second child (PRR: 1.07, 95% CI: 1.05-1.09). Rates of antibiotic prescribing also increased over time.

Conclusions: The first eight weeks after childbirth are a time of high antibiotic use in women. Antibiotic use is particularly high in the first two weeks after childbirth and for those who had a caesarean delivery, with rates being nearly double that of women who had a vaginal birth.

4696 | What medications are prescribed to women during their postnatal check?

Holly C. Smith[1], Sonia Saxena, Prof[2] and Irene Petersen, Prof[1]
[1]*University College London, London, United Kingdom;* [2]*Imperial College London, London, United Kingdom*

Background: In the United Kingdom (UK) every woman has access to midwives and health visitors for the first few days after childbirth. They are then discharged to the care of their General Practitioner (GP) who invites them for a planned postnatal check 6-8 weeks after birth, as recommended by National Institute for Health and Care Excellence (NICE) and the World Health Organisation (WHO). This is an opportunity to review a woman's physical and mental health mental, and assess how they are recovering after pregnancy and birth. It is also a key point to discuss breastfeeding, contraception, smoking cessation, physical activity and dietary advice. While guidelines outline what health needs could be covered during these consultations, few studies have investigated what is addressed in reality and how this relates to national guideline recommendations.

Objectives: To determine what medications are prescribed to women during their postnatal check and how these relate to NICE guidelines.

Methods: We conducted a descriptive cohort study using UK primary care electronic health records from The Health Improvement Network (THIN) database. Women aged 15-49 who gave birth between 1 January 2006 and 31 December 2016 were included. A woman's record was examined to identify evidence of having a postnatal check. The postnatal check typically takes place 6-8 weeks after childbirth, however some women may receive this check slightly earlier or later so the time window for our study was expanded to weeks 5-10. The primary outcome measure was all prescriptions issued at the time of the postnatal check (week 5-10). Prescriptions were grouped by British National Formulary (BNF) subchapter to capture distinct health needs, such as antibiotics or antidepressant drugs. To identify the most common medications issued, the frequency and proportion of each prescription grouping is given as a fraction of all prescriptions in weeks 5-10.

Results: Of the 309,573 women included in this study, 180,059 (58.2%) had at least one prescription issued in the time period of the postnatal check; with 346,975 prescriptions being issued in total. The most common prescriptions related to: contraceptives 116,458 (33.6%); antibiotics 33,594 (9.7%); antidepressants 18,987 (5.5%); pain relief 12,844 (3.7%); local preparations for anal and rectal disorders 12,386 (3.6%); topical corticosteroids 10,309 (3.0%); and laxatives 10,255 (3.0%).

Conclusions: The postnatal check is a unique opportunity for many women to receive key medications and preventative care after childbirth. The medications prescribed to women during their postnatal check are reflective of national guidelines.

4728 | Screening for associations between prescription drug use in pregnancy and risk of congenital malformations

Anne Broe[1], Anton Pottegård[2], Jesper Hallas[2], Irene Petersen[3] and Per Damkier[1]
[1]*Odense University Hospital, Odense, Denmark;* [2]*University of Southern Denmark, Odense, Denmark;* [3]*University College London, London, United Kingdom*

Background: Knowledge about the safety of prescription drug use during pregnancy is limited at the time of marketing authorization. Adverse effects during pregnancy are not systematically captured and observational studies are often the only source of evidence-based information.

Objectives: To design a systematic screening tool to assess the safety of use of prescription drugs during pregnancy using the nationwide Danish health registries.

Methods: We identified all pregnancies with a recorded live-born singleton delivery in Denmark 2004- 2017, excluding infants born with chromosomal abnormalities (ICD-10: Q90-Q99). Exposure to prescription drug classes (ATC level 4) was assessed based on prescription fills between 30 days before pregnancy and the end of first trimester. Outcomes were identified as major malformation records either at delivery or during the first year of life. For any drug with >50 exposed pregnancies, we conducted low-dimensional propensity score adjusted analyses associating drug exposure with major malformations. For drug classes returning odd ratios for major malformations of 1.5 or higher in the main analyses, we performed analysis of 16 major malformation groups defined by EUROCAT classification of malformations.

Results: We included a total of 811,313 pregnancies, of which 48 % was exposed to prescription drug(s), and 3.5 % had a recorded major malformation. Analyses were performed for 231 drug classes (431 single drugs), of which 47 classes (98 single drugs) returned an odds ratio estimate of 1.5 or higher. The top five ranking signals (by OR) were clopidogrel (OR 4.25; 95%CI 2.10-8.61), liraglutide, (OR 4.15; 95%CI

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

1.73-9.94), ferrous glycine sulfate (OR 3.81; 95%CI 1.62-8.97), combination products of losartan and diuretics (OR 3.80; 95%CI 1.61-8.97), and enalapril and diuretics (OR 3.49; 95%CI 1.37-8.88). The screening identified signals for drugs with known teratogenic potentials, e.g. valproic acid returned OR 2.65 (1.73-4.07) and lithium OR 2.55 (1.47-4.43) for major malformations.

Conclusions: Our screening tool has successfully identified associations between drug exposure during pregnancy and risk of malformations. This screening model will provide the basis for future detailed studies of individual associations to further investigate the safety of prescription drugs during pregnancy.

4753 | Effect of decision support tools in pregnancy: A systematic review

Elin Ngo, Hedvig Nordeng and Maria Bich-Thuy Truong
University of Oslo, Oslo, Norway

Background: Women face many health-related decisions during pregnancy. Patient centered decision support tools (PC-DST) are developed to involve the patient in their own health-related decisions, and to complement counseling from health care providers.

Objectives: This systematic review aims to give an overview of studies evaluating the efficacy of PC-DST for pregnant women.

Methods: Five databases (MEDLINE, EMBASE, Web of Science, PsycINFO, and Scopus) were searched from inception to December 1, 2019. Title and abstract screening, full text screening, and data extraction were all performed by two independent researchers. Studies were eligible if they evaluated the efficacy of PC-DST used by pregnancy women for health-related issues and had a comparison group. Outcome measures included were; knowledge, attitudes/perceptions, satisfaction, decisional conflict, decision making, anxiety/independence/fear, quality of life, use experience, alcohol use, control of symptoms, and weight.

Results: A total of 10,726 studies were initially identified from the five databases. Twenty-seven studies were included in this systematic review. The studies covered seven topics in pregnancy: prenatal screening (n=10), gestational diabetes mellitus and weight gain (n=7), blood pressure and pre-eclampsia (n=2), lifestyle (n=4), depression (n=1), asthma (n=1), and physiological wellbeing (n=2). Twenty-six of the PC-DST were digital, and two were paper-based. The studies showed that the use of decision support tools increased the women`s knowledge compared to standard care (11/12). Digital decision support tools were more convenient, as women tracked their symptoms more frequently, compared to paper-based decision support tools. The information provided by the tools were also easily accessible and readable. Real-time feedback and automatic transferring of notes to their physician also gave a positive impact on the communication between the women and their health care providers.

Conclusions: The use of PC-DST was found to increase knowledge, confidence, and communication between pregnant women and their health care providers. Future studies should focus on developing digital patient centered decision support tools tailored for pregnant women.

4756 | Antidepressant use in pregnancy and major birth defects

Laurent Chouchana[1], Nathanael Beeker[1], Jean-Marc Treluyer[1] and Florentia Kaguelidou[2]
[1]*Centre Régional de Pharmacovigilance, Service de Pharmacologie, Hôpital Cochin, AP-HP, Centre – Université de Paris, Paris, France;*
[2]*Centre d'Investigations Cliniques, INSERM CIC1426, Hôpital Robert Debré, APHP; Université de Paris, Paris, France*

Background: Antidepressants (AD) are increasingly used during pregnancy. Several studies have raised concerns about the impact of this exposure on the developing fetus. Hence, an increased risk of major birth defect (MBD), especially cardiac defects, has been associated to antidepressant in utero exposure.

Objectives: Our aim was to assess the association between in utero AD exposure and the risk of MBD.

Methods: In a cohort study using the French national healthcare insurance system database (SNDS), we assessed the association between first-trimester exposure to antidepressants (ATC N06A) and MBD, defined according to EUROCAT classification system. Multiple pregnancies and those exposed to known teratogens or to multiple antidepressants were excluded. Prior maternal AD use was assessed based on data during the year before pregnancy start. We compared the risk of MBD in the offspring of women with first trimester AD exposure (exposed) with the risk in the offspring of women without first trimester exposure but with prior AD use in both an unadjusted analysis and a propensity score-matched analysis.

Results: Among 2,434,830 pregnancies in our cohort, 79,302 (3.3 %) were not exposed to AD during the first trimester but had prior AD use and 45,349 (1.9%) were exposed to one AD during the first trimester, mainly escitalopram (n=11,911) or paroxetine (n=6,231). A total of 1,161 (2.6%) and 1,909 (2.4%) MBD, mainly limb and cardiac defects, were identified in the offspring of exposed women and unexposed women with prior AD use, respectively. Crude and propensity score-matched ORs [95% CI] for overall MBD vs. women with prior AD use were 1.08 [1.00-1.17] and 1.03 [0.94-1.13], respectively. No statistically significant association was found for AD use and cardiac defects.

Conclusions: Our study shows no difference in overall MBD among the offspring of women exposed to AD during pregnancy, compared to women with prior AD use.

4791 | Periconceptional oral contraceptive use and the risk of miscarriage: The PRIDE study

Lieve Tuitjer, Nel Roeleveld and Marleen van Gelder
Radboud University Medical Center, Nijmegen, Netherlands

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Oral contraceptives are widely used by women of reproductive age. Previous studies were inconclusive about the associations between periconceptional oral contraceptive use and the risk of miscarriage, due to methodological limitations.

Objectives: To assess the associations of periconceptional oral contraceptive use with the risk of miscarriage, taking into account the timing of discontinuation and the type of contraceptive pill used.

Methods: We included 4,832 women with an estimated date of delivery between 2012-2017 participating in the PRegnancy and Infant DEvelopment (PRIDE) Study, an ongoing prospective cohort study in the Netherlands. Information on periconceptional use of oral contraceptives and pregnancy outcomes was collected using web-based questionnaires and obstetric records. Periconceptional oral contraceptive use was defined as use within the year before conception and/or during pregnancy. Timing of discontinuation, pill generation, and amount of estrogen were used for stratification of the exposure. The risk of a miscarriage in relation to the use of oral contraceptives was estimated using Cox proportional hazards regression models adjusted for confounders. In sensitivity analyses, we used exposure data from prescription records.

Results: Any self-reported periconceptional oral contraceptive use was not associated with the risk of miscarriage (hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.64-1.25). Using pharmacy records to assess exposure and stratification on timing of discontinuation and type of oral contraceptive did not influence this result. Among women aged <30 years, however, oral contraceptive users had a decreased risk of miscarriage (HR 0.55; 95% CI 0.32-0.97) in comparison to non-users. When participants with ≥1 previous miscarriage were excluded, periconceptional oral contraceptive use also seemed to be associated with a decreased risk of miscarriage (HR 0.69; 95% CI 0.48-1.01).

Conclusions: Although no evidence was found for periconceptional oral contraceptive use in general to be associated with the risk of a miscarriage, the risk might be decreased among oral contraception-using women without previous miscarriages and those <30 years of age.

4836 | Patterns of antibiotic medication use during pregnancy among publicly and commercially insured women in the United States

Yanmin Zhu[1], Brian T. Bateman[1], Sonia Hernandez-Diaz[2], Kathryn J. Gray[1], Helen Mogun[1] and Krista F. Huybrechts[1]

[1]*Brigham and Women's Hospital and Harvard Medical School, Boston, MA*; [2]*Harvard T. H. Chan School of Public Health, Boston, MA*

Background: Bacterial infections are common during pregnancy necessitating the use of antibiotics; however, the comparative safety data are sparse. Defining maternal patterns of antibiotic use is important in establishing research priorities in this area.

Objectives: To describe patterns of maternal use of antibiotics among publicly and commercially insured women in the US.

Methods: Using the Medicaid Analytical eXtract (MAX) 2000-2014 and the IBM Health MarketScan Research Database (MarketScan) 2003-2015, we defined cohorts of publicly and commercially insured pregnancies, respectively, among women with continuous insurance enrollment from 3 months before the date of the last menstrual period (LMP) through 1 month after delivery. We described the use of antibiotic classes, including aminoglycosides, cephalosporins, macrolides, penicillins, quinolones, sulfonamides, tetracyclines, urinary anti-infectives (including nitrofurantoin and trimethoprim), and miscellaneous anti-bacterials, as well as the most commonly used individual antibiotics, during the 90 days before LMP, each trimester and the entire pregnancy (1st-3rd trimester). We also evaluated the indications for use based on diagnoses recorded in the 7 days prior to the date of each antibiotic dispensing.

Results: We identified 65.3% of 1,889,352 publicly insured and 44.9% of 1,319,428 commercially insured pregnancies with >=1 antibiotic dispensing during pregnancy. The most commonly prescribed classes included penicillins (MAX 24.8%; MarketScan 16.2%), macrolides (19.9; 16.6%) and urinary anti-infectives (23.1; 11.5%). Although compared to 90 days before LMP, the use of tetracyclines (contraindicated in pregnancy), quinolones and sulfonamides (considered to have possible harmful effects) decreased in 1st trimester, a substantial number of mothers were exposed. Medications with suggested harmful effects - trimethoprim and sulfamethoxazole (2.0; 0.7%), ciprofloxacin (1.1; 0.7%), doxycycline (0.7; 0.8%) - were also among the top 15 most commonly used antibiotics during 1st trimester in both populations. The most frequently recorded indications were urinary tract infections in MAX (19.4%) and sinusitis in MarketScan (17.7%).

Conclusions: More than 6 out of 10 and 4 out of 10 pregnancies were exposed to antibiotics in publicly and commercially insured populations, respectively, with a substantial number of pregnancies exposed to potentially harmful antibiotics. Given the frequency with which antibiotics are used during pregnancy, comparative safety evidence is needed to support treatment selection.

4842 | Incidence and predictors of surgical site infection following cesarean section: Retrospective analysis of electronic health records

Stephen S. Johnston[1], Joseph E. Guilfoyle[1], Nivesh Elangovanraaj[2], Giovanni A. Tomaselli[3] and Brian Chen[4]

[1]*Johnson and Johnson, New Brunswick, NJ*; [2]*Mu Sigma, Bangalore, India*; [3]*Ethicon Italy, Naples, Italy*; [4]*Ethicon, Somerville, NJ*

Background: Though rare, surgical site infection (SSI) following cesarean section (CS) is a significant cause of maternal perioperative morbidity and mortality.

Objectives: To examine the incidence and predictors of antibiotic-treated SSI within 30 days of CS among patients under care in an integrated delivery network within the midwestern United States.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: Retrospective cohort study of electronic health records (EHRs). Patients included for study were females aged 18-50 years, undergoing CS between 1/1/2016 and 9/30/2019 in an integrated delivery network comprising >40 hospitals and 350 outpatient facilities. Only those with clinical records in the HER from ≥30 days before and ≥30 days after CS were included. The primary outcome was occurrence of SSI within 30 days of CS, defined as the presence of both: (a) documented diagnosis of infection of obstetric surgical wound or infection following a procedure; and (b) non-prophylactic antibiotic treatment within ±1 day of SSI diagnosis. Multivariable logistic regression was used to examine the association of patient demographics (e.g. age), general comorbidities (e.g. hypertension), high-risk pregnancy factors (e.g. previous CS), and other factors (e.g. provider volume) with the occurrence of SSI. Recycled prediction was used to calculate adjusted risks for selected predictors of SSI.

Results: A total of 18,602 patients met the study criteria; 48.1% aged <30 years, 78.6% Caucasian. Overall, 362 (1.9%) patients had an SSI within 30 days of CS. The multivariable logistic regression exhibited good overall discriminative accuracy (C-statistic=0.72). Statistically significant predictors of occurrence of SSI included prolonged OR time (adjusted incidence proportion: 0-26 mins=1.4% [reference]; 27-33 mins=1.6%, P=0.411; 27-40 mins=2.2%, P=0.027; ≥41 mins=2.9%, P<0.001), diagnosed obesity (3.0% vs. 1.6%, P<0.001), uterine scar not from previous CS (3.3% vs. 1.9%, P<0.001), trial of labor after previous CS vs. no previous CS (2.9% vs. 1.8%, P=0.001), diagnosed hypertension (2.8% vs. 1.7%, P<0.001), iron deficiency anemia (3.1% vs. 1.9%, P=0.028), and diagnosed drug abuse (4.3% vs. 1.9%, P=0.017), among other factors.

Conclusions: In this study of patients undergoing CS in the midwestern US, antibiotic-treated SSI had several strong risk factors which can be readily identified in clinical practice. Concerted efforts to develop, validate, and deploy an EHR-based predictive model for SSI after CS could assist in prospectively identifying candidates for targeted SSI prevention measures.

4863 | Eculizumab in pregnant women: A viable alternative to prevent invasive hemolysis?

Pamela S Azevedo[1], Isabella Zuppo[1], Túlio Tadeu Sarmento[1], Kennedy Ribeiro[2], Nélio Ribeiro[1], Natália Brandão[2], Ludmila Gargano[2], Carolina Nader[3], Juliana Alvares-Teodoro[2], Francisco Acurcio[2] and Augusto Guerra[2]

[1]SUS Collaborating Centre Technology Assessment and Excellence in Health, Belo Horizonte, Brazil; [2]Federal University of Minas Gerais, Belo Horizonte, Brazil; [3]Federal University of Minas Gerais, Belo Horizonte, Brazil

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare chronic hemolytic anemia, mediated by the complement, whose only medication available for treatment in Brazil is eculizumab, recently listed by the Brazilian national health service. Despite the chronic nature of the disease, it is known that pregnancy and lactation trigger an increase in hemolysis, increasing the risk of complications during pregnancy, cases in which eculizumab may be required.

Objectives: To evaluate the safety of eculizumab in the treatment of pregnant and breastfeeding with PNH using real-world evidence, as support for the development of a national guideline for the treatment of the disease.

Methods: A systematic review (SR) conducted in May 2019, evaluated the safety of eculizumab in the treatment of pregnant and/or breastfeeding women with PNH, by consulting the PUBMED, EMBASE, LILACS, Cochrane Library databases and gray literature. Two independent reviewers carried out the studies selection. The data were summarized and presented with the main information from the cohort studies, in addition to a pool of data collected in the case reports. The main evaluated outcomes were: abortion, fetal malformation and the presence of eculizumab in breast milk.

Results: Of the 2,012 retrieved studies, 11 were included in the SR. Among these studies one was a cohort design and 10 were case reports. The cohort study evaluated the use of eculizumab during 75 pregnancies of 61 women with PNH. Six abortions were observed during the first trimester of pregnancy and three stillborn were reported. In addition, the presence of eculizumab was evaluated in 10 breast milk samples and the drug was not identified in any of them. Additionally, a pool of 10 case studies involving 17 patients were included, of which 53% used eculizumab throughout pregnancy and the average time of eculizumab use was 14 weeks. In the sample, 71% of cases presented complications, with the main reports of hemolytic crisis (29.4%), pre-eclampsia (11.7%) and anemia (11.7%). All children were born healthy. Eculizumab was not identified in breast milk in all 10 samples evaluated.

Conclusions: Real-world evidence suggests that the risks of using eculizumabe did not outweigh the benefits of treating pregnant women with PNH. This systematic review, together with a panel of experts, validated the relevance of using eculizumab during pregnancy, allowing the development of a clinical guideline that promotes safe and comprehensive care for women with PNH in Brazil.

4877 | Safety of disease modifying drugs in pregnant women with relapsing-remitting multiple sclerosis: Systematic review and meta-analysis

Túlio Tadeu R Sarmento[1], Isabella F Zuppo[1,2], Pâmela S Azevedo[1], Nélio G Ribeiro[1], Natália D Brandão[1,2], Carolina MFF Nader[1], Ludmila P Gargano[1,2], Francisco A Acurcio[3,1], Juliana Alvares-Teodoro[1,3] and Augusto A Guerra[1,3]

[1]SUS Collaborating Centre Technology Assessment and Excellence in Health, Belo Horizonte, Brazil; [2]Federal University of Minas Gerais, Belo Horizonte, Brazil; [3]Federal University of Minas Gerais, Belo Horizonte, Brazil

Background: Relapsing-remitting multiple sclerosis (RRMS) is a chronic, immune-mediated and neurodegenerative disease that usually affects young adults, especially around 30 years, which coincides with the mean reproductive age of women. Although clinical

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

manifestations of RRMS in pregnancy are usually milder, there are cases of progression of the disease in which disease modifying drugs (DMD) may be required, raising the need to assess the safety of these drugs in pregnancy in order to support health decisions and improve public healthcare in Brazil.

Objectives: To evaluate the safety of DMD in RRMS pregnant women using real-world evidence.

Methods: We conducted a systematic review (SR) and meta-analysis of cohort studies evaluating the safety of DMD in RRMS during pregnancy. The search was carried out in November 2019, through MEDLINE, EMBASE, LILACS, Cochrane Library databases and gray literature. We included only drugs provided by the Brazilian Unified Health System and without contraindication in package insert for use during pregnancy (fingolimod; glatiramer acetate; interferon-beta 1b and natalizumab). The selection of the studies was performed by two independent reviewers. The meta-analysis was conducted in Review Manager® 5.3 software. The safety outcomes evaluated were: fetal/neonatal mortality, pregnancy complications, abortions, premature births and malformations. The methodological quality of the included studies was assessed using the Newcastle-Ottawa scale.

Results: From the 905 studies found, ten were selected to the SR. The majority of the studies presented high methodological quality and very low certainty of evidence for all assessed outcomes. We did not find statistical significance in any of the outcomes evaluated when comparing the use of any DMD versus no-use of DMD. However, sensitivity analysis pointed greater odds of occurring induced abortion in patients using glatiramer acetate when compared with those without using DMD (OR 5,19; IC95%:1,36-19,88) and of spontaneous abortion in patients using interferon-beta 1b (OR 2,58; IC95%: 1,07-6,24).

Conclusions: Real-world evidence suggests a good safety profile of DMD, except for interferon-beta 1b and glatiramer acetate, which presented greater abortion rates. In these cases, the benefits promoted by the treatment may not overcome its risks. The results here presented may support the development of clinical guidelines and arise discussions about the care of pregnant women with RRMS.

4889 | Trends in post-approval pregnancy safety studies required by the United States food and drug administration, 2015-2019

Jason C. Simeone and Beth L. Nordstrom
Evidera, Waltham, MA

Background: The US Food and Drug Administration (FDA) may require drug manufacturers to complete post-marketing commitments upon approval of a novel drug application, including pregnancy safety studies. These may be prospective pregnancy registry and/or complementary pregnancy studies, such as retrospective studies using administrative claims or electronic medical record databases.

Objectives: To understand trends in pregnancy safety post-marketing commitments for drugs approved in 2015-19.

Methods: The FDA's Post-marketing Requirements and Commitments database was used to identify pregnancy safety studies required by the Center for Drug Evaluation and Research (CDER) for New Drug Applications and Biologic License Applications approved from Jan. 2015 through Dec. 2019. Milk-only lactation and animal studies were excluded. Pregnancy study commitments were stratified by type, year of application approval, and therapeutic area of approved drug.

Results: Of 220 applications approved from 2015-19, CDER required 36 pregnancy registry and 21 complementary pregnancy studies. Approvals requiring a pregnancy registry study increased from 5 (11.1%) in 2015 to 13 (27.1%) in 2019, while those requiring a complementary study increased from 0 (0%) in 2015 to 8 (16.7%) in 2019. Pregnancy studies were most likely to be mandated for drugs for autoimmune disorders, such as plaque psoriasis; a registry and a complementary study were required for most (52.9%) of those approvals. More than one-third (35.7%) of CDER approvals for rare diseases required a registry; none required a complementary study. Fewer than 5% of oncology or infectious disease approvals mandated pregnancy studies. Complementary studies were always paired with registry studies unless an existing, ongoing registry (e.g., the North American Antiepileptic Drug Pregnancy Registry) was capturing drug exposures and pregnancy outcomes.

Conclusions: The frequency of pregnancy safety studies and percentage of new drug approvals with required pregnancy safety studies increased from 2015-19. By 2019, more than one-in-four approvals from CDER required a pregnancy registry and nearly one-in-five required a complementary pregnancy study. Pregnancy study commitments varied across therapeutic areas and were requested for more than half of autoimmune drug approvals but few oncology or infectious disease drug approvals. Despite recent use of retrospective studies to assess real-world drug safety, these designs are currently used to provide supplemental data and not as the primary source of information for pregnancy outcomes.

4893 | Opioid use during pregnancy and ischemic placental disease

Daina B. Esposito[1], Brian Bateman[2], Martha Werler[3], Loreen Straub[2], Sonia Hernandez-Diaz[4], Helen Mogun[2] and Krista Huybrechts[2]
[1]*Boston University School of Public Health & Ciconia, Inc, Boston, MA;* [2]*Brigham and Women's Hospital, Boston, MA;* [3]*Boston University School of Public Health, Boston, MA;* [4]*Harvard School of Public Health, Boston, MA*

Background: Prescription opioids are commonly used during pregnancy. While they have been shown to affect placental development and function in animal models, limited data are available.

Objectives: The objective of this study was to assess the relation between opioid use in pregnancy and ischemic placental disease.

Methods: Using a cohort of pregnant women and their liveborn infants nested in the US nationwide Medicaid Analytic eXtract database (2000-2014), we compared women with 2+ opioid dispensings in

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

pregnancy to unexposed women. Given uncertainty around the etiologically relevant window, we assessed early pregnancy exposure, late pregnancy exposure among those without early exposure, and both early and late exposure. Outcomes were placental abruption, preterm delivery, small for gestational age (SGA), and pre-eclampsia. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using cox proportional hazard models adjusting for demographics, opioid indications, comorbidities, and other medications. For analyses including late pregnancy, we used a time-varying exposure with gestational age as the time scale.

Results: Of 1,833,871 eligible pregnancies, 5.1% had 2+ opioid dispensings in early pregnancy, 1.6% had 2+ dispensings in late but not early pregnancy, and 1.8% had 2+ dispensings in both early and late pregnancy. Estimates of adjusted HR and 95% CI associated with early exposure were 1.34 (1.26-1.43) for placental abruption, 1.21 (1.18-1.23) for preterm delivery, 1.13 (1.09-1.17) for SGA, and 0.95 (0.91-0.98) for pre-eclampsia. Estimates for late exposure without early exposure were slightly attenuated. Women using opioids both early and late in pregnancy were at higher risk for placental abruption (1.62, 1.47-1.78), preterm delivery (1.37, 1.33-1.42) and SGA (1.26, 1.19-1.33), but not pre-eclampsia (0.99, 0.93-1.05). Results were generally consistent across multiple sensitivity analyses. Bias analyses suggested that misclassification of exposure, misclassification of outcome, and residual confounding due to smoking are unlikely to fully explain observed increases in risk.

Conclusions: Opioids may slightly increase risk of placental abruption, preterm birth and SGA, especially when exposure occurs both early and late in pregnancy. They do not appear to impact the risk of pre-eclampsia. These findings may help shed some light on the mechanism through which opioids affect placental function.

4901 | Paternal isotretinoin and the risk of major malformations and spontaneous abortion

Jon T. Andersen, Niklas Andersson, Mia Nørgaard, Ditte Gotfredsen and Thomas Bo Jensen

Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark

Background: Isotretinoin is a synthetic vitamin A analogue and is commonly used in the treatment of severe acne. Four cases of fetal anomalies and 25 uncomplicated births have previously been reported following paternal exposure. Moreover, manufacturers have reported that the amount of isotretinoin delivered via semen is 1,000,000 times lower than with an oral dose. Despite this, manufacturers continue to recommend contraception for men in treatment with isotretinoin.

Objectives: Therefore, we aimed to study the association between paternal exposure to systemic isotretinoin within three months before pregnancy and during the first trimester of pregnancy and major congenital malformation and spontaneous abortion.

Methods: We conducted a nationwide cohort study identifying all registered pregnancies in Denmark from 1997 to 2016. All births were identified using the Medical Birth Registry, and all records of induced and spontaneous abortions were identified from the National Patient Register. Data on drug use were from the National Prescription Register. Cox proportional hazard regression models were used to calculate the hazard of spontaneous abortion in women with a partner exposed to isotretinoin and logistic regression was used to estimate the association between exposure to isotretinoin and major malformations. The study was approved by the Danish Data Protection Agency (2015-41-4309).

Results: We identified 1,477,252 registered pregnancies with known paternity, of whom 1014 of the fathers were exposed to isotretinoin within three months before pregnancy to the end of the first trimester. Among the exposed pregnancies, 85 (8.4%) ended as a miscarriage compared to 131,191 (8.9%) among the unexposed. 26 (3.2%) fathered a child diagnosed with a major malformation among the isotretinoin exposed compared to 40542 (3.5%) among the unexposed. There was no association between exposure to isotretinoin from three months before pregnancy to the end of the first trimester and spontaneous abortion (aHR 1.04 (CI95% 0.84-1.29)), and there were no association between major malformations and paternal exposure to isotretinoin (aOR 0.88 (CI95% 0.60-1.30)). Subgroup analyses of paternal exposure only in the three months before pregnancy and only in the first trimester reviled similar results.

Conclusions: We found no association between major malformations or spontaneous abortion and paternal exposure to systemic isotretinoin before and during early pregnancy. Recommendations should reconsidered accordingly.

4902 | Bayesian latent class model for predicting gestational age at birth in an automated database

Shuang Wang[1], Gavino Puggioni[2] and Xuerong Wen[1]

[1]*University of Rhode Island, Kingston, RI*; [2]*University of Rhode Island, Kingston, RI*

Background: The use of automated databases is potentially limited in obstetric and perinatal research due to a lack of accurate estimations of gestational age at birth (GAB). Although several algorithms, either parametric or nonparametric, have been proposed to estimate GAB in the context of claims database, few have accounted for the unique distributional shape of GAB, which might induce bias into estimates.

Objectives: To propose a Bayesian latent class model to predict gestational age at birth using a claims database.

Methods: We developed a Bayesian latent class model, in which we assumed a mixture of Gaussian distributions and fitted a normal linear model within each class. Our Bayesian approach allows for modeling heterogeneity of the study population by identifying latent classes and estimating class-specific regression coefficients. Posterior computation was conducted using Markov Chain Monte Carlo Gibbs sampler steps. We used deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for selecting the optimal number

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of components and measured predictive accuracy by a series of root mean square error (RMSE) statistics.

Results: We applied the model to a cohort of 10,043 women aged 12-55 years with a live birth from 2008 to 2015 identified from the Rhode Island Medicaid administrative claims data linked to vital statistics. Mixture models, among which the 3-class and 6-class mixture maximized prediction accuracy, demonstrated notable improvement in predicting GAB compared with a normal linear model (RMSE: 1.84-2.15 vs. 2.34). Given our results, Medicaid women were partitioned into three classes featuring extreme preterm or preterm birth, preterm or "early" full-term birth, and "late" full-term birth. The 6-class model seemed to be a subclassification on the basis of the 3-class model. Obstetric complications appeared to have more influence on class-membership allocation than other patient-level characteristics.

Conclusions: Our model shows greater flexibility and accuracy in prediction performance when modeling a skewed continuous variable, as compared to traditional normal linear models.

4907 | Validation of claims-based estimates of the last menstrual period using electronic health records

Ryan M. Seals, Kelesitse Phiri, Robin Clifford, Michael C. Doherty and Florence T. Wang

Optum Epidemiology, Boston, MA

Background: Accurate dating of pregnancies is a crucial component of epidemiologic studies. While ICD-10 codes that specify gestational age in weeks (Z3A) allow dates of the last menstrual period (LMP) to be estimated within administrative databases, the validity of such LMP estimations is not well described.

Objectives: To validate estimates of LMP based on Z3A codes in insurance claims data with LMP derived from gestational age recorded in the clinical notes of an electronic health record (EHR) database.

Methods: Pregnancy episodes with information captured in both the insurance claims and EHR were identified in Optum's Dynamic Assessment of Pregnancies and Infants (DAPI) database, a US-based pregnancy database. From insurance claims data, LMP was calculated using both the first observed Z3A code and the median of all Z3A codes observed during that pregnancy episode. From the EHR, gestational age was parsed using generalized natural language processing of the free-text clinical notes to estimate the LMP.

Results: We identified a total of 4,026 pregnancy episodes with at least one Z3A code from the insurance claims and a mention of "gestational age" in the EHR. The median age of mothers at LMP was 30 (IQR 26-34) years. The median number of mentions of "gestational age" in the EHR per pregnancy episode was 1 (IQR 1-2; range 1-35). EHR mentions appeared most frequently in the final weeks of pregnancy (41% of EHR mentions were associated with 36+ weeks of gestation), with earlier peaks at 20 (3%) and 28 (2%) weeks. The two Z3A-based LMP estimates (first observed and median) had high agreement, with a mean difference in dates of 0.4 days (median 0). The LMP derived from EHR had a median difference of 0 days with both Z3A-based estimates, with slightly better agreement with the median Z3A LMP (mean 4.6 days difference vs 5.1 days with the first observed Z3A code). LMPs derived from EHR skewed earlier than those obtained from Z3A codes in claims: the EHR-based LMP fell between 36 days earlier and 15 days later than the Z3A-based LMPs in 90% of pregnancy episodes.

Conclusions: LMP estimates derived from insurance claims had high overall agreement with LMP estimates derived from clinical notes in the EHR. Mentions of "gestational age" in free-text clinical notes provide an accessible source of validation for claims-based estimates of LMP.

4911 | Variability in date of last menstrual period estimated using ICD-10 weeks of gestation codes

Ryan M. Seals, Kelesitse Phiri, Li Zhou, Michael C. Doherty and Florence T. Wang

Optum Epidemiology, Boston, MA

Background: Accurate dating of pregnancies is a crucial component of epidemiologic studies. The ICD-10 codes that specify gestational age in weeks (Z3A) may allow the last menstrual period (LMP) to be estimated from administrative databases more directly than was previously feasible.

Objectives: To characterize the distribution and variability in LMP dates estimated from multiple ICD-10 Z3A codes over the course of a single pregnancy.

Methods: Pregnancy episodes were identified from Optum's Dynamic Assessment of Pregnancies and Infants (DAPI) database, a US-based pregnancy database. Z3A codes and selected covariates were obtained for a sample of 10,000 pregnancy episodes. Individual LMP dates estimated from individual Z3A codes were compared to the median LMP, estimated from all observed Z3A codes for a single pregnancy. Descriptive statistics and variability in LMP estimates are presented across weeks of gestational age and by the following covariates: maternal age, provider specialty, trimester and timing of ultrasound procedures. Variability in LMP is assessed via the empirical 90% range (5^{th} to 95^{th} quantiles).

Results: A total of 631,720 women were identified with at least one pregnancy between 2015 and 2019. The median number of Z3A codes per pregnancy episode was 4 (IQR 2-8; range 1-108). Z3A codes appeared most frequently in the final weeks of pregnancy (34% were associated with 36+ weeks of gestation), with earlier peaks at 12 (3%), 20 (3%), 28 (3%) and 32 (4%) weeks. Variability in estimated LMPs was at a minimum in week 39 (90% of LMPs estimated within 7 days of the median), with other minima at weeks 20 and 36 (9 days). Variability was highest at week 24 (18.5 days). LMP variability was lower when estimated from claims associated with OB/GYN visits (8.5 vs 10 days for all other visits), particularly in the second trimester. LMP variability decreased across trimesters (12.5, 10, and 9.5 days). 58% of Z3A codes occurred in the two weeks following a claim for an ultrasound, and these were associated with less variability in LMP estimates, particularly

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

in the first trimester (12 vs 17.5 days). 64% of pregnancies resulted in live births, and these births had lower variability in LMP estimates, particularly in the third trimester (8.5 vs 12.5 days).

Conclusions: LMP date estimated by multiple Z3A codes is generally stable across the span of a pregnancy. Prioritizing Z3A codes associated with OB/GYN visits, and in the weeks following an ultrasound in the first two trimesters, may result in more stable and valid estimates of LMP.

4957 | Developing methodology to estimate gestational age using administrative claims

Aziza Jamal-Allial[1], Xintong He[1], Ramya Avula[2], Jade Dinh[1] and Stephan Lanes[1]

[1]*HealthCore Inc, Wilmington, DE;* [2]*HealthCore Inc, Wilmington, DE*

Background: The need to utilize administrative claims data to estimate gestational age (GA) with sufficient accuracy is growing, especially in identifying drug exposure and pregnancy outcomes. Currently, there is no standardized approach to estimate GA using current coding system. A prior approach is centered on assigning a fixed GA based on trimester/term; 287 day for full-term or 91 day for 1st-trimester termination

Objectives: Develop an algorithm to estimate GA using administrative claims based on GA specificity

Methods: A hierarchical approach that favors certain pregnancy codes based on GA specificity was applied. For end of pregnancy (EOP) event, an assigned lookup period-birth/delivery (-294 +3 day) or termination (-140 +14 day)-was used to search for GA codes. Our primary approach prioritizes week of gestation, Z3A% codes-ICD-10CM. Single Z3A ± 3 day of EOP was prioritized; if none found, at least two Z3A within lookup period that should be in a monotonically decreasing stand for a distinct pregnancy. In the absence of Z3A, the secondary approach uses other codes with a range of GA. If multiple codes were found, codes indicate specific GA or longer GA were prioritized, e.g., P0739-Preterm newborn 36 week, or S2260-Induced abortion 17-24 week. For codes with GA range, an approximate mid-point of GA +4 day was applied. When no codes indicating GA, the tertiary approach assigns a fixed GA based on trimester or term status e.g., full-term is 287 day, 273 day for no pre/postterm codes, 1st-trimester termination is 91 day. Study was conducted in HealthCore Integrated Research DatabaseSM (HIRD) using claims data from January 2016 to October 2019 from the US

Results: An algorithm for defining EOP events identified 11,698 pregnancies for women ages 15-49 years. GA was estimated using the primary method for 10,066 pregnancies (86%), while GA was estimated using the secondary method for 1,632 pregnancies (14%), and none had their GA calculated using the third approach. Most pregnancies that ended with birth/delivery had GA estimated using the preferred method compared to termination, 99%, and 53%, respectively

Conclusions: The accurate estimation of GA of any pregnancy is integral to improving maternal health outcomes. It is imperative for maternal research to accurately determine the start of any pregnancy for situations like assessing drug exposure, as incorrect assessment may lead to inaccurate drug safety profiles for use during pregnancy. The results support our recommendation to utilize this primary method to estimate GA for pregnancies, especially ones that resulted in birth/delivery, validation study is needed to assess its sensitivity

4958 | Clinical lactation studies: Are they meeting an unmet need for scientific evidence?

Dava W Vandall, Susan M Sinclair and Deborah L Covington

University of North Carolina Wilmington, Wilmington, NC

Background: Studies in various countries indicate that the vast majority of nursing mothers are prescribed medications immediately postpartum. Yet there is little scientific evidence on the extent of transfer of drugs into breast milk, their effects on milk production and composition, or their effects on the breastfed infant. Due to this dearth of scientific evidence, regulatory agencies in the EU and US have recently responded with guidance on conducting lactation studies and enhanced requirements for product labeling. These regulatory initiatives seek to inform clinical practice and produce useful information for families on drug safety in breastfeeding.

Objectives: To examine the status of completed and ongoing clinical lactation studies in the US and the availability of results produced by these studies.

Methods: Clinicaltrials.gov was searched for studies in the US, using the terms: lactation, breastfeeding, breast milk, and human milk. These were reviewed to determine study type, study status (active, completed, terminated), availability of study results, and study endpoints. Manual review was conducted to remove duplicates and unrelated studies.

Results: The search identified 221 lactation studies and 273 human milk studies; the majority were interventional (78.7% and 72.9% respectively) vs. observational. About one-third of the lactation studies (28.5%) and human milk studies (35.5%) were active. Although 63.8% of the lactation studies (n=141) and 54.2% (n=148) were completed, few had published results (n=19, 8.6% and n=24, 8.8%, respectively). Among the 43 studies with published results, endpoints included breast milk production and composition (51.2%), outcomes of breastfed infants (51.2%), and PK analysis examining drug transfer into breast milk (44.2%). In both groups combined, 24 studies had been suspended, terminated or withdrawn, primary reasons included lack of funding or recruitment issues (n=16, 66.7%). Other reasons included withdrawn by IRB, investigator/sponsor decision, and safety concerns.

Conclusions: Nearly 150 completed lactation and human milk studies are listed in clinicaltrials.gov, yet very few have published results. However, those studies measured endpoints of greatest concern where scientific evidence is sorely needed, including quantifying drug transfer into breast milk, drug effects on milk production and composition, and the effects on the breastfed infant.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4971 | Birth control utilization among mothers of infants with an extended stay in the NICU

Sara Z. Dejene, Alison Stuebe, Christine Tucker, Virginia Pate, Katherine Bryant and Michele Jonsson-Funk
University of North Carolina Chapel Hill, Chapel Hill, NC

Background: Optimizing the time intervals between births (aka birth spacing) is an important aspect of postpartum care. Contraception is the most common method for doing so and is recommended during the postpartum period. Birth spacing is particularly important for mothers of infants experiencing medically complex conditions that require extended stays in the neonatal intensive care unit (NICU). The mothers of these medically fragile infants (MMFIs) also experience barriers to accessing the health services needed during the postpartum period and may be less likely to receive contraception.

Objectives: To estimate the effect of newborn health status on birth control receipt in a population of commercially insured women receiving care at North Carolina Women's Hospital.

Methods: We identified women with a delivery at the North Carolina Women's Hospital between July 1, 2014 and June 30, 2016. We linked the electronic health records (EHR) from the hospital with their insurance claims data. We included women who were continuously insured one year before through 12 weeks after their delivery date. MMFIs were defined as women whose infants had a stay in the NICU of 3+ days or died while in the NICU. Mothers of well babies (MWBs) were defined as mothers whose infants were never admitted to the NICU or had a stay shorter than three days. A log binomial model adjusted for demographic and clinical characteristics was used to compare the incidence of birth control receipt.

Results: Among 1,292 women, 122 (9.4%) were categorized as MMFIs. Median age was 34 (IQR: 31-37) and was similar between MMFIs and MWBs. MMFIs were more likely than MWBs to be black (16.8% vs 10.5%), have chronic conditions such as hypertension (32.0% vs 16.0%) and diabetes (14.8% vs 6.2%), and deliver preterm (79.5% vs 5.1%). Fifty-eight (47.5%) MMFIs and 555 (47.4%) MWBs received at least one form of birth control within 12 weeks of delivery. Similar proportions of MMFIs and MWBs received oral contraception (14.8% vs 18.5%) and intrauterine devices (23.0% vs 24.6%). After adjusting for maternal age, race/ethnicity, chronic disease, prenatal care, parity, and preterm status, MMFIs were slightly less likely to receive postpartum birth control (adjRR 0.91, 95% CI 0.71, 1.18).

Conclusions: Birth spacing is an important preventative measure for future adverse pregnancy outcomes. Less than half of mothers received birth control in the 12 weeks following delivery. While MMFIs were not at substantially greater risk of inadequate contraception, improving access to effective contraception may be of particular benefit to these women. Further work is needed to improve postpartum care for MMFIs.

4982 | Medication safety during breastfeeding: An analysis of prescribing information

Dava W Vandall, Susan M Sinclair and Deborah L Covington
University of North Carolina Wilmington, Wilmington, NC

Background: With implementation of FDA's Pregnancy and Lactation Labeling Rule (PLLR) in June 2015, product labels are required to provide human data on safety of product use during pregnancy and lactation. The FDA and EMA have provided guidance documents intended to support the PLLR by assisting manufacturers in conducting human lactation studies. However, these studies are not generally required in pre-approval trials, or routinely, in post-marketing studies. FDA guidance describes 2 study designs, Mother-infant Pair and Lactating Women Only, to guide the collection of human pharmacokinetic (PK) data and assess the transfer of medications to the infant via breast milk.

Objectives: To evaluate labeling for medications with indications relevant to women of reproductive age for consistency with FDA and EMA guidelines and regulations.

Methods: The US prescribing information (USPI) for 8 medications was reviewed for lactation/breastfeeding data, risk communication and risk mitigation. Four of the 8 were established medications (initial approval 1991-2002): escitalopram, sertraline, sumatriptan, and rizatriptan. Four were newly approved medications (2017-2018): elagolix, secnidazole, tildrakizumab-asmn, and dupilumab. The indications included depression/anxiety, migraine, endometriosis pain, plaque psoriasis, atopic dermatitis, and asthma.

Results: Of the 4 newly approved medications, 2 report no lactation data (elagolix, dupilumab) and 2 had animal data only (secnidazole, tildrakizumab-asmn). Among the 4 established medications, 1 reported a mother-infant pair study (sertraline, n=53); 4 reported data from plasma and milk studies with small sample size (escitalopram [n=8], sumatriptan [n=5]); and 1 (rizatriptan) included animal data only. Six of the 8 labels suggested caution in breastfeeding and/or risk-benefit considerations. Dosing recommendations were reported for secnidazole, i.e., not recommended especially within 96 hours of dosing, and sumatriptan, i.e., avoid breastfeeding for 12 hours after subcutaneous dosing with no data for oral dosing. All 4 of the established medications and 1 of the new medications (dupilumab) were involved in post-marketing registries or observational studies.

Conclusions: The USPI for medications used by women of reproductive age does not consistently adhere to regulatory guidance, particularly for newly approved medications. The rapid rate of infant growth and development combined with the benefits of breastfeeding underscore the importance of clinical lactation studies.

4989 | Missing links in pregnancy safety studies: How different are mothers with non-linkable infants in claims databases?

John D. Seeger, Michael Doherty, Kelesitse Phiri, Monica L Bertoia, Ryan Seals and Florence T. Wang
Optum, Boston, MA

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Health insurance claims databases as a source for pregnancy safety studies depend on exposure, covariate, and outcome capture within the database. Mothers can be linked to infants through unique family or subscriber identifiers, and some live-birth deliveries among mothers do not result in infant claims, suggesting that the infant is receiving reimbursement for healthcare services through other sources. In these non-linkable infants, outcomes that do not appear on the maternal medical record, such as malformations or small-for-gestational age, are not observed. If the characteristics of women who are not linked to infants differ from those who are, the generalizability of results of pregnancy safety studies may be limited.

Objectives: To characterize women with non-linkable infants relative to those with linkable infants.

Methods: This study was conducted within Optum's Dynamic Assessment of Pregnancies and Infants (DAPI) database, a US-based pregnancy database between January 2016 and December 2018. In this timeframe, we identified deliveries among women based on CPT codes along with ICD-10 diagnosis and procedure codes. Mothers and infants were linked through subscriber information, as available. Characteristics of the mothers not linked to infants relative to those linked were described.

Results: Among 121,719 pregnancies with live-birth deliveries, 18,474 (15.2%) were not linkable to an infant. The women with non-linkable infants tended to be younger (24.9 years vs 26.9 years), including a substantial difference in women aged 35+ (7.6% vs 25.8%). Women with non-linkable infants had less use of two medications prior to estimated LMP: thyroid medications (2.3% vs 6.3%), metformin (1.5% vs 2.8%). Conversely, women with non-linkable infants had more use of the following medications prior to estimated LMP: contraceptives (20.4% vs 19.0%), metronidazole (5.0% vs 2.2%), and SSRIs (7.7% vs 6.6%). These differences in medication use preceding pregnancy represent treatment for conditions or comorbidities associated with age. Diagnoses differing among women with non-linked infants included infertility (2.6% vs 8.1%), hypothyroidism (2.2% vs 5.0%), similarly reflecting the age difference.

Conclusions: Women with non-linkable infants in this commercial health insurance database tended to be younger and displayed medication use and diagnoses associated with younger age. Study generalizability should be considered when selecting a data source within which to conduct a pregnancy safety study. Further investigation into reasons for non-linkage of infants is warranted.

4992 | Trends in antinausea medication use in pregnancy in New Zealand, 2006-2016

Paige D. Wartko[1], Anna S. Howe[2], Susan M. Shortreed[1], Rita Mangione-Smith[1] and Sascha Dublin[1]

[1]*Kaiser Permanente Washington Health Research Institute, Seattle, WA;* [2]*University of Auckland, Auckland, New Zealand*

Background: With up to 80% of pregnant women experiencing nausea or vomiting, many use antinausea medications, but the prevalence of use has not been well-quantified in recent years. Several studies were published in 2012-2014 suggesting greater risk of birth defects associated with one antinausea medication, ondansetron. It is unknown if publicity about these studies affected use.

Objectives: To describe trends in antinausea medication use during the first trimester of pregnancy in New Zealand and assess whether the prevalence of ondansetron use changed after 2014.

Methods: We used New Zealand national data collections that include essentially all livebirths to identify singleton deliveries from 2006-2016. We determined first trimester exposure by linking maternity data, which provided information such as timing of last menstrual period, with medication dispensings from the pharmaceutical collection using a national health identification number. For each study year, we calculated the proportion and Wald 95% confidence intervals (CI) of women with ≥1 dispensing during their first trimester for specific antinausea medications. We report the average annual change in percentage of births exposed. We conducted a chi-squared test for trend in proportions over the entire study period, as well as for ondansetron from the start of the study period until 2012 and after 2014.

Results: There were 608,774 eligible births. The mean maternal age at delivery was 29.3 years, and 40.0% of births were to nulliparous women. 20.7% of births were to Māori women, 12.3% to Asian women, and 54.6% to European women. First-trimester use of antinausea medications rose from 5.1% (95% CI: 4.9-5.3%) in 2006 to 18.1% (95% CI: 17.8-18.5%) in 2016, representing an additional 1.3% of births exposed each year (p for trend <0.001). This increase was driven by metoclopramide, with 3.8% (95% CI: 3.6-4.0%) of births exposed in 2006 and 12.6% (95% CI: 12.3-12.9%) by 2016, and ondansetron, increasing from 0.2% (95% CI: 0.1-0.2%) in 2006 to 4.0% (95% CI: 3.8-4.1%) in 2014 and 7.6% (95% CI: 7.4-7.6%) in 2016. Ondansetron use increased both in 2006-2012 (additional 0.4% of births exposed each year; p <0.001) and 2014-2016 (additional 1.1% of births exposed each year; p <0.001).

Conclusions: Use of antinausea medications during the first trimester increased substantially in New Zealand in recent years, with nearly 1 in 5 births exposed by 2016. Use of ondansetron did not decrease after some studies reported a greater risk of birth defects. Given the vast number of births exposed, more research is needed on the safety of these medications in pregnancy, for both short- and long-term outcomes.

4998 | Utilization of IV Iron among pregnant women with live births or stillbirths in the sentinel distributed database

Steven T. Bird[1], Nicole Haug[2], Richard S. Swain[1], Kate Gelperin[1], Joy Kolonosky[2], Justin Bohn[2] and Mayura Shinde[2]

[1]*Food and Drug Administration, Silver Spring, MD;* [2]*Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA*

Background: Intravenous (IV) iron can aid in treatment of severe iron deficiency anemia after failure of oral iron in pregnant women.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Reports of fetal adverse effects from maternal hypersensitivity reactions to IV iron have been received by FDA, including fetal bradycardia, and rarely, fetal demise (stillbirth). A recent class-wide label change to IV iron products by the European Medical Agency now requires fetal monitoring during IV iron administration in pregnant women.

Objectives: To evaluate the utilization of IV iron in pregnancy, compare IV iron utilization rates among stillbirths versus live-birth deliveries (LBD), and assess codes consistent with acute hypersensitivity reactions. Case reports of fetal demise in temporal association with IV iron administration will be described.

Methods: The Sentinel Distributed Database was used to retrospectively identify U.S. LBDs and stillbirths among non-dialysis dependent women between 2008 and 2019. Use of IV iron was quantified by gestational week during the 20 weeks prior to delivery. A prevalence ratio was calculated to compare use of IV iron in pregnancies resulting in stillbirths versus LBD. Coding consistent with acute hypersensitivity reactions was quantified.

Results: We observed IV iron exposure in the 20 weeks prior for 11,209 of 4,355,396 LBD (0.26%; 2.8 weeks with infusions/LBD) and 103 of 68,469 stillbirths (0.15%; 2.5 weeks with infusions/stillbirth) for an unadjusted prevalence ratio of 0.59 (95%CI: 0.48-0.71) in stillbirth vs. live-births. An additional 457 (0.01%) LBDs and 11 (0.02%) stillbirths received IV iron on the delivery date, though some administrations likely occurred postpartum. Among LBDs, 80.0% of administrations were observed in the 10 weeks prior to delivery, peaking 3 weeks prior to LBD. Among stillbirths, administrations peaked on the week preceding and day of delivery. Three LBDs had inpatient or emergency coding for anaphylaxis and 11 LBDs received epinephrine on the same day or following day of IV iron. Diphenhydramine was 2.4 times more likely to be administered with IV iron on the day of LBD (17.5% vs 7.4%) and 4 times more likely on the day of stillbirth (27.3% vs 6.8%), compared to the 20 weeks prior.

Conclusions: Although anemia is a frequent diagnosis among pregnant women, IV iron was administered uncommonly during 2008-2019, consistent with professional society guidelines which state that oral preparations are appropriate and sufficient in most clinical circumstances. Given rare case-reports of fetal adverse effects after IV iron administration, benefit - risk balance should be carefully considered.

5042 | Antiepileptic drug use in pregnancy and the incidence of neurodevelopmental disorders in children

Oluwadolapo Lawal[1], Kimford Meador[2], Justin Gold[1], Anne Hume[3], Kelly Matson[3] and Xuerong Wen[1]

[1]University of Rhode Island, Kingston, RI; [2]Stanford University School of Medicine, Palo Alto, CA; [3]University of Rhode Island, Kingston, RI

Background: Evidence from observational studies suggest that maternal use of antiepileptic drugs (AEDs) may be associated with increased risks of childhood cognitive impairments. However, inferences from these studies on the long-term risks of neurodevelopmental outcomes in children with prenatal AED exposure have been hampered by methodological issues including small sample-size and limited adjustment for confounding by the underlying indication.

Objectives: The aim of this retrospective cohort study was to evaluate the relationship between prenatal AED exposure and neurodevelopmental disorders in children.

Methods: This study was conducted using claims data submitted to Optum Clinformatics Data Mart™ from January 2010 through December 2017. We included mothers aged 12 - 55 years, and their liveborn infants born prior to December 2013. Infants were followed till incidence of neurodevelopmental disorders, loss of insurance eligibility, or study end, whichever came first. We adjusted for confounders using propensity score fine stratification with 50 strata. Infants were considered exposed if mothers filled ≥1 AED prescription during pregnancy; the comparison group comprised of infants whose mothers had no fill of AEDs ≥3 months prior and during pregnancy. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional models.

Results: Our analysis cohort comprised of 85,421 mothers and 90,159 live-born infants. About 0.6% (561) infants were exposed to AEDs during pregnancy. Of the 78 children born to mothers with diagnosis of epilepsy, 32% (25) were prenatally exposed to AEDs. Overall, 8003 children were diagnosed with neurodevelopmental disorders, with incidence rates of 47.1 in exposed children vs. 37.9 per 1000 person-years in unexposed children (HR [95%CI]: 1.26 [0.98, 1.64]). Following covariate adjustment, there was no association between prenatal AED exposure and neurodevelopmental disorders (0.95 [0.74, 1.24]) and after adjusting for mother's epilepsy indication (1.02 [0.70, 1.48]). Similarly, we observed no association after redefining the exposure to ≥2 AED prescriptions (1.14 [0.71, 1.83]), the outcome measure as ≥2 claims on two separate days (1.03 [0.62, 1.71]), or restricted our analyses to infants with cumulative AED exposure ≥30 days (1.18 [0.74, 1.87]), or considered exposure by specific trimester, or ≥2 trimesters during pregnancy.

Conclusions: About 8 in every 100 children were diagnosed with neurodevelopmental disorders, with no significant association observed with prenatal AED exposure. Further research is needed to confirm these findings.

5045 | Prescription medication use during pregnancy in the US

Katherine C Hughes, Robin Clifford, Kelesitse Phiri, Rachel Ogilvie and Florence Wang

Optum Epidemiology, Boston, MA

Background: The majority of pregnant women are prescribed at least one medication during pregnancy, yet there are limited data regarding safety of use during pregnancy. Risks of medications may vary according to trimester of use.

Objectives: To describe prescription drug use in a cohort of commercially insured pregnant women.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods: Using the Optum Dynamic Assessment of Pregnancies and Infants (DAPI) database, pregnancies were identified from October 2015 through July 2019. The start of each pregnancy, defined by the last menstrual period (LMP), was estimated in two ways. For pregnancies where at least one ICD-10 Z3A code was observed (83.5%), LMP was estimated by subtracting the specified number of gestation weeks from the service date of each Z3A code within the pregnancy episode, and taking the median of these dates. For pregnancies without Z3A codes, a published algorithm that estimates LMP based on date and type of pregnancy outcome was used. We used pharmacy dispensing records to identify medication use during pregnancy episodes, and identified the most commonly dispensed medications overall and during each trimester. Medications were grouped according to American Hospital Formulary Service (AHFS) pharmacologic-therapeutic classification.

Results: A total of 621,124 pregnancies were identified from DAPI. The median age at LMP was 31 years and 76.1% of pregnancies resulted in livebirths. At least one dispensing was observed in 58.9% of pregnancies. The most common class of drug dispensed during pregnancy was antibacterials (22.1% of pregnancies), followed by analgesics and antipyretics (11.9%), multivitamin preparations (10.8%), antiemetics (9.8%), and urinary antiinfectives (7.6%). Use of antibacterials, analgesics and antipyretics, antiemetics, and progestins peaked during the first trimester, while use of diagnostics for diabetes and antidiabetic agents peaked during the third trimester. The most common specific drugs dispensed during pregnancy were azithromycin (7.5%), nitrofurantoin (7.4%), amoxicillin (6.2%), progesterone (5.1%), and metronidazole (5.1%).

Conclusions: Medications indicated to treat infection were the most commonly dispensed during pregnancy. The pattern of drug use according to gestational age generally matched expectations, with progestins and nausea treatments being more common in the first trimester, and diagnostics and treatments for gestational diabetes being more common in later pregnancy.

5079 | Isotretinoin during pregnancy and the risk of spontaneous abortion

Ditte Gotfredsen[1], Mia Nørgaard[1], Niklas Andersson[1], Thomas Bo Jensen[1] and Jon T. Andersen[2]

[1]*Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark;*

[2]*Copenhagen University Hospital Bispebjerg, København NV, Denmark*

Background: Isotretinoin is a synthetic vitamin A analogue and is commonly used in the treatment of severe acne. Isotretinoin is apart from thalidomide considered as one of the strongest teratogens known in human. Use during pregnancy has been associated with several different birth defects and can lead to the characteristic retinoid embryopathy. Furthermore, exposure to isotretinoin has been associated with an increased risk of spontaneous abortion, but the data is still limited.

Objectives: Therefore, we aimed to study the association between exposure to systemic isotretinoin from one months before pregnancy and during the first trimester of pregnancy and spontaneous abortion.

Methods: We conducted a nationwide cohort study identifying all registered pregnancies in Denmark from 1997 to 2016. All births were identified using the Medical Birth Registry, and all records of induced and spontaneous abortions were identified from the National Patient Register. Data on drug use were from the National Prescription Register. Cox proportional hazard regression models were used to calculate the adjusted hazard of spontaneous abortion in women exposed to isotretinoin from one month before pregnancy to the end of the first trimester. The study was approved by the Danish Data Protection Agency (2015-41-4309).

Results: We identified 1,704,501 registered pregnancies in the study period, of whom 352 pregnant women were exposed to isotretinoin within one month before pregnancy to the end of the first trimester. Among the exposed pregnancies, 28 (8.0%) ended as a spontaneous abortion compared to 177,920 (10.4%) among the unexposed. When taking the time into account in an adjusted Cox proportional hazard regression model we found an adjusted hazard ration of 1.56 (CI95% 1.08-2.26) of experiencing a spontaneous abortion among women exposed to systemic isotretinoin. Exposure in the month before pregnancy was associated with a non-significant increase in the hazard of spontaneous abortion aHR=1.27 (0.71-2.11). Exposure during the first trimester was also associated with an increased hazard of spontaneous abortion aHR= 1.77 (CI95% 1.16-2.72).

Conclusions: We found an association between maternal exposure to isotretinoin during pregnancy the first trimester of pregnancy. This is in accordance with the existing literature.

5083 | Podophyllotoxin is an antimitotic agent primarily used in the local treatment of anogenital warts. Data That Enable the Assessment of the Fetal Safety of Podophyllotoxin Use During Pregnancy are Lacking

Niklas Andersson and Jon T. Andersen

Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark

Background: Podophyllotoxin is an antimitotic agent primarily used in the local treatment of anogenital warts. Data that enable the assessment of the fetal safety of podophyllotoxin use during pregnancy are lacking.

Objectives: To investigate the association between local podophyllotoxin exposure during pregnancy and risk of adverse fetal outcomes

Methods: This cohort study obtained individual-level pregnancy data from various nationwide registries in Denmark from the study period of January 1, 1997, through December 31, 2016, resulting in a cohort of 1 650 649 pregnancies. Local podophyllotoxin-exposed pregnancies were compared with unexposed pregnancies and matched in a 1:10 ratio according to propensity scores on a wide set of

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

baseline characteristics. Five distinct study cohorts were constructed, one for each outcome analysis. Sensitivity analyses included a comparison of podophyllotoxin-exposed pregnancies with pregnancies with podophyllotoxin use only before pregnancy onset. Exposure was defined as a filled prescription for local podophyllotoxin.

Primary outcomes were major birth defects and spontaneous abortions. Secondary outcomes were preterm births, small-for-gestational-age (SGA) size, and stillbirths.

Results: This study included 9229 pregnancies (mean [SD] maternal age at pregnancy onset, 27.7 [5.2] years) for the analyses of major birth defects and 18 590 pregnancies (mean [SD] maternal age at pregnancy onset, 26.4 [6.0] years) for the analyses of spontaneous abortions. Among the podophyllotoxin-exposed pregnancies, 29 infants (3.5%) were diagnosed with major birth defects, compared with 286 (3.4%) among the unexposed pregnancies. A total of 141 podophyllotoxin-exposed pregnancies (8.3%) ended in spontaneous abortion, compared with 1626 (9.6%) among the unexposed pregnancies. No statistically significant associations were found between podophyllotoxin exposure during pregnancy and major birth defects (prevalence odds ratio [OR], 1.02 95% CI, 0.69-1.50), spontaneous abortions (HR, 0.87; 95% CI, 0.73-1.04), preterm births (prevalence OR, 1.08; 95% CI, 0.86-1.35), SGA size (prevalence OR, 1.01; 95% CI, 0.85-1.22), or stillbirths (HR, 0.58; 95% CI, 0.18-1.86).

Conclusions: Findings from this study suggest that podophyllotoxin use during pregnancy may be safe, as it did not appear to be associated with an increased risk of adverse fetal outcomes. These findings may help guide clinicians, patients, and drug regulatory authorities when prescribing podophyllotoxin.

5085 | Prediction of future cardiovascular diseases for women with hypertensive disorders of pregnancy

Ugochinyere Vivian Ukah[1], Natalie Dayan[2], Nathalie Auger[3] and Robert Platt[1]

[1]McGill University, Montreal, QC, Canada; [2]McGill University Health Centre, Montreal, QC, Canada; [3]Institut National de Santé Publique du Québec, Montreal, QC, Canada

Background: Cardiovascular disease (CVD) is the number one cause of mortality in women. Women with hypertensive disorders of pregnancies (HDP) are at increased risk of developing future CVD. As most CVD are preventable, it is important to identify which women with hypertensive disorders of pregnancies have the greatest risk of developing cardiovascular disease. This will help direct intervention, lifestyle (diet and exercise) modification, and early treatment with medications such as statins, for women who may benefit more from CVD prevention.

Objectives: To develop a 10-year CVD prediction model to identify which women, who had hypertension during pregnancy, are at the highest risk of cardiovascular disease.

Methods: A population-based cohort of women aged 18-45 years who delivered between April 1989 and March 2017 with HDP in Quebec, Canada, was used. HDPs were defined as chronic hypertension, gestational hypertension, pre-eclampsia/eclampsia, and superimposed pre-eclampsia, using International Classification of Diseases (ICD) codes. Cardiovascular outcomes included heart diseases e.g. heart failure, cerebrovascular diseases e.g. stroke pulmonary heart diseases, procedures involving the heart and blood vessels, and coronary care unit admission, also identified using ICD codes. Cox regression was used to develop a 10-year prediction model and the model was assessed based on discrimination, calibration and risk stratification ability.

Results: Among women with HDP (N= 95,537) who contributed a total of 1,401,084 person-years follow-up, the rate of CVD within ten years was 1.6% (1585 events). The model had modest discriminatory performance (AUC 0.66 [95% confidence interval (CI) 0.65-0.67]) and good calibration with slope of 0.95 and intercept of -0.19. There was moderate classification accuracy (LR+: 5.90 (95% CI 5.01-6.95)) in the highest risk group upon risk stratification.

Conclusions: Our final model had a modest prediction ability to predict CVD risk within 10 years after HDP. Using our model, women in the highest risk category may be targeted for CVD prevention through lifestyle and drug intervention. However, we suggest that the model be improved with the addition of clinical variables, and external validation, before consideration for clinical use.

5116 | Antipsychotic use during pregnancy and neurodevelopmental outcomes in children: A nordic population register-based study

Óskar Ö. Hálfdánarson[1,2], Jacqueline M. Cohen[3], Øystein Karlstad[3], Carolyn E. Cesta[4], Maarit K. Leinonen[5], Buket Öztürk[6], Kari Furu[3], Kristjana Einarsdóttir[1], Mika Gissler[5,7,4], Mette Nørgaard[6], Helle Kieler[4], Marte-Helene Bjørk[8,9], Johan Reutfors[4] and Helga Zoega[1,2]

[1]University of Iceland, Reykjavik, Iceland; [2]UNSW Sydney, Sydney, Australia; [3]Norwegian Institute of Public Health, Oslo, Norway; [4]Karolinska Institutet, Stockholm, Sweden; [5]Finnish Institute for Health and Welfare, Helsinki, Finland; [6]Aarhus University, Aarhus, Denmark; [7]University of Turku, Turku, Finland; [8]Haukeland University Hospital, Bergen, Norway; [9]University of Bergen, Bergen, Norway

Background: Pregnant women are increasingly exposed to antipsychotics. Previous studies have focused on the risks of congenital anomalies and short-term neonatal complications associated with *in-utero* exposure to antipsychotics, while data on risks of neurodevelopmental disorders in the offspring are sparse.

Objectives: To determine whether children exposed to antipsychotics *in-utero* have an increased risk of attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD).

Methods: A population-based cohort study based on nationwide data from the Nordic health registers including children born in Denmark

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(1997-2016), Finland (1996-2015), Iceland (2004-2017), Norway (2005-2017), and Sweden (2006-2016). We used Cox proportional hazard regression models to assess the association between antipsychotic exposure *in-utero* (defined as at least one dispensing from last menstrual period until birth) and childhood risks of being diagnosed with ADHD or ASD; calculating hazard ratios (HRs) and 95% confidence intervals (CIs) separately for each outcome. To account for antipsychotic indication, we restricted the analyses to children whose mothers had a diagnosis of bipolar disorder or schizophrenia.

Results: We identified 1,940,888 singleton births in Iceland, Norway, and Sweden, thereof 7444 (0.4%) were exposed to antipsychotics *in-utero*. During an average follow-up of 7.1 years, we observed a cumulative incidence of 2.9% (219) *vs*. 1.4% (27,058) for ADHD and 1.6% (120) *vs*. 0.8% (16,174) for ASD, respectively among exposed and unexposed children. Adjusting for maternal age and birth year, our preliminary analyses suggest a HR of 1.5 (95% CI: 1.34-1.75) for ADHD and 1.7 (95% CI: 1.44-2.06) for ASD. Restricting the analyses to children whose mothers had a recorded diagnosis of bipolar disorder or schizophrenia yielded a HR of 1.4 (95% CI: 1.00-2.00) for ADHD and 3.2 (95% CI: 2.28-4.53) for ASD.

Conclusions: Further analyses are needed before concluding on the association between antipsychotic use in pregnancy and risks of ADHD and ASD in childhood. Our next steps are to include data from Denmark and Finland; conduct analyses with further adjustments; employ different comparison groups; and to stratify according to specific antipsychotics. We will also employ a sibling design to account for unmeasured confounding.

Rare Disease

2687 | Incidence and risk factors of 30-day readmission after hospitalization for chemotherapy among acute lymphocytic leukemia patients

Phuong T. Tran[1,2], William B. Slayton[3] and Joshua Brown[4,2]
[1]*Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL;* [2]*Center for Drug Evaluation and Safety, University of Florida, Gainesville, FL;* [3]*University of Florida Health Shands Children's Hospital, Gainesville, FL;* [4]*Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL*

Background: Due to immunodeficiency and intensive treatment, patients with acute lymphocytic leukemia often require hospitalization for chemotherapy, placing them at high risk for unintentional readmissions.

Objectives: To identify the incidence, top causes, and risk factors of 30-day readmission after chemotherapy admission among children and adults with acute lymphocytic leukemia.

Methods: This was a retrospective cohort of acute lymphocytic leukemia patients who received at least one inpatient chemotherapy treatment in 2016 using National Readmission Database. We excluded patients without risk for readmission such as those that died or transferred during the index admission, not a resident in the state, or index admission was in December. Causes of readmission were classified by Clinical Classifications Software Refined using primary and secondary diagnoses codes. For risk factor analysis, we applied 3 different outcome definitions: (1) nonelective readmission which was based on readmission type reported by hospitals, (2) unplanned readmission was defined by the algorithm developed by the Center for Medicare and Medicaid, and (3) unintended readmission was the combination of the two previous outcome measures. Patients were followed 30 days after discharge to assess the outcomes. We used a weighted survey procedure to calculate incidence and unweighted, multivariable Poisson regression with robust estimates for risk factors analysis, including age, sex, disease states, disease severity, length of stay, daily charge, expected payers, hospital characteristics, and type of admission. Sensitivity analyses include stratifying by age group, disease states and admission type.

Results: Weighted readmission rates for nonelective readmission, unplanned readmission, and unintended readmission were 33.3%, 22,4%, and 18.5%, respectively. Top 3 causes for readmission were neutropenia/agranulocytosis (27.8%), septicemia (15.3%) and aplastic anemia (11.5%). Risk ratios for unintended readmission were 1.21 (1.08-1.36) for nonelective vs elective admission, 1.19 (1.06-1.33) for public vs private insurance enrollees, 0.96 (0.95-0.98) for length of stay (days), 0.77 (0.62-0.95) for large, teaching, 0.87 (0.70-1.08) for small teaching vs nonteaching hospitals.

Conclusions: Risk factors for readmission vary based on outcome definitions. Using the most stringent definition, opportunity exits to reduce readmission among patients with acute lymphocytic leukemia.

3927 | The inclusion of real-world data in health technology assessment submissions is associated with a higher likelihood of positive decisions

Christina J. Qian, Alison M. Deighton, Meagan M. Harwood, Alexis T. Mickle and Shelagh M. Szabo
Broadstreet HEOR, Vancouver, BC, Canada

Background: Clinical trial data to characterize the efficacy and safety of rare disease treatments are scarce. In the past decade, the use of real-world data (RWD) in health technology assessments (HTAs) of rare-disease medications appears to be increasing in several countries. Whether the use of RWD in HTA submissions is associated with a positive outcome remains unclear.

Objectives: To estimate the association between the use of RWD and outcomes of HTA appraisals for medications for rare diseases in the UK and Canada.

Methods: Appraisals for medications of rare diseases with a prevalence of 10-50 per 100,000 from NICE (UK) and CADTH (Canada) published between 2009-2019 were reviewed. Extracted data included the indication, medication, country of HTA, date of published recommendation, whether inclusion of RWD was part of evidence submission, whether

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the medication of interest was a new drug in the country, and whether this medication was previously reviewed and/or recommended in the other country of interest. A mixed-effects logistic regression model was used to estimate the effect of RWD use on the outcome of the HTA review (recommended vs. not recommended), accounting for random effects within the same indication.

Results: Among the 130 appraisals published between 2009 and 2019 in Canada and UK, a total of 33 unique rare diseases (23 from CADTH; 24 from NICE) were included. The majority (83%) of published appraisals were recommended (75% among CADTH; 93% among NICE); and more appraisals submitted to CADTH (67%, vs. 37% for NICE) included RWD. The final model adjusted for country of review, and whether the medication had been reviewed previously. Compared to appraisals that did not include RWD as part of their evidence submission, appraisals that included RWD were associated with approximately four times higher odds of being recommended (odds ratio=3.96 [95%CI 1.2 to 21.4]).

Conclusions: This study shows that the inclusion of RWD in HTA submissions for rare disease medications in the UK and Canada is associated with a higher likelihood of having a positive outcome. A more in-depth understanding of the types of RWD considered meaningful to decision makers is warranted. Additionally, understanding other factors that vary between submissions with positive vs. negative outcomes are necessary to help guide the inclusion of RWD in HTA.

4073 | Representativeness of komodo claims and identification of patients with rare disease

Carey Strader[1], Tom Haskell[2] and Meghan Dierks[3]
[1]*Kantar, St. Louis, MO;* [2]*Kantar, Horsham, PA;* [3]*Harvard, Boston, MA*

Background: It is challenging to estimate prevalence of rare diseases given the small case numbers. Due to large sample sizes in Real-World Data, a claims analysis may be a feasible approach to better estimate disease occurrence. Health insurance administrative data are a rich data source and utilized increasingly more; however, to be considered reliable in rare disease, we must first explore national representativeness of the claim data's population against the US Census projections.

Objectives: This study first aims to compare patient characteristics using Komodo claims and the US Census; subsequently, exploring prevalence of several rare diseases.

Methods: Komodo Health is a US healthcare data and software provider which has built a large database of both open (N=150 million) and closed (N=78 million) medical and pharmacy claims. The 2018 Komodo closed claims and US Census Bureau population estimates were compared using descriptive statistics of patient characteristics (age, gender, region, and insurance). Then the prevalence of cystic fibrosis, hemophilia A, and myasthenia gravis were compared between Komodo open claims and Epi Database® (a tool based on comprehensive literature review).

Results: In comparing the Komodo sample to the US Census, highly similar distributions were observed for geography and demographic characteristics. By region, the Komodo sample aligns to the US population as estimated by the US Census (Northeast: 19% Komodo 17% Census; South: 38% Komodo 37% Census; Midwest: 21% Komodo 22% Census; West: 22% Komodo 24% Census) along with a slightly higher representation of females (54% Komodo, 51% Census) and comparative age distributions (age 60+ 18% Komodo, 22% Census). US Census[1] reports 92% of the US population is insured and among those with insurance most have a commercial versus a public plan (commercial: 75% Komodo, 74% Census; Medicare: 14% Komodo, 19% Census). The prevalence of myasthenia gravis in the Komodo claims was 34 per 100,000 while Epi Database reports a range of 14-40 per 100,000. An investigation of cystic fibrosis and hemophilia A resulted in 45,000 and 18,000 cases while Epi Database reports 37,000 and 15,000 cases (respectively).

Conclusions: Since claims data are a valuable resource for epidemiology research, it is important to confirm sample representativeness. In comparing the geographic distribution and demographic characteristics of the Komodo sample to the US Census estimates, the claims data appear reflective of the US population. Further, the claims data can be used to estimate prevalence of rare disease as shown by comparing several well studied diseases.

4093 | Using electronic data to validate Fournier's gangrene diagnoses

Gregory A. Nichols[1], Anouk Deruaz-Luyet[2], Hristo Iliev[2] and Kimberly G. Brodovicz[3]
[1]*Kaiser Permanente Northwest, Portland, OR;* [2]*Boehrniger Ingelheim GmbH, Ingelheim am Rheim, Germany;* [3]*Boehrniger Ingelheim Pharmaceuticals, Ridgefield, CT*

Background: The accuracy of recorded diagnoses of Fournier's Gangrene (FG) using ICD9/ICD10 codes in electronic medical records or claims databases in the United States is unknown.

Objectives: To validate ICD9/ICD10 diagnoses of FG recorded in the electronic medical record (EMR) of an integrated health system and to compare the demographic and clinical characteristics of patients with FG diagnoses that could be validated vs. those that could not be validated diagnosis and with matched patients with a differential diagnosis.

Methods: We identified all patients with a diagnosis of FG from inpatient (any position), outpatient or emergency department diagnoses from 2005-2018 and patients with a differential diagnosis of other infection or abscess of the genitalia or perineum matched on age, sex and year of diagnosis. We used a combination of codes to identify cases in women since diagnosis codes in ICD9 are specific to men. We conducted an EMR review to confirm cases with a clear clinical notation of FG and described the demographic and clinical characteristics of confirmed cases and unconfirmed cases and of patients with a differential diagnosis and calculated the sensitivity and specificity of ICD9/ICD10 FG diagnoses.

Results: Of the 218 patients with an FG diagnosis, only 48 (22%) had clinical notations indicating FG. No patients with a differential

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

diagnosis had confirmed FG. Thus, an FG diagnosis provided perfect sensitivity but only 56% specificity. Case confirmation was 65% among the 34 patients identified with ICD10 diagnoses, but only 14% among the 184 patients identified with ICD9 diagnoses. Patients with an FG diagnosis were similar to patients with a differential diagnosis, but FG patients differed by whether their diagnosis was confirmed. Confirmed patients were older (56 vs. 50 years), less likely to be men (83% vs. 91%), more likely to smoke (35% vs. 16%), drink alcohol (35% vs. 24%), abuse alcohol (21% vs. 10%), to be obese (65% vs. 38%) and to have diabetes (58% vs. 24%). Procedures consistent with an FG diagnosis (e.g., debridement) were more common among confirmed cases (92% vs. 76%).

Conclusions: Diagnoses of FG may not be well documented in EMRs. However, most patients received treatments consistent with FG regardless of clinical notation. We speculate that because there is little ambiguity in an FG diagnosis, clinicians may not have considered further documentation necessary. We were unable to create an algorithm to facilitate diagnostic confirmation. We noted that patients with an FG diagnosis that could be confirmed with EMR review had higher frequency of known risk factors of FG.

4341 | Development of a robust real-world data platform for rare diseases

Kristina Cotter, Brenda Simpson, Charlene Fernandez, Brett Chung and Leo Vandriel
RDMD, San Francisco, CA

Background: Drug development for rare diseases is limited by geography and lack of natural history data. Real-world data (RWD) can be utilized to assess natural history, health utilization, and outcomes. While medical records are a rich source of RWD, there is a need to develop new methodologies that ensure high-quality data capture in an efficient manner.

Objectives: To describe development of a rare disease RWD platform and associated best data practices. A cohort of patients with chronic demyelinating polyneuropathy (CIDP) is used as a case example.

Methods: A RWD platform was designed to structure data from medical records under an umbrella consent. Patients were recruited via digital marketing and patient groups. Complete records from patient-reported institutions were requested, digitized, and updated annually. Data was abstracted according to a flexible protocol and an electronic audit trail to source documents was retained. Data was analyzed using descriptive statistics.

Results: Record completeness and depth are critical elements of data quality. Completeness was evaluated by record receipt, recency, gaps in care, and presence of key clinical documents. Records were reviewed from 18 CIDP patients with 75%+ of records received (78% male, average age 55). On average, patients had 6 years of data; N=17 had data from 2019 and neurology notes for review. Gaps in data are resolved by contacting hospitals or patients. To assess depth and inform future work, data relating to diagnosis, utilization, and medications were abstracted. Diagnosis was confirmed via clinician documentation. Electromyograms were available for 83% of patients (average 2.9 EMGs/patient). 89% of patients had a surgery or procedure reported in their records (average 3.7/patient). 78% percent had visited the emergency room (average 3.3 visits/patient) and 61% had been hospitalized (average 2.7 visits/patient). N=17 had medication data; of these, all received immunoglobulin and 6 required prednisone.

Conclusions: High quality RWD requires complete medical records with sufficient depth to address research questions of interest. We developed an audit-trailed platform allowing for record collection from all patient institutions, removing geographical restrictions common in rare disease research. An umbrella consent allows for patient recontact to resolve data gaps, and a flexible protocol enables high-level data capture to identify limitations before initiating larger studies. In the future, this work will be expanded across larger cohorts of patients. Additional elements of data quality, such as record accuracy and internal consistency, will also be incorporated.

4350 | Clinical burden and healthcare resource utilization in patients with generalized pustular psoriasis: A claims database study

Nirali Kotowsky[1], Ran Gao[1], David Singer[1], Elizabeth M. Garry[2] and Amanda K. Golembesky[3]
[1]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; [2]Aetion, Inc., Boston, MA; [3]Boehringer Ingelheim International GmbH, Ingelheim, Germany

Background: Generalized pustular psoriasis (GPP) is a rare, severe, potentially life-threatening systemic disease, characterised by recurrent acute flares consisting of disseminated erythematous skin rash with sterile neutrophil-filled pustules. To date, there is little real-world evidence characterising GPP patients.

Objectives: This study describes the clinical burden and healthcare resource utilization (HCRU) in patients with GPP in the USA compared to those with psoriasis vulgaris (PsO) to understand and evaluate unmet needs in this poorly understood patient population.

Methods: Patients were diagnosed as having GPP or PsO if they had ≥1 inpatient or 2 outpatient diagnostic claim(s) for ICD-10 L40.1 or L40.0 respectively, separated by 30 to 365 days. All analyses were conducted via the Aetion Evidence Platform™ v3.17, using IBM® MarketScan® Research Databases. The study period was from 1 October, 2015 to 30 September, 2018, with the first diagnostic claim marking the index date. A general population matched cohort (MC) of 4:1, based on age and sex that excluded subjects with any psoriasis other than psoriatic arthritis, and the PsO cohort provided context to the GPP burden of disease and HCRU. Patient characteristics during the 180-day baseline and all-cause HCRU calculated for each visit type (inpatient, outpatient and emergency department [ED]) among patients with 12 months of follow-up (FU) were analysed. All analyses were descriptive in nature; no formal comparisons were conducted.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: A total of 1175 patients with GPP and 75,494 with PsO were identified at baseline; 637 GPP and 38,950 PsO patients had ≥12 months' FU. At baseline, patients with GPP were more likely to suffer from psoriatic arthritis (GPP: 20.6%; PsO: 6.4%; MC: <0.1%), anxiety (GPP: 9.0%; PsO: 6.0%; MC: 5.1%), and depression (GPP: 7.0%; PsO: 4.0%; MC: 3.1%) compared with the PsO cohort and the MC. GPP patients also had more outpatient visits than the PsO cohort and MC (median [interquartile range]; GPP: 17.0 [9.0, 32.0]; PsO: 14.0 [8.0, 25.0]; MC: 7.0 [3.0, 15.0]). More GPP patients had inpatient (GPP: 12.2%; PsO: 6.5%; MC: 6.2%) and ED visits (GPP: 24.6%; PsO: 20.0%; MC: 18.0%) and required longer hospitalisations (GPP: 5.0 [3.0, 12.0]; PsO: 4.0 [3.0, 7.0]; MC: 4.0 [3.0, 7.0] days) during the 12-month-FU compared to the PsO cohort and MC.

Conclusions: These findings suggest that patients with GPP have a higher clinical burden and more HCRU than those with PsO or in the MC, highlighting an unmet need in this patient population.

4369 | Remaining 'Undiagnosed' in the healthcare system: The lack of diagnosis codes for rare diseases

Aisling R. Caffrey[1,2,3], Mohammad A. Al-Mamun[1] and Hans P. Schlecht[4]

[1]College of Pharmacy, University of Rhode Island, Kingston, RI; [2]Providence Veterans Affairs Medical Center, Providence, RI; [3]School of Public Health, Brown University, Providence, RI; [4]Baystate Health, Springfield, MA

Background: Rare diseases cumulatively affect roughly 10% of the world population, and of the estimated 10,000 rare diseases, only about 5% have a diagnosis code. Most rare diseases are genetic in origin and can only be diagnosed from genetic testing. With the increase in genetic testing, patients who would have previously gone undiagnosed are now receiving diagnoses. However, due to the lack of specific rare disease diagnosis codes within disease classification systems (e.g. the International Classification of Diseases), these patients remain 'undiagnosed' in the healthcare system.

Objectives: To characterize diagnoses present after genetic testing has been conducted.

Methods: This study utilized the de-identified Optum Clinformatics™ DataMart, an administrative claims database from a national commercial health plan in the United States (2010-2017). Pediatric patients (<18 years old) undergoing whole exome sequencing (WES) or chromosomal microarray analysis (CMA) were identified from Current Procedural Terminology (CPT®) codes (81415, 81228, 81229). As genetic testing results take anywhere from 3-6 weeks or more, we reviewed diagnosis codes present in the 30-180 day period after genetic testing occurred.

Results: Of the 10,675,403 pediatric patients in the data source, only 181 underwent WES (0.002%) and 4,781 underwent CMA (0.04%). "Unspecified lack of expected normal physiologic development in childhood" (R62.50) was the most commonly reported diagnosis code following WES (14.4%) and third most common following CMA (8.1%). "Autism" (F84.0) was the most common diagnosis for patient after CMA (14.4%) and third most common for those following WES (11.6%). Other common diagnoses included "specific developmental disorder of motor function" (F82, WES 10.0%, CMA 4.5%),"feeding difficulties" (R63.3, WES 9.4%), "delayed milestone in child" (R62.0, WES 9.4%), "mixed receptive-expressive language disorder" (F80.2, WES 9.4%, CMA 6.2%), and "developmental disorder of speech and language" (F80.9, CMA 4.7%).

Conclusions: While not every genetic test yields a definitive diagnosis, one would expect some specific diagnoses from a cohort of this size. Nevertheless, we found that general diagnosis codes persist even after pediatric patients undergo genetic testing. The lack of specific diagnosis codes for most rare genetic disorders impedes surveillance, research, insurance reimbursement, and ultimately limits the advancement of rare disease medicine and science, and a solution is urgently needed.

4416 | Clinical burden and healthcare resource utilization in patients with palmoplantar pustulosis: A claims database study

Nirali Kotowsky[1], Ran Gao[1], David Singer[1], Elizabeth M Garry[2] and Amanda K Golembesky[3]

[1]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; [2]Aetion, Inc., Boston, MA; [3]Boehringer Ingelheim International GmbH, Ingelheim, Germany

Background: Palmoplantar pustulosis (PPP) is a chronic, debilitating, painful inflammatory skin disease characterised by localised, sterile pustules on the palms of the hands and soles of the feet. PPP may persist for decades, substantially affecting patients' quality of life. To date, there is little real-world evidence characterising patients with PPP.

Objectives: By understanding the burden of disease in this population, targeted interventions that improve patients' quality of life should be developed. This study describes the clinical burden and healthcare resource utilization (HCRU) in patients with PPP in the USA to evaluate previously unmet needs in this poorly understood patient population.

Methods: Patients were diagnosed as having PPP if they had ≥1 inpatient or 2 outpatient diagnostic claim(s) for ICD-10 L40.3, separated by 30 to 365 days. All analyses were conducted via the Aetion Evidence Platform™ v3.17, using the IBM® MarketScan® Research Databases. The study period was from 1 October, 2015 to 30 September, 2018, with the first diagnostic claim marking the index date. A general population matched cohort (MC) of 4:1, based on age and sex, that excluded subjects with any psoriasis other than psoriatic arthritis was generated for context. Patient characteristics during the 180-day baseline and all-cause HCRU calculated for each visit type (inpatient, outpatient and emergency department [ED]) in patients with 12 months of follow-up (FU) were analysed. All analyses were descriptive in nature; no formal comparisons were conducted.

Results: A total of 1579 patients with PPP were identified at baseline, and 807 had ≥12 months' FU. At baseline, patients with PPP were more likely to have a diagnosis of hyperlipidaemia (PPP: 21.3% vs MC:

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

11.4%), anxiety (PPP: 6.4% vs MC: 4.9%) and depression (PPP: 5.3% vs MC: 3.1%) compared with the MC. During the 12-month FU, 507 patients with PPP (62.8%) were treated with a systemic therapy (biologic or non-biologic). Compared with the MC, patients with PPP had more outpatient visits (median [interquartile range]; PPP: 17.0 [10.0, 30.0] vs 7.0 [3.0, 16.0]) and a higher proportion had inpatient (9.4% vs 6.5%) and ED (22.4% vs 17.7%) visits during the 12-month FU. The length of hospitalisation was similar between patients with PPP and the MC (4.0 [3.0, 6.0] vs 4.0 [3.0, 6.0] days) during the 12-month FU.

Conclusions: Patients with PPP tend to have higher levels of comorbidities and higher HCRU compared with the MC, highlighting an unmet need among these patients.

4500 | Estimation of the prevalence of spinal muscular atrophy in the era of treatment, newborn screening, and updated standards of care: A novel epidemiologic study

Cathy A. Lally[1], Susan A. Hall[2], Anne B. Dilley[2], Nicole B. Johnson[2] and W. Dana Flanders[1]

[1]*Epidemiologic Research and Methods LLC, Atlanta, GA;* [2]*Biogen, Cambridge, MA*

Background: Disease prevalence is a function of incidence and survival. A reexamination of the population prevalence of spinal muscular atrophy (SMA) is necessary following the 2016 advent of nusinersen, a treatment that improves survival. In addition, newly established newborn screening programs for SMA will likely result in an increased diagnosis rate.

Objectives: To determine the current prevalence of SMA in eight countries.

Methods: We developed a population-based method of analysis that simultaneously accounts for the influence of treatment, survival, newborn screening, and other variables, built on a life-table approach. Using peer-reviewed published literature, regional estimates of birth prevalence (a proxy for incidence), and type distribution (Types I through III) were applied to national birth cohorts beginning 50 years prior to the baseline prevalence date (December 31, 2018). A range of disease-specific survival curves were derived from the published literature for SMA Types I and II and applied in accordance with the regional standard of care. Age-specific general population survival was applied in accordance with the survival expectation for SMA Type III (Arnold 2015; Wang 2007). After 2016, the proportion of the prevalent population using treatment and treatment-specific survival were applied. After 2017, the proportion of the population covered by newborn screening was included. Life tables were used to calculate the number of prevalent patients by age, type, and region.

Results: For 2018, the estimated prevalence of SMA across the US, Canada, France, Germany, Italy, Japan, Spain, and United Kingdom was 18,536, or 2.3 cases per 100,000 population. Geographic variation was driven by differences in survival and birth prevalence. Approximately 13.5%, 38.3% and 48.2% of cases were Types I, II and III, respectively. By current age, approximately 4.0%, 37.2% and 58.8% fell into the 0 to <2 years, 2 to <18 years, and 18+ age categories.

Conclusions: Strengths of this population-based study include incorporation of secular demographic trends, reliance on peer-reviewed published literature and national census data, and the multivariable approach. There are very few population-based studies of SMA prevalence for comparison to our results. A previous population-based study in the UK found SMA prevalence was approximately 1.9 per 100,000 (Norwood, 2009). Based on this limited comparison, we conclude the prevalence of SMA has increased, as would be expected in the treatment era.

4502 | On urbanisation and haematological malignancies in a South African population

Diana Oelofse and Ilse Truter

Nelson Mandela University, Port Elizabeth, South Africa

Background: Urbanisation, with increased societal aggregation, industrialisation, modernisation and its associated lifestyle changes are relatively recent events in the context of South Africa's indigenous populations. It is commonly believed that the modern experience of cancer is somehow connected to the a rapidly urbanising and industrial world. The Eastern Cape Province, home to 14.4% of the South Africa's population, is regarded as one of the least urbanised regions. Haematological malignancies (HMs), many usually regarded as rare cancers, are not infrequently diagnosed in hospitals in the Eastern Cape Province. Limited data however exist regarding the incidence and spatial distribution of HMs in populations undergoing these accelerated changes.

Objectives: The aim of the study was to compute incidence and regional distribution of HMs in the Eastern Cape Province of South Africa, juxtaposed with regional population numbers and urbanisation levels.

Methods: Tentative incidence rate (IR) computations were based on a primary laboratory database of ICD-10 categorised HM incident cases collated for the six district and two metropolitan municipalities of the Eastern Cape Province, for the ten-year period between 2004 and 2013. Mid-year census estimates for 2008 and 2009 and small areas data were utilised for denominator-population data. Regional urbanisation estimates were extracted from Census 2001. Statistical analyses were conducted with Excel® 2010 and Statistica® version 13 software-packages.

Results: Approximately 3,603 patients were identified as incident cases for the 10-year period between 2004 and 2013. Spatial data was unavailable for approximately 20% of cases and some patients could only be traced to a regional hospital. The Nelson Mandela Bay Metropolitan area and Sarah Baartman district were the two most urbanised areas (97.5% and 76%) and had the highest total incidence rates for HMs of 13,9 (11,8-16.1). and 10.4 (7.4-13.4) per 100,000 population, respectively. Alfred Nzo district, with a population, which

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

far outnumbers that of the Sarah Baartman district, but with a lower urbanisation level of 4.5%, yielded very few cases.

Conclusions: Higher incidence rates were demonstrated for HMs among the residents in areas of the Eastern Cape Province of South Africa characterised by higher urbanisation levels. Further research is required to clarify the role of societal aggregation as a potential modulating agent in cancer incidence in populations undergoing accelerated transitions from predominantly rural to urban lifestyles.

4535 | The diagnostic journey for rare genetic disorders

Aisling R. Caffrey[1,2,3] and Mohammad A. Al-Mamun[1]
[1]*College of Pharmacy, University of Rhode Island, Kingston, RI;* [2]*Providence Veterans Affairs Medical Center, Providence, RI;* [3]*School of Public Health, Brown University, Providence, RI*

Background: Though symptoms of rare genetic disorders often present early in life, the diagnostic journey can take several to many years. The diagnostic journey is the process of seeing physician after physician and specialist after specialist, and having test after test and procedure after procedure, before receiving a correct definitive diagnosis. It is estimated that more than 80% of the 10,000 rare diseases are due to genetic causes, and can therefore only be diagnosed by genetic testing. However, the diagnostic journey leading up to genetic testing is not well-defined.

Objectives: To map timelines of procedures and testing leading up to genetic testing.

Methods: We identified children (<18 years) with Current Procedural Terminology (CPT®) codes for whole exome sequencing (WES, 81415) or chromosomal microarray analysis (CMA, 81228, 81229) from the de-identified Optum Clinformatics™ DataMart, an administrative claims database from a national commercial health plan in the United States (2010-2017). Additionally, as negative findings from testing for other conditions may be required to demonstrate medical necessity for insurance coverage of WES and CMA, we also included patients with CPT codes for Fragile X testing (81243). The year prior to genetic testing was assessed to identify common CPT codes present in the timeframe leading up to genetic testing.

Results: We identified 181 children with WES (0.002% of source population <18 years of age), 4,781 with CMA (0.04%), and 2,996 with Fragile X testing (0.03%) during the study period. Mean age at the time of testing was 7 years for WES (standard deviation [SD] 5, median 7, interquartile range [IQR] 3-12), 6 years for CMA (SD 5, median 5, IQR 3-9), and 6 years for Fragile X (SD 4, median 5, IQR 3-9). Males underwent CMA (67%) and Fragile X (78%) testing more often than WES (40%). Common CPT codes in the year prior to testing included "other pathology and laboratory procedures (unlisted miscellaneous pathology test)" (89240; WES 40%, CMA 81228 35%, CMA 81229 23%), "other diagnostic radiology (diagnostic imaging) related procedures" (76499; WES 35%, CMA 81228 30%, CMA 81229 22%) "complete blood count" (85025; WES 31%, CMA 81228 38%, CMA 81229 27%, Fragile X 22%), "comprehensive metabolic panel" (80053; WES 24%, CMA 81228 28%), "esophageal intubation" (91000; WES 22%), and "thyroid testing" (84439; WES 19%, CMA 81229 17%, Fragile X 17%; 84443; CMA 81228 34%, CMA 81229 30%, Fragile X 32%).

Conclusions: Unspecified lab and diagnostic imaging procedures were common in the year prior to genetic testing, as was cumulative testing burden among these children. Lifetime testing burden may be reduced with utilization of WES/CMA at younger ages.

4550 | A pilot study with real world data in clinical pharmacology: Height, weight and serum creatinine in a pediatric population with sickle cell disease

Stephen E. Schachterle[1,2], Charles Wentworth[1], Brinda Tammara[1], Satyaprakash Nayak[1], Lutz O Harnisch[1] and David Readett[1]
[1]*Pfizer, New York, NY;* [2]*City University of New York, New York, NY*

Background: Real World Data (RWD) has been used extensively in post marketing drug safety and comparative effectiveness research. However, RWD has been applied less often in early drug development and clinical pharmacology research such as in the determination of starting doses for renally excreted drugs through the estimation of the Glomerular Filtration Rate (eGFR).

Objectives: To describe, in a pilot study, the identification of the components of a model based GFR estimate (serum creatine (SrCr), race, weight and height) in pediatric patients with homozygous Sickle Cell (Hb-SS) disease and to compare those patients to a matched cohort of non-Sickle Cell patients.

Methods: A pediatric population (< 18 years of age) was identified with diagnostic codes for Hb-SS disease. Each available SrCr measurement from a Hb-SS patient was identified and linked to the patient's recent height and weight measurement. Hb-SS patients were then randomly matched to patients without Sickle Cell Disease but with the same birth month and year, sex, race and ethnicity (i.e. matched controls). Data were drawn from the Optum EHR Integrated Delivery Network (IDN) database, which includes information on over 81 million patients starting in 2007. SrCr, height and weight for the Sickle Cell patients were described with summary statistics, including sample means, and compared to these same measurements for the matched controls using paired t-tests.

Results: Within the Optum EHR data, 35,914 SrCr measurements for 2,559 patients with Hb-SS disease were identified along with the same number of SrCr measurements from 16,440 matched control patients. On average, Hb-SS pediatric patients weighed significantly less (31.8 kg vs 37.47 kg, $p < 0.001$), were significantly shorter (124.94 cm vs 126.25 cm, $p < 0.001$), and had significantly lower SrCr values (0.42 mg/dl vs 0.65 mg/dl, $p < 0.001$) than matched controls.

Conclusions: Pediatric patients with Hb-SS disease were smaller than patients without Sickle Cell Disease when matched for age, sex, race and ethnicity-- an expected finding that may be attributable to the chronic morbidities known to be associated with Hb-SS disease. Hb-

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

SS disease is also characterized by renal hyperfiltration in childhood which may have contributed to the lower SrCr measurements in the pediatric Sickle Cell patients. Height, weight and SrCr measurements allow for estimation of GFR which may be used to predict starting doses for renally excreted drugs. The current pilot study suggests that RWD has a place in pharmacological dose predictions for new treatments.

4574 | Postmarketing safety of orphan drugs: A longitudinal analysis of U.S. Food and Drug Administration database between 2006 and 2015

Adrienne Y. L. Chan[1], Min Fan[1], Vincent K. C. Yan[1], Eliza Y. T. Tam[2], Esther W. Chan[1], Ian C. K. Wong[1,3] and Xue Li[1,4,5]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong; [2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong, Hong Kong; [3]Research Department of Policy and Practice, University College London School of Pharmacy, London, United Kingdom; [4]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong; [5]Department of Social Work and Social Administration, Faculty of Social Sciences, The University of Hong Kong, Hong Kong, Hong Kong

Background: Limited by inherently small sample sizes, both volume and quality of evidence for orphan drugs safety are scarce and inconsistent. An evaluation of postmarket safety events can provide insights into the current orphan drugs approval process.

Objectives: To describe the postmarket safety events among orphan drugs and to identify any approval factors associated with them.

Methods: We identified approved orphan drugs between 2006 and 2015 from the U.S. Food and Drug Administration (FDA) database, along with their approval information and any safety-related label changes until December 31, 2018. Withdrawal, suspension, and boxed warning were recorded as a Severe Postmarket Safety Event (SPSE). We used Kaplan-Meier analysis to describe the time-to-first SPSE for each approved orphan drug and applied Cox regression to identify the approval factors associated with the SPSE. Approval factors include expedited approval, approved for long term use, approved with a boxed warning, amended or extended Prescription Drug User Fee Act goal, approved near regulatory deadline, and approved in the first cycle.

Results: In the study period, 103 new molecular entities with orphan drug designation were identified. 79.6% (n=82/103) of them had at least one expedited approval. Over one third (34.0%) of the orphan drugs were approved with boxed warning. 70.9% (n=73/103) of the orphan drugs had recorded safety events since approval. Ten drugs (9.71%) had recorded SPSE (1 suspended marketing and 9 additional boxed warning). The median time from the drug approval date to their first SPSE is 5.92 (IQR 3.98-8.87) years. The hazard ratio of SPSE for drugs with at least one expedited approval and approved with boxed warning are 2.79 (95% CI, 0.35-22.06, p=0.332) and 8.23(95% CI: 1.75-38.77, p=0.008) respectively.

Conclusions: Among 103 orphan drugs approved by the FDA between 2006 and 2015, 9.71% had a severe postmarket safety event before December 31, 2018. The orphan drugs approved with a boxed warning have a higher hazard of SPSE. More evidence is needed to understand the relationship between other approval factors and postmarket safety events in orphan drugs.

4616 | Risk of influenza vaccine-induced immune thrombocytopenia

A nationwide population-based study in France

Margaux Lafaurie[1,2,3], Bérangère Baricault[1,2], Laurent Sailler[4,2,3], Maryse Lapeyre-Mestre[1,2,3], Agnès Sommet[1,2,3] and Guillaume Moulis[4,2,3]

[1]Clinical pharmacology department, University Hospital Center, Toulouse, France; [2]CIC 1436, University Hospital Center, Toulouse, France; [3]UMR 1027 INSERM - Université de Toulouse, Toulouse, France; [4]Department of Internal Medicine, University Hospital Center, Toulouse, France

Background: Epidemiological studies suggest a risk of immune thrombocytopenia (ITP) following viral infections, particularly influenza. Conversely, an increased risk of ITP following vaccination has been proven in children for Measles-Mumps-Rubella vaccine. However, the risk of ITP induced by influenza vaccine is debated. Two case-controls studies (Garbe E. EJCP. 2012; Grimaldi-Bensouda L. Blood. 2012) has been conducted, with contradictory results: in a German study, an increased risk has been found (OR: 3.8 [95% CI: 1.5-9.1]. Conversely, the French PGRx study, suggested no increased risk of ITP [OR: 0.9; 95% CI: 0.4-2.1]. These studies were limited by the number of ITP patients included (<200) and other limitations.

Objectives: We aimed to assess the risk of ITP induced by influenza vaccine.

Methods: We conducted a population-based study in France within the FAITH cohort which includes all incident primary ITP adult patients recorded in the National Health Insurance database between July, 2009 and June, 2017. We included patients aged ≥65 years at diagnosis (indication of influenza vaccination in the general population in France). We conducted a case-control design. ITP cases were matched with four controls from the general population for age, sex and place of residency. Cases and controls were compared for exposure to influenza vaccine in the 6 weeks before the index date using conditional logistic regression models adjusted for exposure to drugs known as inducers of ITP. Sensitivity analyses were conducted by stratifying on the duration of ITP disease: acute (<3 months) and persistent or chronic (≥3 months).

Results: We included 4,282 ITP patients aged ≥65 years matched with 17,071 controls. Overall, 198 cases (4.6%) and 819 controls (4.8%) were vaccinated with influenza vaccine during the 6 weeks prior to

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the index date (aOR: 0.88; 95%CI: 0.73-1.07]). Analyses by stratifying on the duration of ITP disease shown similar results.

Conclusions: This nationwide population-based study showed no increased risk of ITP following influenza vaccine.

4793 | Epidemiology of Duchenne muscular dystrophy: A population-based study in Southern Italy from 2003-2018

Salvatore Crisafulli[1], Janet Sultana[1], Andrea Fontana[2], Sonia Messina[3,4] and Gianluca Trifirò[1]

[1]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy; [2]Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy; [3]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [4]NEuroMuscularOmnicenter, NEMO-SUD, University Hospital "G. Martino", Messina, Italy

Background: Duchenne Muscular Dystrophy (DMD) is a rare neuromuscular X-linked disorder. DMD epidemiology is poorly characterised.

Objectives: To estimate DMD prevalence using tailored algorithms in a general population of Southern Italy.

Methods: This retrospective, population-based study was conducted using the Caserta Local Health Unit claims database from 2003-2018. Data was obtained from pharmacy and hospital claims, as well as the healthcare service co-pay exemption database. Three DMD algorithms were developed with increasing complexity. In algorithm 1, males aged ≤40 years having ≥ 1 International Classification of Diseases codes, 9th edition code 359.0 (congenital hereditary muscular dystrophy) and/or 359.1 (hereditary progressive muscular dystrophy) and/or the co-pay exemption code RFG080 (muscular dystrophies) were identified. Of these, patients meeting ≥ 1 of the following criteria were included in algorithm 2: >2 systemic corticosteroid pharmacy claims; ≥ 1 cardiomyopathy diagnosis; ≥ 1 angiotensin converting enzyme inhibitor, angiotensin receptor blockers or beta-blocker pharmacy claims; ≥ 1 diagnosis of respiratory failure or claims for respiratory therapy. As additional criteria, algorithm 3 excluded patients with diagnosis of cerebral degeneration, spinocerebellar disease, anterior horn cell disease or hereditary idiopathic peripheral neuropathy. DMD prevalence was estimated per 100,000 persons and per 100,000 males based on these algorithms.

Results: From the general population of 1,212,764 persons residing in Caserta from 2003 to 2018, 404 patients met criteria for algorithm 1. Of these, 110 and 101 met criteria for algorithm 2 and 3, respectively. DMD prevalence ranged from 14.0 (95% CI: 12.1-16.3) cases per 100,000 persons with algorithm 1 to 8.3 (95% CI: 6.9-10.1) cases per 100,000 persons with algorithm 3. The estimates for algorithm 3, the most detailed, were in line with the range reported in the scientific literature: 0.7-7.7 cases per 100,000 persons. Considering males only, the prevalence ranged from 28.3 (95% CI: 24.3-32.9) cases per 100,000 males with algorithm 1 to 16.8 (95% CI: 13.8-20.4) cases per 100,000 males with algorithm 3. The estimate from algorithm 3 was in line with the range reported in the scientific literature: 0.9-16.8 cases per 100,000 males.

Conclusions: Using multiple algorithms increasing in complexity with comparison to the literature is a useful approach to study the epidemiology of rare diseases using secondary data. Validation of these algorithms through linkage with regional rare disease center database will help improving accuracy.

4823 | Global epidemiology of Duchenne muscular dystrophy: An updated systematic review and meta-analysis

Salvatore Crisafulli[1], Janet Sultana[1], Andrea Fontana[2], Francesco Salvo[3], Sonia Messina[4,5] and Gianluca Trifirò[1]

[1]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy; [2]Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy; [3]Université de Bordeaux, Inserm UMR 1219, Pharmacoepidemiology Team, Bordeaux, France; [4]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [5]NEuroMuscularOmnicenter, NEMO-SUD, University Hospital "G. Martino", Messina, Italy

Background: Duchenne Muscular Dystrophy (DMD) is a rare disorder caused by mutations in the dystrophin gene. A recent systematic review and meta-analysis of global DMD epidemiology is not available.

Objectives: This study aimed to estimate the global overall and birth prevalence of DMD through an updated systematic review of the literature.

Methods: MEDLINE and EMBASE databases were searched for original research articles on the epidemiology of DMD from inception until 1st October 2019. Studies were included if they were original observational research articles written in English, reporting DMD prevalence and/or incidence along with the number of individuals of the underlying population. The quality of the studies was assessed using a STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist adapted for observational studies on rare diseases. To derive the pooled epidemiological prevalence estimates, a meta-analysis was performed using random-effects logistic models for overall and birth prevalence and within two different underlying populations (i.e. all individuals and in males only), separately. Heterogeneity was assessed using Cochran's Q-test along with its derived measure of inconsistency I^2.

Results: A total of 44 studies reporting the global epidemiology of DMD were included in the systematic review and only 40 were included in the meta-analysis. The pooled global DMD prevalence was 7.1 cases (95% CI: 5.0-10.1) per 100,000 males and 2.8 cases (95% CI: 1.6-4.6) per 100,000 persons in the general population, while the pooled global DMD birth prevalence was 19.8 (95% CI:16.6-23.6) per 100,000 live male births. A very high between-study heterogeneity was found for each epidemiological outcome and for all underlying populations (I^2>90%). The test for funnel plot asymmetry suggested the absence of publication bias. Of the 44 studies included in this

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

systematic review, 36 (81.8%) were assessed as being of medium and 8 (18.2%) of low quality, while no study was assessed as being of high quality.

Conclusions: Generating epidemiological evidence on DMD is fundamental to support public health decision-making. The high heterogeneity and the lack of high quality studies highlights the need to conduct better quality studies on rare diseases.

4895 | Assessing the fitness of patient registry data for real world evidence generation: Lessons learned from the my retina tracker® registry of rare inherited retinal disorders

Emily W. Bratton[1] and Todd A. Durham[2]
[1]*IQVIA, Durham, NC;*[2]*Foundation Fighting Blindness, Cumberland, MD*

Background: My Retina Tracker® Registry (MRTR) is provided by the Foundation Fighting Blindness for patients affected by inherited retinal degenerative diseases (IRDs) caused by mutations in over 270 genes. MRTR collects information on the global IRD community to better understand the patient journey. It also provides a means to identify candidates for trials and other research studies.

Objectives: The Framework for FDA's Real-World Evidence (RWE) Program outlines the plan to evaluate RWE to support regulatory decision-making, potentially accelerate drug approval, and satisfy post-approval study requirements. To utilize MRTR data for RWE and to improve future data collection, a comprehensive data review was conducted to examine data quality and reliability.

Methods: Five de-identified patient questionnaires were included: General Health, Family History, Genetic Testing, Vision Self-evaluation, and Assistive Devices. Descriptive analyses were performed to understand the qualitative and quantitative nature of data collected and overall patient characteristics. Continuous variables were reported as means (standard deviation) or median (range) where appropriate. Categorical variables were summarized as number and proportion of the total respondents or by subgroups, if appropriate.

Results: Overall, 25,858 participants enrolled in MRTR (2013-2019). Participants who completed the 5 questionnaires varied, with full or partial responses: n=10,474 General Health, n=9,129 Family History, n=3,878 Genetic Testing, n=8,339 Vision Self-evaluation, and n=8,439 Assistive Devices. There were 3,465 (13%) participants who answered at least 1 question across all 5 questionnaires. Out of 5,761 responses, 90% of participants rated their general health as 'good' or 'very good'. Approximately 3,800 (42%) respondents could identify a family member with the same IRD; n=5,325 responded 'unknown' or 'none'. There were 2,220 out of 3,841 respondents who confirmed that their disease-causing gene was identified; nearly all of these (n=2,174) knew the number of disease-causing genes identified.

Conclusions: Patient registries are a source of data that can be used to generate RWE, but their fitness for rare disease research requires sufficient data collection and curation. MRTR has the potential to provide diagnosis-specific patient information to support research of IRD, having collected a relatively high volume of responses. Increased engagement, retention efforts, and genetic testing will continue to enhance MRTR as a tool for research.

5081 | Eosinophilia in atopic and non-atopic individuals in the United States

Chi H. H. Le[1], Phuong H. U. Le[2], Chi T. L. Truong[3] and Hoa V. Le[4]
[1]*School of Medicine, Vanderbilt University, Nashville, TN;* [2]*University of Toronto, Mississauga, ON, Canada;* [3]*MedCodeWorld, Chapel Hill, NC;* [4]*Bristol-Myers Squibb, Berkeley Heights, NJ*

Background: A rise in eosinophils in the blood is observed in certain disease states such as atopy, allergy or parasitic infections. While helminth parasitic infections are the most common cause of eosinophilia globally, eosinophilia in industrialized nations is generally attributed to atopic causes. However, there is a paucity of updated data to examine eosinophilia in the US population.

Objectives: To determine the prevalence of eosinophilia in atopic vs. non-atopic individuals in a nationally representative sample, NHANES 2015-2016.

Methods: Eosinophilia cases defined as individuals with eosinophil count over 500/uL were identified in the National Health and Nutrition Examination Survey (NHANES) 2015-2016. Atopic cases were determined by ICD-10 codes and medical conditions questionnaire for diseases (e.g. atopic dermatitis, atopy, asthma, allergic dermatitis, allergic rhinitis, and allergic conjunctivitis). Among atopic and non-atopic cases, prevalence of eosinophilia and 95% CIs were analyzed in the overall sample and by age groups, sex, and race/ethnicity. Multivariate logistic regression was performed to compare prevalence among different subgroups. Statistical analyses accounted for complex survey design with examination sample weights and adjusted for non-response with 2-sided p value of 0.05 for significance. Sensitivity analyses included unadjusted, sex- and age-adjusted modeling.

Results: Among 8,116 U.S. individuals from 2015-2016, the atopic prevalence was 18.8%. The prevalence of eosinophilia was 12.1% (95% CI: 9.5-14.8%) in atopic and 7.3% (95% CI: 6.3-8.4%) in non-atopic cases. However, 72.2% (95% CI: 66.8-77.6%) of individuals with eosinophilia lacked a known atopic condition. Among atopic cases, compared to adults aged 20-29 years old, there were an increased prevalence of eosinophilia in children aged ≤ 11 years (28.1%, p ≤ 0.01), and a decreased rate in elderly aged 70-79 years (2.1%, p=0.037). Among non-atopic individuals, children aged ≤ 11 years had higher eosinophilia prevalence than other age groups (15.5%, p=0.0005), and in men than women (9.4% vs. 5.2%, p < 0.0001), but lower rates in non-Hispanic blacks than non-Hispanic whites (5.7% vs. 7.4%, p=0.006). In contrast, no difference was observed between different sex and race subgroups in atopic population.

Conclusions: Although our study demonstrates that higher prevalence of eosinophilia is observed in atopic individuals, our findings suggested that the majority of eosinophilia may not be attributed to atopic causes. These findings provided an updated understanding of eosinophilia in the context of atopy in the US population.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Safety End Points -> Cancer

71 | The safety of antibody drug conjugates: A literature review

Joan Forns[1], James A. Kaye[2], Fabio A. Lievano[3], Jerzy E. Tyczynski[3] and Andrea V. Margulis[1]

[1]RTI-HS, Barcelona, Spain; [2]RTI-HS, Waltham, MA; [3]AbbVie Inc., North Chicago, IL

Background: Antibody-drug conjugates (ADCs) are a class of treatment agents for cancer combining the relative selectivity of targeted treatment with the cytotoxicity of chemotherapy drugs. Over 100 ADCs are under evaluation in clinical trials worldwide, but only 5 had been approved by both the US Food and Drug Administration and the European Medicines Agency at the time of study conduct: brentuximab vedotin (BV), ado-trastuzumab emtansine (T-DM1), gemtuzumab ozogamicin (GO), inotuzumab ozogamicin (IO), and polatuzumab vedotin (PV).

Objectives: To identify the most common toxicities reported from phase 2-4 clinical trials or observational studies for the five mentioned ADCs.

Methods: We searched PubMed and Embase in July 2019 for peer-reviewed, English-language articles published since 2015 that reported the toxicity of ADCs. We first identified the most commonly reported adverse events (AEs) (reported in at least 10% of patients in each study) and then calculated the median reported incidence for each AE and drug.

Results: The literature search identified 357 unique publications. After reviewing titles and abstracts, we selected 58 articles for full-text review; 48 of these qualified for data extraction. Among the 48 selected studies, 18 (38%) reported AEs for BV, 15 (31%) for T-DM1, 7 (15%) for GO, 7 (15%) for IO, and 1 for PV (1%). Most included articles reported on both efficacy and safety; 40 reported on clinical trials (22 phase 2, 17 phase 3, and 1 phase 4), and 8 reported on observational studies. Of the 2 ADCs with more included studies, the median incidences of AEs of any grade were higher for BV than for T-DM1 for many AEs: anaemia (31% vs. 24%), neutropenia (32% vs. 13%), thrombocytopenia (57% vs. 29%), peripheral sensory neuropathy (23% vs. 13%), fatigue (40% vs 30%), nausea (40% vs. 36%), vomiting (26% vs. 18%), and diarrhoea (29% vs. 18%). On the other hand, median incidences were lower for BV than for T-DM1 for anorexia (18% vs. 21%), pyrexia (19% vs. 25%), myalgia (12% vs. 16%), and headache (14% vs. 27%). IO had higher median AE incidences than BV and T-DM1 for neutropenia (42%), thrombocytopenia (72%), fatigue (45%), nausea (49%), and pyrexia (32%). For GO, safety information was scarce; the median incidence was 45% for thrombocytopenia, 45% for increased aspartate aminotransferase, and 50% for fatigue. Finally, PV had the highest incidence of fatigue (60%) and diarrhoea (47%) based on a single study.

Conclusions: The five approved ADCs were found to have somewhat distinct safety profiles. Most studies, especially most observational studies, reported on BV and T-DM1, which have been in the market longer than the other ADCs.

2396 | Pre-existing autoimmune disease and immune-related adverse events (irAE) with checkpoint inhibitors in metastatic melanoma

Marina AA Machado[1], Cristiano S Moura[1], Kelvin Chan[2], Jeffrey R Curtis[3], Marie Hudson[4], Michal Abrahamowicz[5], Ines Colmegna[6], Rahima Jamal[7], Louise Pilote[6], An-Wen Chan[2] and Sasha Bernatsky[6]

[1]Research Institute of the McGill University Health Centre, Montreal, QC, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]University of Alabama at Birmingham, Birmingham, AL; [4]Lady David Research Institute for Medical Research, Montreal, QC, Canada; [5]McGill University, Montreal, QC, Canada; [6]McGill University, Montreal, QC, Canada; [7]Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada

Background: Melanoma patients with pre-existing autoimmune disease were excluded from clinical trials testing checkpoint inhibitors because of concerns of irAE.

Objectives: We used real-world data to evaluate irAE in metastatic melanoma patients with and without pre-existing autoimmune diseases using checkpoint inhibitors.

Methods: We assembled a cohort of adults with metastatic melanoma using US MarketScan® Databases. All patients were assigned a time-zero as the date of first exposure to ipilimumab (IPI), pembrolizumab (PEM), nivolumab (NIV) or NIV/IPI over Jan 2012-July 2017. We required health/drug plan coverage for 12 months before time-zero and identified in this period all autoimmune disease diagnostic codes from physician claims/hospitalizations. Outcomes (incident irAE) following time-zero were identified from physician claims/hospitalizations primary diagnostic codes. Patients were censored due to in-hospital death, loss of health/drug plan, end of study period (Dec 2017), gap between doses ≥ 60 days or therapy switch. We estimated irAEs rates, stratified by pre-existing autoimmune disease and sex, and hazard ratios (HR) with 95% confidence intervals (CI), using Cox model, adjusted for age, sex, calendar year, comorbidities, past health care use, past and current cancer therapy, and pre-existing autoimmune disease.

Results: We studied 2315 patients initiating IPI (62.2%), PEM (16.8%), NIV/IPI (11.8%), and NIV (9.3%). The median age was 60 years (interquartile range 52-67), 62.1% were male, and 27.7% had pre-existing autoimmune disease including hypothyroidism (12.5% in men, 22.8% in women), interstitial lung disease (2.7% in men, 2.3% in women), and myositis (2.3% in men, 4.9% in women). Most frequent irAEs were hypothyroidism (new cases) and inflammatory bowel disease. The rate (per 100 person-years) of irAEs in patients with pre-existing autoimmune diseases was 7.3 (95% CI 4.2-12.6) versus 4.1 (95% CI 2.5-6.6) in those without autoimmune disease. The rate was 5.4 (95% CI 3.5-8.3) in men and 4.4 (95% CI 2.4-8.3) in women. In multivariate analyses, presence of pre-existing autoimmunity was associated with higher irAE risk vs absence (HR 2.17, 95% CI 1.01-4.66); irAE risk was lower with IPI vs NIV/IPI (HR 0.19 95% CI 0.04-0.86); we did not to see difference in women vs men (HR 0.77, 95% CI 0.35-1.70).

Conclusions: Over a quarter of metastatic melanoma patients starting checkpoint inhibitors had pre-existing autoimmune disease. We

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

observed higher irAE risk in patients with pre-existing autoimmunity and lower irAE risk in IPI, although 95% CIs around estimates were wide.

2466 | Risk of skin cancer in new users of thiazides and thiazide-like diuretics: A cohort study using an active comparator group

Rahel Schneider[1,2], Daphne Reinau[1,2], Seline Stoffel[1], Susan S. Jick[3,4], Christoph R. Meier[1,2,3] and Julia Spoendlin[1,2]
[1]*University of Basel, Basel, Switzerland;* [2]*University Hospital Basel, Basel, Switzerland;* [3]*Boston Collaborative Drug Surveillance Program, Lexington, MA;* [4]*Boston University School of Public Health, Boston, MA*

Background: Long-term use of hydrochlorothiazide (HCTZ) has been associated with an increased risk of skin cancer. It remains unclear whether the risk of skin cancer is increased for all thiazides and thiazide-like diuretics (TZs).
Objectives: To examine whether the use of different TZs increases the risk of skin cancer compared to calcium channel blockers (CCBs).
Methods: We conducted a cohort study using the United Kingdom Clinical Practice Research Datalink (CPRD). We established a comparative cohort including patients aged 18 to 85 years with a first-time prescription for a TZ or a CCB between 1998 and 2017. We excluded patients with recorded use of TZs and CCBs. The three co-primary outcomes of interest were basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and cutaneous malignant melanoma (CMM). We estimated incidence rates (IR) per 100,000 person-years and IR ratios (IRRs) in short-term users (< 20 prescriptions) and long-term users (≥ 20 prescriptions) of TZs and CCBs using negative binomial regression. We used fine stratification on the propensity score (PS) to control for 23 baseline covariates. We conducted analyses for TZs overall and for bendroflumethiazide (BFT), indapamide, and HCTZ separately.
Results: We identified 271,154 TZ users (87.6% BFT, 5.8% indapamide, and 3.6% HCTZ) vs 275,263 CCB users. Crude IRs for BCC were 460 (95% CI, 446-475) for short-term and 398 (381-415) for long-term TZ use. After PS-weighting, we observed IRRs for BCC of 1.24 (1.17-1.31) for short-term and 1.17 (1.10-1.23) for long-term TZ use. Results were not meaningfully different when we evaluated BFT, indapamide, and HCTZ separately. Crude IRs for SCC were 65 (60-70) for short-term and 72 (65-80) for long-term TZ use, which resulted in weighted overall IRRs of 1.07 (1.05-1.09) for short-term and 1.15 (1.12-1.18) for long-term TZ use. HCTZ showed a weighted IRR for SCC of 1.29 (1.24-1.35) in short-term users, which increased to 1.95 (1.87-2.02) in long-term users. BFT and indapamide revealed null results. Crude IRs for CMM were 72 (66-77) for short-term and 61 (54-68) for long-term TZ use. We observed overall IRRs of 1.11 (1.09-1.13) for short-term and 1.02 (0.99-1.05) for long-term TZ use. Long-term use of indapamide was associated with an increased risk of CMM (IRR, 1.43 [1.35-1.50]), whereas HCTZ and BFT showed null results.
Conclusions: Our results corroborate the previously reported increased risk of SCC in association with long-term use of HCTZ and do not suggest a class effect for all TZs. Long-term use of indapamide may be a risk factor for CMM, but further evidence is needed.

2522 | Proton pump inhibitors are not associated with an increased risk of colorectal cancer

Josephina G. Kuiper[1,2], Myrthe P. P. Van Herk-Sukel[3], Valery E. P. P. Lemmens[4,2], Ernst J. Kuipers[5] and Ron M. C. Herings[1,6]
[1]*PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands;* [2]*Erasmus University Medical Center, Rotterdam, Netherlands;* [3]*University Medical Center Utrecht, Utrecht, Netherlands;* [4]*Netherlands Comprehensive Cancer Organisation, Utrecht, Netherlands;* [5]*Erasmus University Medical Center, Rotterdam, Netherlands*[6]*VU University Medical Center, Amsterdam, Netherlands*

Background: The clinical relevance of proton pump inhibitors use as a risk factor for colorectal cancer in humans is still unclear.
Objectives: To investigate the risk of colorectal cancer after the use of proton pump inhibitors within a linked Cancer Registry-General Practitioner Database cohort.
Methods: Colorectal cancer patients diagnosed between 2007-2014 with at least six years of primary care data available prior to diagnosis (index date) were identified and matched to four controls on gender, birth year, general practice and period of primary care data availability. Proton pump inhibitor use was determined in the six years prior to the index date and analysed with conditional logistic regression, adjusted for potential confounders.
Results: 1,041 cases (53%) and 3,751 controls (47%) ever used a proton pump inhibitor, yielding an odds ratio (OR) of 1.08 (95% confidence interval (CI) 0.97-1.21). Current use showed the highest OR (1.30 (95% CI 1.16-1.47). Long-term use of proton pump inhibitors (≥4 years) was not associated with colorectal cancer (OR 0.92 (95% CI 0.76-1.11)). A variation in OR for tumour stage and tumour subsite was observed with the highest OR for stage I tumour (1.28 (95% CI 0.87 - 1.87) and proximal colon (1.19 95% CI 0.87-1.63).
Conclusions: No increased risk in colorectal cancer was seen with the use of proton pump inhibitors. Current use was associated with an increased likelihood to be diagnosed with colorectal cancer, but this is likely the result of reverse causality. No increased risk was seen for long-term use of proton pump inhibitors.

3702 | To what extent are topical tacrolimus or pimecrolimus associated with increased risk of skin cancer and lymphoma? Long-term results from Joelle study

Alejandro Arana[1], Anton Pottegård[2], Josephina G. Kuiper[3], Elizabeth Crellin[4], Johan Reutfors[5], Marcus Schmitt-Egenolf[6], Lars Christian Lund[2], Eline Houben[3], Helen Booth[4], Brian Calingaert[7], James A. Kaye[7], Karin Gembert[5], Kenneth J Rothman[7], Daniel Dedman[4], Helle Kieler[5], Lia Gutierrez[1], Jesper Hallas[2] and Susana Perez-Gutthann[1]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]RTI-HS, Barcelona, Spain; [2]University of Southern Denmark, Odense, Denmark; [3]PHARMO Database Network, Utrecht, Netherlands; [4]Clinical Practice Research Datalink, London, United Kingdom; [5]Karolinska Institutet, Stockholm, Sweden; [6]University of Umeå, Umeå, Sweden; [7]RTI-HS, Research Triangle Park, NC

Background: Observations of transplant recipients receiving systemic calcineurin inhibitors have raised concern of a potentially increased risk of lymphoma and skin cancer with topical use of tacrolimus (TAC) or pimecrolimus (PIM) for atopic dermatitis.

Objectives: To estimate the long-term risk of skin cancer and lymphoma associated with use of topical TAC or PIM in adults and children

Methods: A multinational cohort study was conducted using available health data from 2002 through 2017 in the United Kingdom's Clinical Practice Research Datalink, the PHARMO Database Network in the Netherlands, and the Danish and Swedish nationwide health registers. Mantel-Haenszel methods were used to estimate incidence rate ratios (IRRs) and differences in children and adults of study malignancies, comparing new users of topical TAC and topical PIM with two propensity score-matched cohorts of users of moderate- to high-potency topical corticosteroids. Malignancies included Hodgkin's lymphoma, non-Hodgkin's lymphoma other than cutaneous T-cell lymphoma (CTCL), CTCL, and skin cancer (melanoma and nonmelanoma).

Results: The study included 126,908 adults and 32,605 children initiating treatment with topical TAC and 61,841 adults and 27,961 children initiating treatment with topical PIM. Follow-up was 10 years or more for 19.4% of adults and for 31.9% of children. Among adults and children, the median number of topical TAC or PIM prescriptions was one, and for the 80th percentile, three. In adults, IRRs were not increased other than the IRR of CTCL for topical TAC: 1.80 (95% confidence interval [CI], 1.25-2.58) corresponding to an excess rate of 3 cases per 100,000 person-years (95% CI, 1-6). The IRR of melanoma for topical PIM was 1.21 (95% CI, 1.03-1.41) for an excess rate of 10 cases per 100,000 person-years (95% CI, 1-18). The IRR of nonmelanoma skin cancer for topical PIM was 1.28 (95% CI, 1.20-1.35) for an excess rate of 91 cases per 100,000 person-years (95% CI, 68-114). In children, results were inconclusive due to few events. For adult users of topical TAC in whom the time since first exposure to treatment was ≥ 5 years, the IRR for CTCL was 0.25 (95% CI, 0.03-1.87).

Conclusions: Overall, we found little evidence associating use of topical TAC and topical PIM with skin cancer and lymphoma; confounding by indication, surveillance bias, and reverse causation may have influenced these results. If there were a causal association, our data indicate that any public-health impact of CTCL associated with the use of topical TAC and of skin cancer associated with the use of topical PIM would be low.

3852 | Tumor necrosis factor inhibitors (TNFis) and cancer risk in older adults with rheumatoid arthritis (RA)

Monica E. D'Arcy[1], Daniel Beachler[2], Jeffrey Curtis[3], Ruth M. Pfeiffer[1], Donna R. Rivera[1], Xavier Mariette[4], Raphael Seror[4] and Eric A. Engels[1]

[1]National Cancer Institute, National Institute of Health, Rockville, MD; [2]Healthcore Inc, Wilmington, DE; [3]University of Alabama, Birmingham, AL; [4]Université Paris-Saclay, Saint-Aubin, France

Background: TNFis are used to treat RA, but immune effects may increase the risk of some malignancies, especially lymphomas.

Objectives: To examine the association between TNFi use and cancer risk, including lymphoma subtypes, in older US patients with RA enrolled in Medicare.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER) Medicare linked database to perform a case-control study. We selected all first cancers diagnosed in SEER (2007-2015) and cancer-free controls from Medicare. Study participants (aged 66-99) had ≥1 month Medicare Part A/B/D coverage, and ≥1 Medicare claim between study entry and 1 year prior to selection. All participants had Medicare claims for an inpatient RA diagnosis, or an RA diagnosis in the outpatient setting with a rheumatologist. TNFi (etanercept, infliximab, adalimumab, golimumab, certolizumab) exposure was ascertained from Medicare parts B and D claims. Cutaneous basal cell carcinoma (BCC) (2012-2015) and squamous cell carcinoma (SCC) (2012-2015), and non-melanoma skin cancer not otherwise specified (NMSC NOS) are not captured by SEER registries and were instead identified from Medicare using claims-level diagnoses and procedures. Logistic regression was used to estimate adjusted odds ratios (aORs) for each TNFi-cancer association, adjusted for race, sex, age, selection year, evidence of smoking history, methotrexate (MTX) use, and markers of disease severity (e.g. Sjogren's syndrome, interstitial lung disease, steroid use). A Bonferroni correction was applied to previously unreported associations.

Results: There were 10,739 SEER cases (22 cancer types), 519 NMSC NOS, 165 BCCs, 158 SCCs and 30,507 controls among RA patients. TNFi use was present in 16.2% of controls and 16.6% of cases but varied by cancer site (12.8%-33.4%). Compared to TNFi unexposed, TNFi use was associated with melanoma (aOR=1.4, 95% CI=1.1-1.9) and with non-Hodgkin lymphoma (NHL) overall (1.3, 1.1-1.6). The TNFi-NHL association varied by NHL subtype and was significant only with follicular lymphoma (FL) (aOR=2.6, 95%CI=1.6-4.2) and not with other examined subtypes. TNFi use was associated with BCC (aOR=1.7, 95%CI=1.2-2.5) but not SCC (0.9, 0.6-1.4). There was a negative interaction (p = 0.007) between TNF and MTX use, and TNF only use (aOR=2.3, 95%CI 1.5-3.4) was associated with greater melanoma risk compared with TNF+MTX risk.

Conclusions: Among older adults with RA, TNFi use is not associated with risk of most cancers. However, the immune changes caused by TNFi use may increase risk of certain skin cancers and subtypes of NHL.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3925 | Cancer risk of ranitidine and nizatidine versus other H2 blockers: An analysis of the Japan medical data center claims database

Masao Iwagami[1], Ryosuke Kumazawa[2], Yoshihisa Miyamoto[3], Yuri Ito[4], Nanako Tamiya[1] and Hideo Yasunaga[2]
[1]*University of Tsukuba, Tsukuba, Japan;* [2]*University of Tokyo, Tokyo, Japan;* [3]*University of Tokyo, Tokyo, Japan;* [4]*Osaka Medical College, Osaka, Japan*

Background: In September 2019, ranitidine and nizatidine were suggested to contain N-nitrosodimethylamine (NDMA), a carcinogenic substance. People are concerned about the potential impact of previous ranitidine/nizatidine use on cancer risk.
Objectives: To investigate the risk of cancer among people receiving ranitidine/nizatidine, compared to other H2 blockers (cimetidine, famotidine, roxatidine, or laftidine).
Methods: In the Japan Medical Data Center claims database, a database of middle and large company employees and their family members (up to 74 years old) from January 2005 to August 2018, we identified new adult users of H2 blockers (based on no evidence of prescription for at least six months since their registration to the database). We classified them into the ranitidine/nizatidine group and the other H2 blockers group (i.e., comparison group). If new users of other H2 blockers subsequently received ranitidine/nizatidine, they were censored from the comparison group and regarded as new users of ranitidine/nizatidine from that time point forward. A patient was followed until the earliest of: incidence of cancer diagnosis, leaving the database, or August 2018. We conducted multivariable Cox regression analyses for incident cancer diagnosis, overall and by follow-up length, cumulative dose, and cancer site.
Results: We identified 114,106 new users of ranitidine/nizatidine (mean age 41.6±12.7 years, men 49.1%, median follow-up 2.4 years [IQR 1.1-4.5]) and 502,803 new users of other H2 blockers (mean age 41.4±12.9 years, men 51.0%, median follow-up 2.3 years [IQR 0.9-4.2]). There were 2,289 (top 3 sites: colon 15.2%, breast 14.8%, and gastric 11.5%) and 8,946 (top 3 sites: colon 15.5%, breast 13.6%, and gastric 11.1%) incident cancer cases, providing the incidence rate of 6.4 (95% CI, 6.1-6.6) and 6.1 (6.0-6.2) per 1,000 person-years in the ranitidine/nizatidine and comparison groups, respectively. The adjusted hazard ratio (aHR) was 1.04 (0.99-1.08). The aHR was 1.05 (0.99-1.10) during the first 5 years and 0.98 (0.87-1.12) after 5 years since the first prescription, 1.05 (0.99-1.10) until the cumulative dose reached 180 daily defined doses and 0.97 (0.77-1.24) thereafter. By cancer site, the aHR was 1.03 (0.91-1.15), 1.05 (0.93-1.19), and 1.11 (0.97-1.27) for colon, breast, and gastric cancer, respectively.
Conclusions: In this database mainly consisting of people of working age, there was no evidence that ranitidine/nizatidine was associated with increased risk of cancer, although its generalizability to older people remains unknown and longer follow-up may be needed.

4077 | Use of hydrochlorothiazide and risk of melanoma and nonmelanoma skin cancer

Julie Rouette[1,2], Hui Yin[2], Anton Pottegård[3] and Laurent Azoulay[1,2]
[1]*McGill University, Montreal, QC, Canada;* [2]*Jewish General Hospital, Montreal, QC, Canada;* [3]*University of Southern Denmark, Odense, Denmark*

Background: Hydrochlorothiazide (HCTZ) is one of the most commonly prescribed antihypertensive drugs worldwide. While this drug has been shown to have clinical benefits, there are concerns that its photosensitizing properties might increase the risk of skin cancer. To date, studies investigating this association compared HCTZ to either non-use or other classes of antihypertensive drugs, and none directly compared HCTZ to other thiazide diuretics.
Objectives: To determine whether use of HCTZ is associated with an increased risk of melanoma and nonmelanoma skin cancer (basal cell carcinoma [BCC], squamous cell carcinoma [SCC]), when compared with use of other thiazide diuretics.
Methods: The UK Clinical Practice Research Datalink was used to identify patients initiating either HCTZ or other thiazide diuretics (e.g., bendroflumethiazide, chlorthalidone, indapamide) between 1988 and 2018, with follow-up until 2019. Each HCTZ user was matched, in a 1:1 ratio, to another thiazide diuretic user on propensity score, calendar year, and previous use of other antihypertensive drugs. All patients were required to have at least one year of follow-up for latency considerations, and were followed using an intention-to-treat approach. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) separately for melanoma, BCC, and SCC, comparing use of HCTZ with use of other thiazide diuretics. Secondary analyses assessed whether there were duration-response relationships with these outcomes in terms of cumulative duration of use.
Results: A total of 20,513 HCTZ users were matched to an equal number of other thiazide diuretic users. After a median follow-up of 7.6 years, HCTZ was not associated with an increased risk of melanoma (56 vs 68 per 100,000 person-years, respectively; HR: 0.82, 95% CI: 0.63-1.08) or BCC (382 vs 380 per 100,000 person-years, respectively; HR: 1.01, 95% CI: 0.91-1.13), when compared with other thiazide diuretics. There were no duration-response relationships with these outcomes in secondary analyses. In contrast, HCTZ was associated with an overall increased risk of SCC (47 vs 32 per 100,000 person-years, respectively; HR: 1.50, 95% CI: 1.06-2.11). In secondary analyses, the HRs gradually increased as a function of cumulative duration of use (<5 years, HR: 1.26, 95% CI: 0.86-1.83; 5-10 years, HR: 2.10, 95% CI: 1.20-3.67; >10 years, HR: 3.70, 95% CI: 1.77-7.73).
Conclusions: In this population-based study, use of HCTZ was not associated with an increased risk of melanoma and BCC. In contrast, an association was observed with SCC, with evidence of a duration-response relationship.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4200 | Description of acute kidney injury and breast cancer outcome validation processes across three databases

Jade Dinh[1], Heather E Danysh[2], Catherine Johannes[2], Lia Gutierrez[2], Rita Schmid[3], Alejandro Arana[2], James A Kaye[2], Manel Pladevall-Vila[2], Xabier Garcia de Albeniz[2], Phillip R Hunt[4], Alicia Gilsenan[2], Daniel C Beachler[1] and Cindy Ke Zhou[1]

[1]HealthCore, Inc., Wilmington, DE; [2]RTI Health Solutions, Research Triangle Park, NC; [3]South Bend Clinic, Granger, IN; [4]AstraZeneca, Gaithersburg, MD

Background: Standard outcome validation processes can differ between organizations and data sources, which challenges harmonization for multi-database studies. The data sources used in this study were: The HealthCore Integrated Research Database (HIRD), a US commercial medical insurance claims database; Medicare, a US federal medical insurance program mainly for individuals age 65 and older; and the Clinical Practice Research Datalink (CPRD), a UK primary care electronic medical records (MR) database.

Objectives: To describe the outcome validation process, source verification retrieval rate, and ability to determine a final case status from two ongoing multi-database studies with focus on acute kidney injury (AKI) and breast cancer.

Methods: Possible cases diagnosed in 2012-2018 were first identified using an electronic algorithm, and validation was conducted using predefined clinical case definitions and information from redacted MRs (HIRD), MR abstraction forms (Medicare), clinical patient profiles and general practitioner questionnaires (GPQx) (CPRD). To limit variability, the study team aimed to align the following validation components for each outcome across the data sources: uniform adjudication trainings, designation of adjudication committee members, and case definitions.

Results: The overall retrieval rate for MRs was 50.4% (HIRD), 56.4% (Medicare), and 64.4% for GPQx (CPRD). The adjudication committee assigned a definitive case status for 79% (HIRD), 80% (Medicare), and 63% (CPRD) of AKI cases and 98% (HIRD), 86% (Medicare), and 90% (CPRD) of breast cancer cases. The proportion of reviewed cases with insufficient information in the available records for assigning a definitive case status (and/or due to lack of response from GPQx in CPRD): 21% (HIRD), 20% (Medicare), and 38% (CPRD) for AKI (case definition required information on laboratory values) and 2% (HIRD), 14% (Medicare), 10% (CPRD) for breast cancer (case definition required evidence of diagnosis and either a cancer-specific therapy or encounter).

Conclusions: A higher proportion of reviewed breast cancer cases were assigned a final case status compared to AKI cases. The AKI case definition required laboratory values which were often incomplete or missing from available records. Although the adjudication process in this study was aligned across data sources to the extent possible, with similar results in the two US claims-based data sources, some reviewed cases were not adjudicated. Harmonization of validation approaches is important to minimize potential variation in safety study results.

4480 | Risks of acute gastrointestinal adverse events associated with metastatic melanoma therapies: A retrospective cohort study

Sascha Van Boemmel-Wegmann[1], Joshua D. Brown[1], Vakaramoko Diaby[1], Jinhai Huo[2], Natalie L. Silver[3] and Haesuk Park[1]

[1]University of Florida, Gainesville, FL; [2]University of Florida, Gainesville, FL; [3]University of Florida, Gainesville, FL

Background: The association between the use of immune checkpoint inhibitors (ICIs) and an increased risk of acute moderate to severe gastrointestinal adverse events (GI-AEs) was shown in clinical trials. However, little is known about this association in real-world settings.

Objectives: This study aimed to compare risks of acute GI-AEs among metastatic melanoma (MM) patients using MM therapies in first-line.

Methods: We conducted a retrospective cohort study of patients with MM using MarketScan commercial claims data (2012-2017). Adult patients with a diagnosis of MM were included if they newly initiated a CTLA-4-inhibitor (i), PD-1-i, CTLA-4-i + PD-1-i combination or BRAF-i + MEK-i combination. A GI outcome was measured based on (1) a hospitalization for an acute GI event or (2) an outpatient GI-AE diagnosis plus the initiation of a long-term corticosteroid (supply >14 days) within a 5 day span. Follow-up continued until the occurrence of a GI-AE, discontinuation or switching of index regimen, or loss of insurance eligibility, whichever occurred first. We used propensity score (PS) weighted Cox regression models to compare the hazards of GI-AEs in users of PD-1-i, CTLA-4-i + PD-1-i and BRAF-i + MEK-i to the CTLA-4-i group, respectively.

Results: We identified 1,112 MM patients including 581 CTLA-4-i, 235 PD-1-i, 148 CTLA-4-i + PD-1-i and 148 BRAF-i + MEK-i users. 13.6% (n=79), 9.8% (n=23), 28.4% (n=42) and 14.9% (n=22) of patients using CTLA-4-i, PD-1-i, CTLA-4-i + PD-1-i, and BRAF-i + MEK-i experienced GI-AEs, respectively. In the PS weighted Cox regression models, CTLA-4-i + PD-1-i users showed a two-fold higher risk for acute GI-AEs compared to CTLA-4-i users (hazard ratio [HR] 2.07; 95% confidence interval [CI] 1.33-3.23); PD-1-i users had significantly lower hazards for GI-AEs compared to CTLA-4-i users (HR 0.41; 95% CI 0.24-0.72). No difference in risks for GI-AEs were found between BRAF-i + MEK-i users and the CTLA-4-i group (HR 0.58; 95% CI 0.33-1.04).

Conclusions: In this population-based cohort study, risks for GI-AEs varied significantly among MM therapies and appeared to mirror risk differences measured in pivotal clinical trials reasonably well. CTLA-4-i + PD-1-i combination therapy was associated with a higher risk, PD-1-i monotherapy use was associated with a lower risk of GI-AEs when compared to CTLA-4-i monotherapy, respectively. The risk of GI-AEs following molecular targeted BRAF-i + MEK-i combination therapy appeared to be similar to CTLA-4-i users.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4659 | Statins and breast cancer risk in a cohort of postmenopausal women

Laure Dossus[1], Véronique Chajès[2], Mathilde His[1], Manon Cairat[1], Marie Al-Rahmoun[3], Guy Fagherazzi[3,4], Gianluca Severi[3], Marc J Gunter[1] and Agnès Fournier[3]

[1]Nutrition and Metabolism Section, International Agency for Research on Cancer, Lyon, France; [2]Nutrition and Metabolism Section, International Agency for Research on Cancer, Lyon, France; [3]CESP "Exposome, Heredity, Cancer and Health", Université Paris-Saclay, UVSQ, Inserm, Gustave Roussy, Villejuif, France; [4]Digital Epidemiology and e-Health Research Hub, Department of Population Health, Luxembourg Institute of Health, 1A-B, rue Thomas Edison, Strassen, Luxembourg

Background: Statins are widely used drugs that reduce blood cholesterol levels by inhibiting hepatic hydroxymethylglutaryl-coenzyme A reductase within the mevalonate pathway. While their use is associated with better disease-free survival after breast cancer (BC) diagnosis, statins have shown inconsistent associations with primary BC incidence.

Objectives: To assess the association between statin use and BC risk according to BC types, exposure characteristics and BC risk factors in a cohort study.

Methods: The study population included postmenopausal women from the French E3N cohort. Data self-reported in biennial questionnaires were matched with data from a drug reimbursement database that was used to identify statin exposure. Hazard ratios (HRs) of BC were estimated using Cox models, considering statin exposure as time-varying. They were adjusted for known BC risk factors and for potential confounding factors such as personal history of hypercholesterolemia, use of cardiovascular drugs, and frequency of visits to the doctor.

Results: Among 60,582 postmenopausal women followed between 2004 and 2014 (mean duration: 9.1 years; mean age at baseline: 62.9 years; 31.5% ever exposed to statins at the end of follow-up), 2784 primary BCs occurred. Compared to never exposed women, exposed women had an HR of BC of 1.02 [95% CI 0.92-1.12]. Among all BC risk factors, parity was the only effect modifier of the statins-BC risk association, with statin-associated HRs of 1.24 [0.95-1.62], 1.08 [0.95-1.23], and 0.79 [0.64-0.97] among women with 0, 1 or 2, and 3+ full-term pregnancies, respectively (p-interaction = 0.02). We found no significant variation in HRs according to BC characteristics (hormone receptors, HER2, stage, grade, histological type) or exposure characteristics (time since last or first exposure, cumulative dose/duration, age at first use, or statin molecule). We also noted that ever use of bisphosphonates, another class of drugs disrupting the mevalonate pathway that are prescribed for the management of postmenopausal osteoporosis, showed different HRs of breast cancer across parity strata: 1.09 [0.82-1.44], 1.05 [0.91-1.20], and 0.73 [0.57-0.93] among women with 0, 1 or 2, and 3+ full-term pregnancies, respectively (p-interaction = 0.049).

Conclusions: While there was no association between statin use and BC risk overall, we observed a statin-associated decreased BC risk restricted to women with at least 3 full-term pregnancies. Our study being the first assessing effect modification of the statins-BC risk association by parity among postmenopausal women, that result warrants replication in other settings.

4673 | Studies on the effect of drugs on colorectal cancer incidence: Considerable risk of misleading results

Ulrike Haug[1,2] and Sarina Schwarz[1]

[1]Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany; [2]University of Bremen, Bremen, Germany

Background: Several drugs have been suggested to decrease or increase the risk of colorectal cancer (CRC) based on findings from observational studies. However, there is a considerable risk of misleading results if the study does not adequately consider I) the natural history of the disease, II) the phase of carcinogenesis relevant to the drug and III) utilization of colonoscopy which has a strong and long-lasting protective effect on CRC incidence.

Objectives: To illustrate the relevance of these aspects in studies on the effect of drugs on CRC incidence.

Methods: We simulated three different studies, each aiming to estimate the effect of hypothetical drugs on CRC incidence based on an active comparator new user design. We compared the effects of these drugs on CRC incidence observed in these studies to their true effects on CRC incidence (assumed to be known here). Study 1 compared two drugs without a true effect on CRC risk (drug A and drug B). Study 2 compared drug A (i.e. no true effect on CRC risk) to a drug that increases the risk of developing precursor lesions of CRC (drug C). Study 3 compared drug A to a drug that accelerates and promotes progression of precursor lesions to clinical CRC (drug D). For each study, we considered variations in the study design (scenarios): we varied the length of the baseline period (i.e. time before drug initiation), the length of the follow-up period and the assumption on latency periods. We used published estimates regarding natural history parameters for CRC and real-life data on colonoscopy use.

Results: Study 1 suggested an effect of drug B on CRC incidence in several scenarios, particularly if colonoscopy use was different between groups but the baseline period was <5 years, i.e. where information was lacking to adequately adjust for this confounder. Study 2 suggested no effect of drug C on CRC incidence in scenarios with follow-up periods below 10 years. Study 3 suggested no effect of drug D on CRC incidence in several scenarios where latency periods where applied. Application of latency periods also distorted the results - in all three studies - if colonoscopy use after drug initiation was different between groups.

Conclusions: Studies on the effect of drugs on CRC incidence need to be interpreted with caution as there is a considerable risk of misleading results, particularly if observation time before and after drug initiation is limited. When planning such a study, any information on the supposed phase of carcinogenesis relevant to the drug should be taken into account and the application of latency periods may generally be questioned.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4711 | Use of hydrochlorothiazide and risk of skin cancer in a large nested case-control study in Spain

Luz M Leon-Munoz[1], Talita Duarte-Salles[2], Ana Llorente-Garcia[1], Yesika Diaz-Rodriguez[2], Anton Pottegard[3], Dolores Montero-Corominas[1] and Consuelo Huerta-Alvarez[1]

[1]*Spanish Agency of Medicines and Medical Devices (AEMPS), Madrid, Spain;* [2]*Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain;* [3]*Clinical Pharmacology and Pharmacy, Department of Public Health, Faculty of Health Science, University of Southern Denmark, Odense, Denmark*

Background: The use of hydrochlorothiazide (HCTZ) has been linked to skin cancer. However, this association has not been evaluated in a Mediterranean population.

Objectives: To assess the association between HCTZ exposure and risk of malignant melanoma (MM) and non-melanoma skin cancer (NMSC) in Spain.

Methods: Two independent nested case-control studies were conducted using electronic primary healthcare databases in Spain (SIDIAP and BIFAP) from 2007 to 2017. Participants were >=18 years old. Skin cancer registry data were identified and validated in both databases. Cases were matched to 10 controls by age and gender through risk-set sampling. Exposure definition was based on dispensations in SIDIAP and on prescriptions/dispensations in BIFAP. The odds ratios (ORs) and 95% confidence interval (CI) for MM and NMSC associated with previous HCTZ use (ever and cumulative) were estimated using conditional logistic regression. In BIFAP the specific risks of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) were also estimated. Any information on HCTZ use as well as on potential confounders within two years prior to cancer diagnosis was disregarded.

Results: The incidence rate (in cases per 100,000 person-years) of MM was 15.2 in SIDIAP and 13.1 in BIFAP, and for NMSC was 129.2 in SIDIAP and 87.5 in BIFAP (73.8 for BCC and 13.7 for SCC). Regarding exposure, 30.1% of the population have ever used HCTZ in SIDIAP and 19.8% in BIFAP, while 5.3% and 1.6%, respectively, presented a cumulative high use (>=50,000 mg). In adjusted analyses, ever use of HCTZ was associated with higher MM risk (OR (95%CI): 1.20 (1.13-1.28) in SIDIAP and 1.14 (1.04-1.25) in BIFAP), but inconsistent results arose related to its high cumulative use: OR (95%CI): 1.24 (1.08-1.42) and 0.85 (0.64-1.13) respectively. Both ever and high use of HCTZ were associated with higher NMSC risk: OR (95%CI) for ever and high use were 1.13 (1.11-1.15) and 1.30 (1.26-1.34) in SIDIAP, and 1.10 (1.07-1.14) and 1.20 (1.12-1.30) in BIFAP, respectively. A dose-response relationship was observed between cumulative doses of HCTZ and NMSC risk, with the highest OR (95%CI) observed for exposure to 150,000-199,999 mg: 1.44 (1.26-1.64) in SIDIAP and 1.50 (1.17-1.92) in BIFAP. Data from BIFAP revealed a lower risk for BCC than for SCC related to the high-use of HCTZ: OR (95%CI) 1.11 (1.02-1.21) and 1.71 (1.45-2.02), respectively.

Conclusions: In these Mediterranean populations, use of HCTZ was associated with increased risk of NMSC, in particular SCC, and inconsistently associated with MM.

4955 | Use of hydrochlorothiazide and risk of uveal melanoma

Anton Pottegård, Sidsel A. Pedersen and Kasper B. Kristensen

University of Southern Denmark, Odense, Denmark

Background: The antihypertensive agent hydrochlorothiazide possess photosensitizing properties and has recently been associated with an increased risk of non-melanoma skin cancer (NMSC), in particular squamous cell carcinoma. Regarding melanoma, risks were initially reported to be increased for the nodular and lentigo subtype only. While the finding for nodular melanoma is somewhat contrary to expectations, considering the proposed mechanism of UV sensitization and our, albeit limited, understanding of the pathophysiology of nodular melanoma, the risk increase for lentigo melanoma is in line with adult UV exposure being a primary risk factor. The association between hydrochlorothiazide and lentigo melanoma has later been replicated in two independent studies. Other types of melanomas have, to our knowledge, not yet been investigated.

Objectives: To assess the association between hydrochlorothiazide use and risk of uveal melanoma.

Methods: We performed a nationwide Danish case-control study. Using the Danish Cancer Registry, we identified histologically verified cases of uveal melanoma 2004-2015. For each case, we identified 10 population controls matched on age and sex. Cases and controls with a history of cancer (except NMSC), recent migrations, organ transplantation, azathioprine use, and HIV/AIDS diagnoses were excluded. Use of hydrochlorothiazide was obtained using data from the Danish Prescription Registry, and covariates was assessed using data from the Danish National Patient Registry and Danish Education Registries. Odds ratios (OR) associating use of hydrochlorothiazide with uveal melanoma was analysed using conditional logistic regression, adjusting for covariates. The pre-specified primary exposure metric of 'long-term' hydrochlorothiazide was defined as cumulative use of ≥50,000mg.

Results: We identified 473 eligible cases of uveal melanoma of whom 11.6% (n=55) had ever used hydrochlorothiazide and 2.5% (n=12) were classified as 'long-term' users. The corresponding proportions among controls were 10.6% and 2.1%. This yielded an OR for ever use of 1.12 (95%CI 0.80-1.54) and 1.34 (95%CI 0.71-2.53) for 'long-term' use, respectively. There was no apparent dose-response pattern (p_trend=0.24).

Conclusions: In this nationwide observational study, we found no association between use of hydrochlorothiazide and uveal melanoma risk.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5010 | Second cancers in adults with acute promyelocytic leukemia (APL) Treated with or without arsenic trioxide (ATO): A SEER-medicare analysis

Kelly J. Norsworthy[1], Steven Bird[1], Armen Avagyan[2], Yuchen Li[2], Sandia Akhtar[2], Jiemin Liao[2], Michael Wernecke[2], Albert B Deisseroth[1], Meredith Chuk[1], Thomas E MaCurdy[3], Richard Swain[1], Jeffrey A. Kelman[4], Ann T Farrell[1], Richard Pazdur[1], Gideon Blumenthal[1] and David J. Graham[1]

[1]Food and Drug Administration, Silver Spring, MD; [2]Acumen LLC, Burlingame, CA; [3]Stanford University, Stanford, CA; [4]Centers for Medicare & Medicaid Services, Washington, DC

Background: ATO is U.S. approved for relapsed/refractory APL and in combination with all-trans retinoic acid (ATRA) for adults with newly-diagnosed low-risk APL. ATRA and ATO combinations result in long-term remissions in most patients with APL. However, epidemiologic studies have shown associations between exposure to inorganic arsenic and development of second cancers.

Objectives: We performed an exploratory analysis of second cancers and overall survival (OS) in adults with APL treated with ATO compared to other systemic APL therapies.

Methods: Using SEER-Medicare linked data, we identified APL patients diagnosed from 2006-2015 with a first SEER cancer diagnosis of APL, enrolled in Medicare Parts A, B, & D, and who received ≥ 1 systemic APL therapy within 1 year of diagnosis. The cumulative incidence of SEER-confirmed second cancers and OS was calculated for ATO and non-ATO therapy and displayed in Kaplan-Meier curves. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for cumulative incidence of second cancers and OS adjusted for age, sex, and year of diagnosis.

Results: We identified 1,442 APL cases, 246 of which met inclusion criteria. Of these, 64 received ATO and 60 received systemic APL therapy without ATO. Absolute incidence rates of second cancer were 3.4/1000 person-months compared to 1.4/1000 person-months and cumulative incidence rates at 24 months were 9.9% and 6.0%, in patients treated with and without ATO, respectively (p=0.24). Mortality rates were 1.9/1000 person-months compared to 5.1/1000 person-months and OS at 24 months was 90.8% and 81.5%, in patients treated with and without ATO, respectively (p=0.13). The adjusted HR for cumulative incidence of second malignancies in patients treated with ATO was 1.27 (95% CI 0.29-5.49; p=0.75) and for OS was 0.46 (95% CI 0.16-1.29; p=0.14) compared to APL therapy without ATO.

Conclusions: The analysis found a numerically higher, but not statistically significant difference in incidence of second malignancies in APL patients treated with versus without ATO. Most second malignancies were solid tumors, in line with prior epidemiologic studies of inorganic arsenic exposures. There was a tendency towards longer OS in patients treated with ATO. Given the small sample size, short follow-up, and potential for selection bias and confounding, firm conclusions cannot be inferred. However, the nearly 10% cumulative incidence of second malignancies at 24 months in Medicare patients with APL treated with ATO suggests the need for close monitoring for and research into second malignancies.

5150 | Lean body mass is associated with chemotherapy-induced adverse drug effects

Macarius Donneyong[1], Teng-Jen Chang[1], Autumn Carey[2], Jared Huling[3], Jared Huling[3], Christopher Coss[4], James Odei[5] and Lang Li[6]

[1]Ohio State University, Columbus, OH; [2]Ohio State University, Columbus, OH; [3]Ohio State University, Columbus, OH; [4]Ohio State University, Columbus, OH;[5]Ohio State University, Columbus, OH; [6]Ohio State University, Columbus, OH

Background: Chemotherapy-induced adverse drug effects (C-AEs) tend to occur when patients are exposed to higher drug doses than they are able to tolerate. Most cancer drugs are hydrophilic and are distributed in lean body mass (LBM). However, chemotherapy doses are often selected based on total body weight or body surface are and not LBM, this could potentially increase the risk of C-AEs.

Objectives: To measure the associations between LBM and C-AEs in real-world settings.

Methods: We extracted data from The Ohio State University James Cancer center's cancer registry, 2012-2018. A cohort of cancer patients undergoing chemotherapy for the first time was assembled with the chemotherapy date as the index date for covariate measurement and follow-up for C-AEs respectively. We applied our previously developed anthropometric-based algorithms to predict the LBM of cancer patients using height and weight data measured closest to their index date within a 6 month look-back window. All other covariates including demographic, clinical, cancer stage and cancer types were collected in this 6-month pre-chemotherapy window. The predictive algorithms were developed and tested among cancer patients and are age, sex and race/ethnicity specific. The LBM% of individuals were calculated by dividing their predicted LBM with their total body weight. Follow-up for C-AEs began on the next day after chemotherapy through to first of death or end of data availability. The functional form of the relationship between LBM% and C-AE probability was visually inspected with loess plots. Next, logistic regression models were used to quantify the odds ratios (ORs) between LBM% and C-AEs in unadjusted and multivariable-adjusted models.

Results: Of the 5,475 new chemotherapy initiators, majority were diagnosed with breast cancer (37%), lung cancer (33%) or colorectal cancer (16%). More than half of them were aged over 55 years old and about 60% were female. The loess plots showed an inverse relationship between LBM% and C-AE probability. Therefore, LBM% quartiles were modeled. In unadjusted models, increasing LBM% was associated with risk reduction in C-AE; compared to the first quartile, the upper quartile of LBM% was associate with 48% risk reduction (OR=0.62, 95%CI:0.44, 0.88). This risk attenuated after adjusting for multiple confounders. Similar results were observed when stratified by cancer types.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: LBM was significantly associated with lower risk of C-AEs in unadjusted but not in multivariable-adjusted models. This topic warrants further investigation especially regarding how LBM and chemotherapy dose may act in concert to affect C-AE risk.

Safety End Points -> Cardiovascular

47 | Incidence and risk factors for major bleeding among patients undergoing percutaneous coronary intervention: Findings from the norwegian coronary stent trial (NORSTENT)

Per-Jostein Samuelsen[1,2], Anne Elise Eggen[2], Terje Steigen[2,1], Tom Wilsgaard[2], Andreas Kristensen[1], Anne Skogsholm[1], Elisabeth Holme[1], Christian van den Heuvel[1], Jan Erik Nordrehaug[3], Bjørn Bendz[4], Dennis W. T. Nilsen[5,3] and Kaare Harald Bønaa[6,7]
[1]University Hospital of North Norway, Tromsø, Norway; [2]UiT The Arctic University of Norway, Tromsø, Norway; [3]University of Bergen, Bergen, Norway; [4]Oslo University Hospital, Oslo, Norway; [5]Stavanger University Hospital, Stavanger, Norway; [6]St. Olav's University Hospital, Trondheim, Norway; [7]Norwegian University of Science and Technology, Trondheim, Norway

Background: Bleeding is a concern after percutaneous coronary intervention (PCI) and subsequent dual antiplatelet therapy (DAPT).
Objectives: To estimate the incidence of major bleeding and to identify sub groups with the highest bleeding risk among stent naïve patients undergoing PCI with stent implantation and DAPT, and to identify risk factors for major bleeding, including the effect of new or recurrent myocardial infarction (MI) or PCI.
Methods: The Norwegian Coronary Stent Trial (NORSTENT; ClinicalTrial.gov NCT0081177) was a randomized, double blind, pragmatic randomized trial among patients with acute coronary syndrome or stable coronary disease undergoing PCI during 2008-11. The patients (*N* = 9,013) were randomized to receive either a drug eluting stent or a bare metal stent, and were treated with at least 9 months of DAPT. The patients were followed for a median of five years, with BARC 3-5 major bleeding as one of the safety endpoints. We estimated cumulative incidence by a competing risks model and risk factors through cause-specific Cox models.
Results: The 12-month cumulative incidence of major bleeding was 2.3%. Independent risk factors for major bleeding were chronic kidney disease (CKD), underweight (< 60 kilograms), diabetes mellitus, and advanced age (> 80 years). A myocardial infarction (MI) or PCI during follow-up increased the risk of major bleeding (HR = 1.7, 95% CI 1.3-2.2).
Conclusions: The 12-month cumulative incidence of major bleeding in NORSTENT was higher than reported in previous, explanatory trials. This analysis strengthens the role of CKD, advanced age, and underweight as risk factors for major bleeding among patients receiving DAPT after PCI. The presence of diabetes mellitus or recurrent MI among patients is furthermore a signal of increased bleeding risk.

2380 | Fluoroquinolones and risk of aortic aneurysm or dissection

Chandrasekar Gopalakrishnan[1], Katsiaryna Bykov[1], Michael Fischer[1], John G. Connolly[2], Joshua J. Gagne[1] and Michael Fralick[3]
[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; [3]University of Toronto, Toronto, ON, Canada

Background: Recent studies suggest that fluoroquinolones are associated with aortic aneurysm or dissection, but these studies may be subject to confounding by indication or surveillance bias.
Objectives: To assess the safety of fluoroquinolones with respect to aortic aneurysm or dissection in specific indications (pneumonia and urinary tract infections [UTI]), with clinically appropriate comparators, and accounting for potential differences in surveillance.
Methods: In a large US commercial claims database (IBM MarketScan, 01/2003-09/2015), we identified two pairwise 1:1 propensity score (PS)-matched cohorts: (1) adult patients with a diagnosis of pneumonia ≤3 days prior to initiating fluoroquinolone or azithromycin (n=139,772 pairs; mean age: 63 years); (2) adult patients with a UTI diagnosis ≤3 days prior to initiating a fluoroquinolone or trimethoprim/sulfamethoxazole (n=474,182 pairs; mean age: 62 years). The primary outcome was hospitalization for aortic aneurysm or dissection occurring in the 60 days following treatment initiation. We estimated hazard ratios (HR) and 95% confidence intervals (CI) controlling for 85 baseline potential confounders. In secondary analyses, we mimicked a major prior study by comparing initiators of fluoroquinolones to amoxicillin (n=542,649 pairs, mean age: 63 years) ignoring indication. We analyzed this comparison both with and without considering baseline imaging likely to detect aneurysms, if present, to address potential surveillance bias.
Results: After PS-matching, patient characteristics were well balanced between exposure groups. Initiators of fluoroquinolones had similar rates of aortic aneurysm or dissection vs. initiators of azithromycin (HR, 1.05; 95% CI, 0.59-1.87; incidence of 0.02% in both pneumonia groups) and compared to initiators of trimethoprim/sulfamethoxazole (HR, 0.70; 95% CI, 0.43-1.16; incidence <0.01% in both UTI groups). The secondary analysis mimicking a prior study by using amoxicillin as a comparator produced results consistent with those from the prior study (HR, 1.31; 95% CI, 1.10-1.57; incidence <0.01% in both groups). Requiring baseline imaging in this cohort to address surveillance bias yielded an estimate consistent with our primary results (HR, 0.78; 95% CI, 0.61-0.99; incidence of 0.02% for fluoroquinolones vs. 0.03% for amoxicillin).
Conclusions: In this large cohort study, fluoroquinolone use was not associated with an increased risk of aortic aneurysm or dissection after accounting for potential confounding by indication and surveillance bias. Absolute incidence rates varied across the different comparisons but were very low overall.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2426 | Incidence of severe abnormal uterine bleeding following oral anticoagulant use

Ting-Ying Huang[1], Laura Hou[1], Abby Anderson[2], Hui-Lee Wong[3], Rongmei Zhang[4], Peter Waldron[5], David Moeny[6], Audrey Gassman[7] and Efe Eworuke[6]

[1]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [2]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; [3]Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; [4]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; [5]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; [6]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; [7]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD

Background: Recent reports have led to concerns over clinically relevant gynecologic adverse events among women of reproductive age and exposed to oral anticoagulants (OAs).

Objectives: To determine Severe Abnormal Uterine Bleeding (SAUB, defined as vaginal bleeding (VB) requiring medical, transfusion or surgical intervention) incidence rate among OA users in US, overall and by menopausal age group.

Methods: We used a new user cohort design and followed women who had newly initiated an OA, including non-vitamin K antagonist oral anticoagulants and warfarin, in the Sentinel Distributed Database between October 19, 2010 and September 30, 2015. Eligible members had an indicated condition (venous thromboembolism or atrial fibrillation/flutter), no evidence of index exposure, and no history of a qualifying VB management or joint replacement, in the 6-month lookback period. We defined three different SAUB outcomes - VB diagnosis followed by: 1) same-day medical intervention (insertion of intrauterine device, vaginal packing, initiation of an oral contraceptive or antifibrinolytic), 2) same-day transfusion, or 3) gynecologic surgery (hysterectomy, hysteroscopy, hysteroscopic polypectomy, myomectomy, dilation and curettage, endometrial ablation, or uterine artery embolization) within 30 days. Individual OA new users contributed at-risk time from their first valid index exposure date until the earliest of: SAUB occurrence, disenrollment, end of exposed time or study period, or recorded death.

Results: In 1,050,192 OA new users, the overall SAUB incidence rates were 0.6, 1.7, and 5.0 per 1,000 person-years for outcomes with medical, transfusion, and surgical management respectively. When stratified by menopausal age group, the SAUB incidence rates in reproductive-aged (<50 years) women elevated to 11.8, 13.7, and 33.0 per 1,000 person-years; all estimates were consistently higher than those observed in menopause-aged (50+ years) women. SAUB with surgical management was notably more common than SAUB with medical or transfusion management in all ages.

Conclusions: Based on real-world evidence, our findings suggest that patients on OA therapy may experience serious adverse outcomes related to gynecologic conditions such as SAUB while on OA therapy. As clinically significant VB is likely underreported since these women are often referred to gynecologic practices or end up in urgent/emergent care settings, we alert medical practitioners of potential SAUB cases. Further studies are warranted to facilitate the understanding of true SAUB risk in the OA user population and whether the class-wide association exists.

2447 | Cardiotoxic effects of sequential aromatase inhibitors use in women with breast cancer

Farzin Khosrow-Khavar[1], Nathaniel Bouganim[2], Kristian B. Filion[1], Samy Suisssa[1] and Laurent Azoulay[1]

[1]McGill University, Montreal, QC, Canada; [2]McGill University, Montreal, QC, Canada

Background: The treatment of hormone-receptor positive breast cancer includes continuous therapy with either aromatase inhibitors (AIs) or tamoxifen, or sequential treatment with AIs following tamoxifen. While these treatment strategies have been associated with clinical benefits, there are concerns that AIs may be associated with an increased risk of cardiovascular outcomes. To date, observational studies have examined the cardiovascular safety of monotherapy with AIs when compared with tamoxifen. However, little is known about the potential cardiotoxic effects of AIs when used as sequential treatment following tamoxifen.

Objectives: To determine whether use of AIs in sequential treatment following tamoxifen is associated with increased risk of cardiovascular outcomes, when compared with continuous therapy with tamoxifen among women diagnosed with breast cancer.

Methods: We created a cohort of women newly diagnosed with breast cancer using the United Kingdom Clinical Practice Research Datalink linked to the Hospital Episode Statistics and Office for National Statistics databases. Using a prevalent new-user design, time-conditional propensity scores were used to match, in a 1:2 ratio, patients switching from tamoxifen to AIs to patients continuing tamoxifen between 1998 and 2016. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for four study outcomes (myocardial infarction, ischemic stroke, heart failure, and cardiovascular mortality), comparing sequential AI treatment following tamoxifen with continuous tamoxifen therapy.

Results: A total of 1,962 patients switching from tamoxifen to AIs were matched to 3,874 patients continuing tamoxifen. Compared with continuing tamoxifen, switching to AIs was associated with an increased risk of myocardial infarction (HR: 2.08; 95% CI: 1.02-4.27). The hazard ratio was also elevated albeit nonsignificant for ischemic stroke (HR: 1.58; 95% CI: 0.85-2.93) and heart failure (HR: 1.69; 95% CI: 0.79-3.62), but not cardiovascular mortality (HR: 0.87; 95% CI: 0.45-1.54). The effects were similar by cumulative duration of use. The results were consistent in sensitivity analyses using inverse probability of censoring weights to account for informative censoring and multiple imputation for missing data.

Conclusions: In this real-world study, switching from tamoxifen to AIs was associated with an increased risk of myocardial infarction and

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

possibly other cardiovascular outcomes, when compared with continuing tamoxifen among women diagnosed with breast cancer.

2480 | Effect of domperidone, ondansetron, and olanzapine containing antiemetic regimen on QTc interval in patients with malignancy

Ashwin Kamath[1], PU Prakash Saxena[2] and Maneesh K Rai[3]
[1]*Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, India;* [2]*Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, India;* [3]*Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, India*

Background: Domperidone, ondansetron, and olanzapine can prolong the QT interval. The use of combinations of these drugs in various clinical situations is not uncommon; however, there is no data regarding the effect of the drug combination on the QTc interval.

Objectives: To determine the presence of any QTc prolonging effect of the drug combination when used as antiemetic in patients receiving cancer chemotherapy.

Methods: We carried out a prospective, observational study of patients with malignancy, aged 18−80 years of either gender with Eastern Cooperative Oncology Group status ≤ 2, who were to receive domperidone (Day 2 and 3), ondansetron (Day 2 and 3), and olanzapine (Day 1-3) containing antiemetic regimen. The study was approved by the institutional ethics committee, and informed consent was obtained from the study participants. Electrocardiograms were recorded before (Day 0) and during (Day 1-3) the administration of antiemetics, for three consecutive days. The absolute value and the change in the QTc interval compared to baseline value was recorded and analyzed. The QT interval was corrected for heart rate using Bazett's method. Freidman's test was used to determine the presence of any significant difference in the QTc interval before and after the administration of the drugs. If a significant difference was seen, Wilcoxon signed-rank test was used to identify the time points with a significant difference, using Bonferroni correction. A p-value <0.05 was considered statistically significant.

Results: Of the 40 patients enrolled, 36 completed the study; 23 (63.9%) were females; 27.78% (10/36) had breast malignancy, 19.44% (7/36) oropharynx, 16.66% (6/36) ovary, and 11.11% (4/36) oesophageal malignancy. There was a statistically significant change in QTc with time ($\chi 2(4) = 15.910$, $p = 0.003$); QTc on Day 1 (424.50 msec) was more than that during baseline (409.25 msec; $p < 0.001$), second time point of Day 2 (406.50 msec; $p = 0.002$), and Day 3 (412.50 msec; $p = 0.002$). On analysis based on gender, these differences were significant in females ($p = 0.010$) but not in males ($p = 0.285$). Two female patients had an absolute QTc prolongation of >500 ms. More female patients had ΔQTc >30 ms compared with males (56.52% versus 46.15%; $p = 0.8018$).

Conclusions: QTc prolongation is a concern with olanzapine alone and in combination with domperidone and ondansetron. However, no clinically significant adverse events occurred. The clinical relevance of the observed QTc prolongation needs to be investigated further.

2485 | Sex and the risk of acute reduction in kidney function after renin-angiotensin blockade: Parallel analyses of a primary care cohort and two randomised trials

Angel Wong[1], Peggy Gao[2], Kathryn Mansfield[1], Krishnan Bhaskaran[1], Juan Jesus Carrero[3], Sarah-Jo Sinnott[4,1], Dorothea Nitsch[1], Liam Smeeth[1], Johannes Mann[5], Catherine Clase[6] and Laurie Tomlinson[1]
[1]*London School of Hygiene and Tropical Medicine, London, United Kingdom;* [2]*Population Heart Research Institute, Hamilton, ON, Canada;* [3]*Karolinska Institute, Stockholm, Sweden;* [4]*Sanofi Genzyme, Cambridge, MA;* [5]*Friedrich Alexander University of Erlangen, Erlangen, Germany;* [6]*McMaster University, Hamilton, ON, Canada*

Background: Men and women respond differently to renin-angiotensin system blockade. However, it is unknown if sex affects the risk of reduced kidney function after initiating angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and if so, how this affects long-term adverse clinical outcomes.

Objectives: In individuals initiating ACEI/ARB: 1) examine the relationship between sex and change in kidney function; and 2) examine the sex-specific associations between change in kidney function and long-term adverse clinical outcomes.

Methods: We conducted parallel cohort studies using the UK Clinical Practice Research Datalink (CPRD) and combined data from patients randomised to ACEI or ARB in the ONTARGET and TRANSCEND randomised controlled trials (RCTs). We estimated changes in kidney function by calculating the percentage change in estimated glomerular filtration rate (eGFR) using pre- and post- ACEI/ARB initiation serum creatinine measurements. We defined an acute reduction in eGFR as a relative change of ≥15%, compared with <15%. Firstly, we examined the association between sex and change in eGFR after initiating ACEI/ARB, adjusting for potential confounders using logistic regression. Secondly, we used adjusted Cox proportional hazards models to investigate the associations between change in eGFR and adverse cardiovascular, kidney and mortality outcomes; an interaction term was fitted to investigate whether these associations varied by sex.

Results: We included 196,596 individuals from CPRD and 9123 individuals from the RCTs. In both settings, we found that female sex was associated with an increased risk of eGFR reduction ≥15% (Odds ratio, 95% CI: CPRD: 1.19, 1.14-1.24; RCTs: 1.35, 1.19-1.56), after multiple adjustment. We observed increased long-term risk of kidney disease (hazard ratio, 95% CI: CPRD: 2.42, 2.16-2.71; RCTs: 4.11, 2.92-5.78), cardiovascular events in CPRD (myocardial infarction: 1.31, 1.19-1.43; heart failure: 1.44, 1.36-1.53) and mortality (CPRD: 1.45, 1.39-1.52; RCTs: 1.27, 1.09-1.48) associated with eGFR reduction ≥15%; there was no evidence to suggest that these risks differed by sex.

Conclusions: Women are at greater risk of reductions in kidney function after ACEI/ARB initiation than men, and the association between kidney function and clinical outcomes did not vary by sex. If such

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

associations are causal, a greater proportion of women initiating ACEI/ARB would be at risk of adverse outcomes. Results were consistent between analyses based on data from routine-care and RCTs.

2493 | Comparative long-term cardiovascular outcomes between ranibizumab versus aflibercept in patients with maculopathy

Wan-Ju A. Lee[1,2], Shih-Chieh Shao[3,2], Yea-Huei Kao Yang, Prof.[2,4,5], Tzu-Chi Liao[2,5] and Edward Chia-Cheng Lai, Mr.[2,4,5]
[1]*National Cheng Kung University Hospital, Tainan, Taiwan;* [2]*National Cheng Kung University, Tainan, Taiwan;* [3]*Keelung Chang Gung Memorial Hospital, Keelung, Taiwan;* [4]*National Cheng Kung University, Tainan, Taiwan;* [5]*National Cheng Kung University, Tainan, Taiwan*

Background: Intravitreal injection of anti-vascular endothelial growth factors (anti-VEGFs) were effective for patients with maculopathy to maintain their vision. However, few reports indicated anti-VEGFs may associate with higher risk of cardiovascular (CV) events, but little is known about the risk profiles between different anti-VEGFs.
Objectives: To compare the risk of CV events between anti-VEGFs (ranibizumab vs. aflibercept) in patients with maculopathy.
Methods: We conducted a retrospective cohort study using Taiwan's National Health Insurance Database from 2010 to 2017. We included adult patients (aged 20+ years) diagnosed with maculopathy newly receiving Intravitreal anti-VEGFs. Study primary outcomes were hospitalization due to ischemic stroke, myocardial infarction (MI) and transient ischemic attack (TIA). The secondary outcomes included hospitalization due to hemorrhagic stroke and all-cause mortality. We followed up patients for 2 years from initiation of ranibizumab or aflibercept. We performed Cox proportional hazard regression with adjustment of patient's age, sex, comorbidities and co-medications to compare the risk of outcome events between ranibizumab vs. aflibercept.
Results: We included 13,258 and 1972 patients receiving ranibizumab and aflibercept patients, respectively. The average age was 67.6 (SD 11.1) and 71.2 (SD 9.5) years old for ranibizumab and aflibercept users, respectively. We found the incidence rate of ischemic stroke, MI and TIA were 11.2, 7.7, 21.76 per 1000 person-year for ranibizumab users and 8.07, 0.78, 16.69 per 1000 person-year for aflibercept users. Compare to ranibizumab, the adjusted hazard ratio (AHR) of ischemic stroke, MI and TIA were 0.8 (95%CI, 0.5-1.0), 0.3 (95%CI, 0.1-0.8), and 0.8 (95%CI, 0.6-1.0) respectively. The risks of hemorrhagic stroke and all-cause mortality were similar between ranibizumab vs. aflibercept users. The incidence rate was 4.12 vs. 3.37 and 21.97 vs. 23.02 per 1000 person-year for hemorrhagic stroke and all-cause mortality for ranibizumab vs. aflibercept users respectively.
Conclusions: We found patients receiving aflibercept posed lower risks of ischemic stroke, MI and TIA compared to ranibizumab patients. The finding warrants clinical considerations on patients' cardiovascular outcomes while selecting intravitreal anti-VEGFs.

2504 | The magnitude of the warfarin-amiodarone drug-drug interaction varies with renal function: A propensity-matched cohort study

Todd A. Miano[1], Wei Yang[1], Michael G.S. Shashaty[2], Athena Zuppa[3], Jeremiah R. Brown[4] and Sean Hennessy[1]
[1]*Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA;* [2]*Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA;* [3]*The Children's Hospital of Philadelphia, Philadelphia, PA;* [4]*Geisel School of Medicine, Hanover, NH*

Background: Amiodarone inhibits warfarin metabolism and is associated with major bleeding during warfarin therapy. Managing this drug-drug interaction (DDI) is challenging because of substantial inter-patient variability in DDI magnitude. Because renal dysfunction induces changes in drug metabolism and protein binding that could alter cytochrome P450 inhibition mechanisms, we hypothesized that renal dysfunction alters the impact of the warfarin-amiodarone DDI.
Objectives: To determine whether the warfarin-amiodarone drug-drug interaction varies with renal function in hospitalized patients with atrial fibrillation.
Methods: We examined the interaction between renal function, warfarin, and amiodarone in a propensity-matched cohort study. Renal function was estimated with creatinine clearance (CrCL). Propensity score estimation and matching was stratified by baseline renal function. Warfarin response was measured with the warfarin sensitivity index (WSI), a dose-normalized international normalized ratio (INR) measure and was modeled with multilevel mixed-effects linear regression. Time to the first supratherapeutic INR (>4) was modeled using Cox regression.
Results: Propensity score matching resulted in 4518 matched pairs. Renal dysfunction was observed in 54% of patients and the supratherapeutic INR rate was 17.9 per thousand-days. Amiodarone's effect on warfarin response varied three-fold across the renal function range, increasing WSI by 36% in patients with normal renal function (CrCl 115 ml/min), but by only 11.8% in patients with severe renal dysfunction (CrCl 15 ml/min). Similarly, amiodarone had a strong effect in patients with normal renal function, HR 1.80 (1.23,2.64), but a negligible effect on supratherapeutic INR hazard in patients with severe renal dysfunction, HR 1.01 (0.75,1.37).
Conclusions: Our results suggest that renal function is a novel factor that explains substantial variability in the warfarin-amiodarone drug-drug interaction. This information could inform warfarin dosage adjustment and monitoring, and may have implications for the selection of oral anticoagulation agents in patients treated with amiodarone.

2666 | The predictors of major gastrointestinal bleeding among oral anticoagulant new users with atrial fibrillation

Jakub Z. Qazi[1], Mireille E. Schnitzer[1], Marie-Josée Martel[1], Robert Côté[2], Marc Dorais[3] and Sylvie Perreault[1]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada; [2]Faculty of Medicine, McGill University, Montreal, QC, Canada; [3]StatSciences Inc, Notre-Dame-de-l'Île-Perrot, QC, Canada

Background: The real-world characteristics of patients with major gastrointestinal bleeding (GIB) have been well-studied among warfarin users, but less so among direct oral anticoagulant (DOAC) users in patients with non-valvular atrial fibrillation (NVAF).

Objectives: To assess the cumulative incidence of GIB for each DOAC (dabigatran, rivaroxaban and apixaban) and warfarin. To identify GIB predictors for each class of treatment.

Methods: We built a cohort of hospitalized NVAF patients using Quebec hospitalization (Med-Echo) and drugs and medical services (RAMQ) administrative databases from 2011 to 2018. Each participant needed to be enrolled in the insurance plan for a year prior to and at cohort entry, which was defined as the first OAC claim. We determined age, sex, co-morbidities during the AF hospitalisation and 3 years prior to cohort entry using ICD-9 or ICD-10 codes as well as concomitant drug use 2 weeks prior to cohort entry. Patients were new users, defined as having no OAC claims in the year prior to cohort entry. The exposures were warfarin </≥ 5mg and DOACs (dabigatran 110/150 mg, rivaroxaban 15/20 mg and apixaban 2.5/5 mg). GIBs, defined as any GIB leading to a hospitalization within 1-year following cohort entry, were identified using validated ICD-10 codes. Cumulative incidences of GIB across each dose-specific OAC treatment group using Kaplan-Meir curves. Logistic-LASSOs and logistic-adaptive LASSOs were used to identify GIB predictors among warfarin users, DOAC users and both. The models' performances were assessed using cross-validated concordance statistics and brier scores.

Results: The cohort contained warfarin (n=14,741), dabigatran (n=3,722), rivaroxaban (n=6,722) and apixaban users (n=11,196) aged between 70 to 86 years. GIB cumulative incidence ranged from 0.89 to 1.80 GIBs per 100 p-y and 1.48 to 1.68 among DOAC and warfarin users. As GIB predictors among both groups were similar, the pooled OAC model was most relevant. GIB predictors identified by the best model, the logistic-LASSO (cvAUC=0.63, brier score= 0.01), included age ≥ 75 (OR=1.46), hypertension (OR=1.26), chronic heart failure (OR=1.21), COPD (OR=1.33), liver disease (OR=2.43), antiplatelet use (OR=1.33), prior major bleeding (OR=2.05), prior stroke (OR=0.80) and apixaban use (OR=0.64; rel. to warf.). Sex, dose and renal failure were not selected by the method.

Conclusions: GIB predictors being similar among DOAC and warfarin users, the model's ability to identify GIBs and their predictors is comparable to published data.

3728 | The acute effects of azithromycin use, as compared with amoxicillin-clavulanate, on cardiovascular mortality in United States veterans

Maral DerSarkissian[1], Mei S. Duh[1], Rachel Bhak[1], Niki Palmetto[2], Yinong Young-Xu[3], Eric Mortensen[4], Antonio Anzueto[5], Catherine Nguyen[1], Mu Cheng[1], Vera Frajzyngier[2], Suna Park[1], Angie Lax[1], Lisa Weatherby[6] and Alexander M. Walker[6]

[1]Analysis Group, Inc., Boston, MA; [2]Pfizer, New York, NY; [3]Veterans Affairs Medical Center, White River Junction, VT; [4]University of Connecticut School of Medicine, Farmington, CT; [5]University of Texas Health Sciences Center at San Antonio, San Antonio, TX; [6]WHISCON, Dedham, MA

Background: Past studies report mixed findings regarding the comparative risk of cardiovascular (CV) death associated with azithromycin versus other antibiotics. The current study aimed to mitigate limitations of prior studies, such as confounding by indication.

Objectives: This retrospective cohort study investigated the acute effects on CV mortality of azithromycin use relative to amoxicillin-clavulanate use among US veterans with a respiratory or ear-nose-throat (ENT) infection indication.

Methods: Veterans Health Administration (VHA) electronic health record data (2000-2014) were used to identify outpatient oral azithromycin and amoxicillin-clavulanate dispensings for respiratory or ENT indications among patients 30-74 years of age with regular VHA medical care who had no serious illnesses and no antibiotics in the 365 days and 60 days, respectively, prior to dispensing. CV death was identified based on cause of death from the National Death Index, and was determined during the 1-5 and 6-10 ensuing days starting on dispensing date. Demographic and clinical characteristics were used to generate inverse probability of treatment weights (IPTW) for confounder control through IPTW-weighted proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Data were pooled across indications using meta-analysis. Subgroup analyses examined patients with history of CV disease and/or those with a high CV mortality risk score.

Results: 629,345 azithromycin and 168,429 amoxicillin-clavulanate dispensings for the respiratory indication and 143,783 azithromycin and 203,142 amoxicillin-clavulanate dispensings for the ENT indication met eligibility criteria. Patients with dispensings for respiratory and ENT infections had mean ages of 58 and 55 years and were largely white (68% and 67%) and male (89% and 85%), respectively. The pooled HR (95% CI) of CV death for azithromycin compared to amoxicillin-clavulanate was 1.00 (0.55, 1.81) within 1-5 days and 0.66 (0.39, 1.11) within 6-10 days dispensing date. For the respiratory indication, the HRs (95% CI) of CV death within 1-5 and 6-10 days were 1.12 (0.63, 2.00) and 0.65 (0.36, 1.16), respectively. For ENT, they were 0.46 (0.09, 2.30) and 0.70 (0.22, 2.29). Subgroup results for persons with a high CV mortality risk score and those with a history of CV disease resembled the overall values with all CIs overlapping the null.

Conclusions: There was no overall evidence of increased risk of CV death associated with azithromycin as compared to amoxicillin-clavulanate.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3822 | Association between antidepressants use and stroke risk in Taiwan

Lu Hsuan Wu, Ching-Lan Cheng and Yea-Huei Kao Yang
School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background: Antidepressants (ADs) are widely used to ameliorate affective disorder and relieve neuropathic pain. Several case-control and cohort studies discussed the relationship of using ADs and stroke. However, the results of these articles remained inconsistent. Since most studies compared exposures with non-exposures, the differences in distribution of characteristics among patients between the two groups could confound the results of these studies. In addition, confounding by indication was likely to exist. In these regards, the self-controlled case-series (SCCS) method may provide an alternative epidemiological approach to eliminate the potential confounders that are fixed over time, and even extend to undetected confounders.

Objectives: We aimed to assess the association between ADs use and stroke risk using a SCCS design to compare risk within individual person at different times.

Methods: 1. Design and setting: We enrolled new ADs users (≥18 years) who were admitted for first stroke event from 1 January 2004 to 12 December 2015 from Taiwan National Health and Welfare Insurance database. The new ADs users were identified by pharmacy records, who did not receive any ADs during the 12 months prior to the first ADs prescription. The risk period was defined by the calendar days between the start of ADs therapy and the end or change of ADs therapy, while the baseline period included all unexposed times. When the gap between two prescriptions was less than 30 days, the exposure was considered to be continuous.**2. Statistical analysis:** Incidence rate ratios (IRRs) were calculated using conditional Poisson regression to estimate the risk of first stroke during risk periods by compared to other periods outside this window within each individual. The results were presented as adjusted rate ratios and 95% confidence intervals.

Results: There were 55,315 ADs new users who admitted to hospital for first stroke event, of which 80.5% were ischemic stroke. For all stroke, the IRRs of all ADs in the risk period was 3.26 (95% CI 3.18 to 3.36) compared to baseline periods. Either the risk for ischemic stroke (IRRs 3.39, 95% CI 3.29 to 3.49) or the risk for hemorrhagic stroke (IRRs 2.75, 95% CI 2.58 to 2.94) of ADs was significantly higher in the risk period than the baseline periods.

Conclusions: There was a significant elevating risk of stroke, including ischemic and hemorrhagic stroke, when patients taking ADs in Taiwan. Further investigations are warranted to verify the risk extent and risk factors.

3831 | No association between methylphenidate use and myocardial infarction: A multinational self-controlled case series study

Han Eol Jeong[1], Hyesung Lee[1], Edward C. C. Lai[2,3], Kenneth K. C. Man[4,5], Ian C. K. Wong[4,5] and Ju-Young Shin[1]
[1]Sungkyunkwan University (SKKU), Suwon, Republic of Korea; [2]National Cheng Kung University, Tainan, Taiwan; [3]National Cheng Kung University Hospital, Tainan, Taiwan; [4]University College London, London, United Kingdom; [5]University of Hong Kong, Hong Kong, Hong Kong

Background: Methylphenidate (MPH) is known to be the most effective treatment for attention-deficit hyperactivity disorder. Despite such benefits, incidence of adverse cardiovascular events, especially myocardial infarction, associated with its use remain an ongoing debate, as case reports are continuing to be reported.

Objectives: To assess the association between MPH use and incidence of myocardial infarction by conducting a multinational study among three Asian populations.

Methods: We conducted a population-based self-controlled case series study using nationwide healthcare databases of South Korea, Taiwan, and Hong Kong. We conducted our multinational study using a distributed network approach and applied a common data model specific to our pre-specified study protocol. Our study subjects were those with both a diagnosis record of myocardial infarction and a prescription record for MPH within the observation period. For patients with multiple diagnoses of myocardial infarction, only the first event was considered to avoid any bias arising from the second event being influenced by the first. Exposure to MPH was assessed as time-varying and classified into four mutually exclusive periods by each person-day: risk (exposed to MPH), pre-exposure (before first MPH prescription), washout (after end of MPH prescription) and baseline (unexposed to MPH; remaining person-time) periods. Incidence rate ratios (IRRs) with 95% confidence intervals (CI) were estimated in the three periods when compared to the baseline period using conditional Poisson regression, adjusting for time-varying confounders (age, comorbidity, co-medication use).

Results: A total of 2104, 442, and 31 patients were included from Korea, Taiwan and Hong Kong, respectively. Risk of myocardial infarction was elevated in all three periods, with risk being highest in the pre-exposure period in all three populations: Korea, pre-exposure (IRR 3.17, 95% CI 3.04-3.32), risk (1.05, 1.00-1.11), washout (1.92, 1.80-2.04); Taiwan, pre-exposure (1.87, 0.84-4.20), risk (1.28, 0.42-4.59), washout (1.23, 0.17-8.82); Hong Kong, pre-exposure (15.87, 3.14-85.71), risk (17.78, 3.35-94.43), washout (41.66, 5.52-314.32). Despite stratifying for age and sex, analogous trends were found compared to our main findings in all three populations.

Conclusions: The risk of myocardial infarction was higher in the period before the start of MPH treatment and remained elevated after the start of MPH treatment. Our findings do not support a causal association between MPH treatment and myocardial infarction in an Asian population.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3928 | Risk of fracture in patients with nonvalvular atrial fibrillation initiating direct oral anticoagulants versus vitamin K antagonists

Na He[1,2,3], Sophie Dell'Aniello[2], Suodi Zhai[1], Samy Suissa[2,3] and Christel Renoux[2,3,4]

[1]Department of Pharmacy, Peking University Third Hospital, Beijing, China; [2]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [3]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada; [4]Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada

Background: Oral anticoagulants such as direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) are usually given lifelong to prevent stroke in patients with nonvalvular atrial fibrillation (NVAF). VKAs have a potential detrimental effect on bone health, but the safety of DOACs compared with VKAs on the risk of fracture remains uncertain.

Objectives: To assess the risk of fracture associated with DOACs compared with VKAs among patients with NVAF.

Methods: Using Quebec administrative healthcare databases, we formed a cohort of all patients aged 40 years or older newly diagnosed with NVAF, who filled a first prescription for DOACs or VKAs between January 1, 2011 and March 31, 2014. Exposure to anticoagulants was modelled as a time-varying variable whereby patients were considered unexposed up to 180 days of cumulative duration of use (to account for a biologically meaningful exposure) and exposed thereafter. The primary outcome was a composite of hip fracture, vertebral fracture, upper extremity fracture and osteoporosis with pathologic fracture. We adjusted for confounding via propensity score-based fine stratification and weighting. We used weighted Cox proportional hazards models to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) of fracture associated with DOACs compared with VKAs. We also estimated the risk of each type of fracture separately.

Results: The cohort included 10,306 new users of DOACs and 15,357 new users of VKAs. During 35,252 person-years follow-up, 464 fractures occurred, yielding an incidence rate of 13.2 (95% CI 12.0 - 14.4) per 1000 person-years. Compared with VKA duration ≥ 180 days, use of DOACs for 180 days or greater was associated with a 35% decreased risk of fracture (adjusted HR 0.65, 95%CI 0.46 - 0.91). DOACs use was also associated with a lower risk of hip fracture (HR 0.51, 95%CI 0.31 - 0.86) compared with VKAs. There was no difference in the rate of fracture for shorter duration of use (HR 1.10; 95%CI 0.79 - 1.53). The risk was not modified by age, sex, presence of chronic kidney disease, presence of osteoporosis, history of fracture or falls.

Conclusions: Prolonged use of DOACs is associated with a lower risk of fracture, including hip fracture, compared with VKAs. These findings further support the first-line recommendation for DOACs in patients with NVAF, especially for elderly patients initiating lifelong anticoagulation therapy.

4054 | Statin treatment and muscle symptoms: A series of randomised, placebo controlled N-of-1 trials

Emily Herrett[1], Elizabeth Williamson[1], Kieran Brack[1], Danielle Beaumont[1], Alexander Perkins[1], Andrew Thayne[1], Haleema Shakur-Still[1], Ian Roberts[1], Danielle Prowse[1], Ben Goldacre[2], Tjeerd van Staa[3], Thomas M MacDonald[4], Jane Armitage[2], Jon Wimborne[5], Paula Melrose[5], Jayshireen Singh[6], Maurice Hoffman[7] and Liam Smeeth[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]University of Oxford, Oxford, United Kingdom; [3]University of Manchester, Manchester, United Kingdom; [4]University of Dundee, Dundee, United Kingdom; [5]Bay Medical Group, Morecambe, United Kingdom; [6]CRN South London, London, United Kingdom[7]NIHR Patient Representative, London, United Kingdom

Background: Statins reduce cardiovascular disease events in primary and secondary prevention, among men and women, and across all age groups. The extent to which statins cause symptomatic muscle adverse effects remains uncertain.

Objectives: We aimed to establish the effect of statins on muscle symptoms among people who experienced muscle symptoms whilst taking statins.

Methods: We aimed to conduct 200 double-blinded N-of-1 trials in UK primary care, among patients who recently discontinued statins or were considering discontinuing use due to muscle symptoms. Participants were randomised to a sequence of six double-blinded treatment periods (each two months) of atorvastatin 20mg daily or matching placebo. At the end of each period, participants rated their muscle symptoms on a visual analogue scale (0-10). The primary analysis aggregated data from participants' symptom scores, comparing statin versus placebo periods.

Results: 151 participants provided symptoms scores during at least one period each of statin and placebo and were included in the primary analysis. Overall there was no difference in muscle symptom scores between statin and placebo periods (mean difference statin minus placebo -0.11 (95% CI -0.36, 0.14; P=0.40)). Eighteen participants (9%) withdrew during a statin period and 13 (7%) during a placebo period due to intolerable muscle symptoms.

Conclusions: Among people who previously reported severe muscle symptoms while taking statins, this series of randomised N-of-1 trials found no overall effect of statins on muscle symptoms compared to placebo. The slight difference in withdrawals due to muscle symptoms suggests that statins may contribute to symptoms in a small number of patients. N-of-1 trials can assess drug effects at the group level and guide individual therapy.

4115 | Testosterone treatment and the risk of venous thromboembolism: A systematic review and meta-analysis of randomized controlled trials

Henok Tadesse Ayele[1,2], Vanessa C. Brunetti[1,2], Christel Renoux[1,2,3], Vicky Tagalakis[1,2,4] and Kristian B. Filion[1,2,5]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada; [2]Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [3]Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada; [4]Division of General Internal Medicine, Department of Medicine, Jewish General Hospital, Montreal, QC, Canada; [5]Department of Medicine, McGill University, Montréal, QC, Canada

Background: The cardiovascular safety of testosterone therapy is controversial. While several studies have investigated the association between testosterone replacement therapy and the risk of arterial thrombosis, limited information is available regarding the risk of venous thromboembolism (VTE).

Objectives: To compare the risk of VTE in men randomized to testosterone therapy versus placebo via systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: We systematically searched Medline, EMBASE, CINAHL, and CENTRAL, as well as clinical registries (ClinicalTrials.gov, WHO, EMA, and FDA), to identify RCTs comparing testosterone to placebo in men aged 18 years or older. Inclusion was restricted to RCTs available in English or French. Study quality was assessed using the Cochrane Risk of Bias assessment tool. Data were pooled across RCTs using Dersimonian and Laird random-effects models with inverse variance weighting. In addition, the Peto and Hartung-Knapp methods were used in sensitivity analyses.

Results: Our systematic search identified 5,014 potentially relevant articles, of which 13 RCTs (n=5,050) were included in this meta-analysis. A total of 2,636 men were randomized to testosterone, and 2,414 men to placebo. Sample sizes ranged from 101 to 790 men, and duration of testosterone therapy from 3 to 36 months. Five studies had a high risk of bias, largely driven by unclear randomization and outcome measurement. A total of 13 men in the testosterone group (0.5%) and 10 in the placebo group (0.4%) had VTE. When data were pooled across trials, testosterone therapy was not associated with VTE compared with placebo (RR: 0.99, 95% CI: 0.44-2.23; I^2: 0%). Similar estimates were obtained for deep vein thrombosis (RR: 1.14, 95% CI: 0.45-2.90; I^2: 0%) and pulmonary embolism (RR: 0.81, 95% CI: 0.29-2.26; I^2: 0%). We also obtained similar results in subgroup analyses stratified by age, baseline serum testosterone, testosterone dose, route of administration, duration of testosterone treatment, duration of follow-up, risk of bias, and sources of funding. Sensitivity analyses using the Peto method (RR: 1.15, 95% CI: 0.50-2.63; I^2: 30.9%) and the Hartung-Knapp method (RR: 0.99, 95% CI: 0.44-2.23) produced results consistent with those of our primary analysis.

Conclusions: Our systematic review and meta-analysis of RCTs suggests that testosterone therapy is not associated with an increased risk of VTE. However, estimates were accompanied by wide 95% CIs, and a clinically important increased risk cannot be ruled out.

4131 | Suboptimal use of antithrombotic treatments and associated clinical outcomes in Chinese patients with atrial fibrillation

Xue Li[1], Swathi Pathadka[1], Kenneth Man[2], Vanessa Ng[1], Chung Wah Siu[3], Ian Wong[1], Esther Chan[1] and Wallis Lau[2]

[1]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong, Hong Kong; [2]School of Pharmacy, University College London, London, United Kingdom; [3]Department of Medicine, The University of Hong Kong, Hong Kong, Hong Kong

Background: The prescription pattern after the introduction of direct oral anticoagulants (DOACs) and associated clinical outcomes of antithrombotic treatments is unclear in Chinese patients with atrial fibrillation (AF) in the real-world setting.

Objectives: To describe the prescription pattern of antithrombotic treatment and compare their effectiveness and safety outcomes.

Methods: A population-based cohort study using territory-wide electronic health records of Hong Kong. Patients newly diagnosed with AF were identified during 2010-2016 and followed up until 2017. Patients at high risk of stroke (CHA2DS2-VASc≥2) and receiving antithrombotic treatments (antiplatelet [APT] monotherapy, warfarin, DOACs) were 1:1:1 matched using propensity score. Cox proportional hazards regression was used to compare the risks of ischemic stroke, intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality between treatment groups.

Results: Preliminary results showed that there were 52,178 patients newly diagnosed AF and had a high risk of stroke. Of these, 28,656 patients (54.9%) received antithrombotic therapy. There was a decline in APT prescribing (63% to 43%) and warfarin (18% to 13%), while DOAC prescribing increased dramatically (1% to 32%). Two-thirds of warfarin users had a time-in-therapeutic range <60%. Compared to APT, warfarin and DOACs were associated with lower risks of ischemic stroke (warfarin: hazard ratio [HR]=0.51, 95% confidence interval [CI]=0.36-0.71; DOACs: HR=0.69, 95%CI=0.51-0.94) and all-cause mortality (warfarin: HR=0.47, 95%CI=0.39-0.57; DOACs: HR=0.45, 95%CI=0.37-0.55), after the matching. DOACs were associated with a lower risk of ICH compared to warfarin (HR=0.53, 95%CI=0.34-0.83). The risks of GIB were similar among all groups.

Conclusions: APT prescribing and suboptimal warfarin management remains common in Chinese patients with AF and a high risk of stroke. DOAC use may be associated with a lower risk of ischemic stroke and all-cause mortality when compared to APT, and a lower risk of ICH when compared to warfarin.

4163 | A population-based assessment of the cardiovascular safety of 5-alpha-reductase inhibitors

Henok Tadesse Ayele[1,2], Pauline Reynier[2], Laurent Azoulay[1,2,3], Robert W. Platt[1,2,3], Serge Benayoun[4] and Kristian B. Filion[1,2,5]

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[1]Department of Epidemiology, Biostatistics, Occupational Health, McGill University, Montreal, QC, Canada; [2]Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [3]Gerald Bronfman Department of Oncology, McGill University, Montreal, QC, Canada; [4]Department of Surgery, Urology Unit, Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; [5]Department of Medicine, McGill University, Montreal, QC, Canada

Background: 5-alpha reductase inhibitors (5αRIs) are used for the treatment of benign prostatic hyperplasia (BPH). Their mechanism of action involves reducing levels of dihydrotestosterone, which may adversely affect cardiovascular risk factor levels and increase the risk of cardiovascular events. However, the cardiovascular effects of 5αRIs remain poorly understood.

Objectives: To compare the rate of cardiovascular events among men with BPH prescribed 5αRIs to that among men with BPH not prescribed BPH medications.

Methods: Using the Clinical Practice Research Datalink (CPRD) linked with Hospital Episode Statistics and Office for National Statistics, we conducted a population-based cohort study among patients newly-diagnosed with BPH from April 1998 to March 2016. A time-varying exposure definition for current use was used, where person-time was classified into one of the following four mutually-exclusive categories: 5αRIs, α-blockers, combination therapies (5αRIs and α-blockers), and non-use of BPH medications. The primary endpoint was hospitalization for heart failure. Secondary outcomes were myocardial infarction, stroke, and cardiovascular mortality. We used time-dependent Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the outcomes of interest and 5αRIs versus non-use of BPH medications, adjusting for baseline covariates.

Results: Our cohort included 94,598 men with incident BPH. Their mean age at the cohort entry was 66.2 (SD: 10.4) years. A total of 3907 hospitalizations for heart failure occurred over a total of 528,616 person-years (PYs) of follow-up (incidence rate: 7.4, 95% CI: 7.2-7.6 per 1,000 PYs). Compared with non-use of BPH medications, 5αRIs were not associated with an increased risk of hospitalization for heart failure (HR: 1.03, 95% CI: 0.91-1.15), stroke (HR: 0.98, 95% CI: 0.85-1.12), or myocardial infarction (HR: 0.96, 95% CI: 0.81-1.13). However, compared with non-use, 5αRIs were associated with a decreased risk of cardiovascular death (HR: 0.88, 95% CI: 0.79-0.98). Decreases in cardiovascular death were also observed with α-blockers (HR: 0.72, 95% CI: 0.68-0.78) and combination therapy (HR: 0.67, 95% CI: 0.59-0.76) compared with non-use.

Conclusions: The use of 5αRIs was not associated with an increased risk of heart failure, stroke, or myocardial infarction compared with non-use of BPH drugs. However, 5αRIs were associated with a decreased risk of cardiovascular death, a finding that warrants further investigation.

4226 | Tyrosine kinase inhibitors-related vascular occlusive events in Taiwanese chronic myeloid leukemia patients: a population-based, propensity score-matched cohort study

Mei-Tsen Chen[1], Shih-Tsung Huang[1], Ho-Min Chen[2], Bor-Sheng Ko[3] and Fei-Yuan Hsiao[1]

[1]National Taiwan University, Taipei City, Taiwan; [2]National Taiwan University, Taipei City, Taiwan; [3]National Taiwan University Hospital, Taipei City, Taiwan

Background: Tyrosine kinase inhibitors (TKIs) have shown long-term survival benefits in chronic myeloid leukemia (CML) patients. Nevertheless, significant concern has been raised regarding the long-term TKIs associated vascular occlusive events (VAEs).

Objectives: To investigate the incidence of VAEs in Taiwanese CML patients treated with different TKIs (imatinib, nilotinib, and dasatinib) and identify potential risk factors of TKI-associated VAEs.

Methods: We conducted a retrospective cohort study using Taiwan Cancer Registry (TCR) and National Health Insurance Research Database (NHIRD). Adult patients diagnosed with CML from 2008 to 2016 were identified from TCR. In this new-user cohort study, CML patients who received their first prescriptions of TKI were identified and categorized into three groups (imatinib, nilotinib, and dasatinib). Two active-comparator pairs were identified by 1:2 propensity score matching to minimize selection bias: (i) new users of nilotinib vs. new users of imatinib and (ii) new users of dasatinib vs. new users of imatinib. The outcome of interest was VAEs (including myocardial infarction, ischemic heart disease, stroke, other ischemic cerebrovascular disease, arterial occlusive disease, venous thromboembolism). Poisson regressions were used to estimate the incidence rate ratios (IRRs) of VAEs and potential risk factors.

Results: A total of 1,112 CML patients treated with first-line imatinib, nilotinib, and dasatinib, were identified (mean age: 48 years; female: 42%) and followed for a median of 2.2 years. After propensity score matching, the incidence of VAEs for dasatinib (15.4 per 1000 person-years vs. imatinib 5.6 per 1000 person-years) and nilotinib (20.3 per 1000 person-years vs. imatinib 5.8 per 1000 person-years) were significantly higher than imatinib. The IRR of dasatinib and nilotinib were 2.73 (95% CI: 1.05 to 7.08) and 3.50 (95% CI: 1.57 to 7.79) as compared to imatinib. In multivariable Poisson regression, older age (IRR: 1.04 for each one year increase in age, p=0.0014) and history of cerebrovascular diseases (IRR: 4.31, p=0.0048) were associated with increased risk of VAEs.

Conclusions: Second generation TKIs, particularly nilotinib, were associated with higher IRR of VAEs as compared with imatinib. Potential risk factors of TKIs-associated VAEs include older age and prior cerebrovascular diseases.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4270 | A potential safety signal of venous thromboembolic events with the use of DPP-4 inhibitors

Amandine Gouverneur[1], Mickael Arnaud[1], Ana Jarne-Munoz[1], Yohann Mansiaux[1], Jean-Luc Faillie[2], Clara Bouché[3], Annick Fontbonne[4], Antoine Pariente[1] and Francesco Salvo[1]

[1]Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Pharmacoepidemiology Team, Bordeaux, France; [2]CHU de Montpellier, Département de Pharmacologie Médicale et Toxicologie, Montpellier, France; [3]AP-HP, Hôpital Lariboisière, Département d'Endocrinologie et Métabolisme, Paris, France; [4]Université Paris-Saclay, UVSQ, Inserm, CESP, 94807 Villejuif, France, Villejuif, France

Background: A safety signal of venous thromboembolic events (VTE) associated with the use of dipeptidylpeptidase-4 inhibitors (DPP-4i), a second-line glucose-lowering drug (GLD) used for type 2 diabetes, was highlighted in a pilot signal detection study we previously conducted.

Objectives: To assess the risk of hospitalization for VTE associated with the use of DPP-4i.

Methods: Using data from the French nationwide health insurance claim database (*Système National des Données de Santé*, *SNDS*), we conducted both a nested case-control and a cohort study within a population of subjects aged 40 to 80 years newly pharmacologically treated for a type 2 diabetes between 2008 and 2016. VTE were identified using hospitalization diagnoses codes (ICD-10); exposure to GLDs was identified from drug reimbursements (ATC classification) and was grouped according to pharmacological drug classes. In the case-control approach, cases were matched with up to 20 controls on age, sex, history of VTE, and length of diabetes, using the risk-set sampling procedure. The risk of hospitalization for VTE related to the use of DPP-4i was estimated using a conditional logistic regression adjusted on a disease risk score. In the cohort approach, new users of DPP-4i were matched up to 20 never users on age, sex, history of VTE, length of diabetes, number of GLDs, and the numbers of drugs and hospitalizations occurred in the year preceding the initiation of the DPP-4i. The risk of hospitalization for VTE during the year following the initiation of the DPP-4i was estimated using a Cox regression model adjusted according to the *Prior Event Rate Ratio* (PERR) method.

Results: Of the 1 146 540 subjects constituting the source population, 8 366 cases and 117 995 matched controls were included in the nested case-control analysis, while the cohort one included 378 765 new users of DPP-4i matched with 3 378 531 users of other non-insulin GLDs. In the nested case-control analysis, the use of DPP-4i was found associated with a decreased risk of hospitalization for VTE compared to the use in monotherapy of other non-insulin GLD (HR=0.89 [0.83; 0.96]). The cohort analysis also found no association of DPP-4i use to an increased risk of VTE over the year following DPP-4i initiation (PERR=1.09 [0.94; 1.24]).

Conclusions: The results of the present study did not highlight any increase in the risk of VTE associated to the use of DPP-4i that would support the signal previously detected.

4411 | Effectiveness and safety of standard and reduced dose of rivaroxaban compared to vitamin k antagonists, according to stroke and bleeding risk score in non-valvular atrial fibrillation, from a HDPS matched cohort within the SNDS French nationwide claims database

Nicholas Moore[1,2], Patrick Blin[1], Laurent Fauchier[3], Frédéric Sacher[4], Jean Dallongeville[5], Caroline Dureau-Pournin[1], Régis Lassalle[1], Marie-Agnès Bernard[1] and Cécile Droz-Perroteau[1]

[1]Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France; [2]CHU Bordeaux, INSERM U1219, Bordeaux, France; [3]CHU de Tours, Tours, France; [4]LIRYC Institute, Université de Bordeaux, CHU de Bordeaux, Bordeaux, France; [5]Institut Pasteur, Lille, France

Background: In previous studies, we found no difference in stroke and systemic embolism (SSE) prevention but less major bleeding (MB), especially intracranial hemorrhage, for rivaroxaban (R) versus vitamin K antagonists (VKA) in non-valvular atrial fibrillation (NVAF) patients. However, results according to CHA_2DS_2-VASc (C-V) and HAS-BLED (H-B) risk scores are sparse.

Objectives: To compare the 2-year risk of SSE and MB between R standard dose (R20) or reduced dose (R15) versus VKA for NVAF according to the C-V and H-B scores in real-life setting.

Methods: Secondary analysis of a high-dimensional propensity score 1:1 matched cohort from all 2013 NVAF R20, R15 and VKA new users in the French nationwide claims database, SNDS. Two-year event incidence was estimated using cumulative incidence function and compared using Fine and Gray model (HR [95%CI]).

Results: For R20, 15,680 patients were matched to 15,680 VKA patients. C-V score was 0-1, 2, 3 and ≥4 for 24.1%, 23.6%, 23.1% and 29.2% of R20, respectively, with 1.4%, 2.3%, 2.2% and 3.8% SSE incidences for R20 patients, 1.7%, 2.0%, 2.4% and 3.9% for VKA patients, and non-significant HR of 1.0, 1.07, 0.89, 1.02, respectively. H-B score was 0-1, 2-3 and >3 for 35.7%, 59.1% and 5.2% of R20, respectively, with 1.5%, 2.6%, and 5.2% MB incidences for R20 patients, 2.5%, 3.8% and 6.1% for VKA patients, and HR 0.59 [0.41-0.83], 0.70 [0.58-0.85] and 0.89 [0.55-1.43], respectively. For R15, 12,018 patients were matched to 12,018 VKA patients. C-V score was 0-1, 2, 3 and ≥4 for 6.7%, 15.8%, 27.4% and 50.1% of R15, respectively, with 2.3%, 2.0%, 2.8%, and 4.9% SSE incidences for R15 patients, 1.5%, 1.9%, 2.7% and 4.1% for VKA, and non-significant HR of 1.49, 0.95, 1.12 and 1.19, respectively. H-B score was 0-1, 2-3 and >3 for 21.1%, 69.0% and 9.8% of R15, respectively, with 3.1%, 3.8% and 4.0% MB incidences for R15 patients, 2.7%, 4.8% and 7.2% for VKA patients, and HR 1.14 [0.76-1.70], 0.81 [0.68-0.97] and 0.56 [0.37-0.86], respectively.

Conclusions: Increasing risk scores for SSE and bleeding were associated with increasing incidence of the relevant events. There was no difference in effectiveness of rivaroxaban compared to VKA at either dose. There was an apparent benefit of rivaroxaban for safety, which increased with increasing risk score in the high-risk of bleeding patients given reduced dose rivaroxaban.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4412 | Reporting of statin-associated muscle symptoms among Italian dyslipidemic patients enrolled in the PROSISA study: Prevalence and risk factors

Marta Gazzotti[1], Manuela Casula[1,2], Elena Olmastroni[1], Federica Bonaiti[1], Liliana Grigore[2,3], Alberto Zambon[2,4] and Alberico Luigi Catapano[1,2]

[1]*Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy;* [2]*IRCCS MultiMedica Hospital, Sesto S. Giovanni (MI), Italy;* [3]*S.I.S.A. Center for the Study of Atherosclerosis, Bassini Hospital, Cinisello Balsamo (MI), Italy;* [4]*Department of Medicine - DIMED, University of Padua, Padua, Italy*

Background: Statin associated muscle symptoms (SAMS) are one of the main reasons for poor treatment adherence and/or discontinuation, contributing to adverse cardiovascular outcomes. However, a definitive diagnosis of SAMS is difficult because symptoms are subjective, influenced by comorbidities, and there is no "gold standard" diagnostic test.

Objectives: The PROSISA (Project on Statin Intolerance SISA) study is an observational retrospective study aimed at assessing the prevalence of SAMS in dyslipidaemic patients on statins followed by Italian lipid clinics.

Methods: Demographic/anamnestic data, biochemical values, and potential occurrence of SAMS were collected. Adjusted logistic regression was fitted to estimate OR and 95% confidence intervals for association between probability of reporting SAMS and several factors.

Results: This analysis was carried out on 16,717 statin-treated patients (mean age 60.5±12.0 years; 52.1% men). During statin therapy, 9.6% of patients reported SAMS, mainly myalgia (71.9%). Women and physically active subjects were more likely to report SAMS (OR 1.23 [1.10-1.37] and OR 1.35 [1.14-1.60], respectively), while older patients (OR 0.79 [0.70-0.89]), presence of type II diabetes mellitus (OR 0.62 [0.51-0.74]), use of concomitant non-statin lipid-modifying drugs (OR 0.87 [0.76-0.99]), of high-potency statins (OR 0.79 [0.69-0.90]) and of potential interacting drugs (OR 0.63 [0.48-0.84]) were associated with a lower probability of reporting SAMS. Among patients reporting SAMS, 761 underwent dechallenge, with disappearance of muscular symptoms in 87.2% of cases, while overall 908 patients underwent rechallenge (468 with change of statin/dose reduction without interruption of therapy), with reappearance of muscular symptoms in only 248 patients.

Conclusions: This analysis offers a real-life outlook of SAMS in Italian contest. The reported prevalence of SAMS was 9.6%, but the percentage of patients in whom intolerance has been confirmed by dechallenge/rechallenge was between 23-28%, emphasizing the need for a better management of SAMS to provide a definitive diagnosis and, if needed, treatment re-evaluation.

4478 | Evaluating signals generated in a large-scale sequence symmetry analysis: Macrolides and heart failure; NSAIDs and pneumonia

Sarah-Jo Sinnott[1], KJ Lin[2], Shirley Wang[2], Jesper Hallas[3], Rishi Desai[2], Sebastian Schneeweiss[2] and Joshua J. Gagne[2]

[1]*Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School and Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, Boston, MA;* [2]*Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA;* [3]*Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark and Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark*

Background: In prior research using Danish data we found safety signals for (1) macrolides and heart failure; and (2) non-steroidal anti-inflammatory drugs (NSAIDs) and pneumonia in a large-scale screening analysis using a self-controlled sequence symmetry design.

Objectives: To further investigate these signals in US claims data with an active-comparator, new user design and confounding adjustment tailored to the exposure and outcome.

Methods: We used Truven Marketscan data, a database of approximately 180 million commercially insured individuals, to conduct two new-user, active-comparator cohort studies. In the macrolides example, the exposure was clarithromycin or azithromycin and the comparator was amoxicillin/clavulanate, in patients with sinusitis. In the NSAIDs example, the exposure was oral NSAIDs and the comparator was topical diclofenac, in patients with osteoarthritis. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) to adjust for approximately 50 investigator-specified confounders in a propensity score (PS) matched analysis. In a secondary analysis, we used high-dimensional PS (hd-PS) to adjust for 200 additional proxy confounders. We performed multiple sensitivity analyses to assess the robustness of exposure, outcome, and follow-up definitions.

Results: We had 1,012,364 propensity score matched patients exposed to clarithromycin or azithromycin *versus* amoxicillin/clavulanate (mean age 52.2 years; 59% female). With 162 heart failure outcomes among clarithromycin or azithromycin exposed patients and 134 among amoxicillin/clavulanate, the HR for overall heart failure was 1.14 (95% CI 0.90 - 1.43). In the NSAIDs example, we included 94,490 patients after propensity score matching (mean age 60.5 years; 72% female). With 794 pneumonia outcomes among oral NSAID patients and 700 among topical diclofenac, we found an HR of 0.98 (95% CI 0.89 - 1.09). Some upward bias was suspected in both examples as larger HRs were observed in the 5-7 days immediately following exposure; HR 3.49 (95% CI 1.15 - 10.60) and HR 3.5 (95% CI 1.59 - 7.66), for the macrolides and NSAIDs examples, respectively. For both examples, we found similar results in the hd-PS matched analysis.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: Our findings for NSAIDs and pneumonia suggest the original signal may have been due to protopathic or detection bias. Our analyses for macrolides and heart failure with short-term follow-up also suggest bias, although we encourage further research.

4592 | Incidence of venous thromboembolism in users of combined oral contraceptives in North America and Eastern Europe - Final results from the international active surveillance - Folate and oral contraceptives utilization study (INAS-FOCUS)

Clare Barnett, Thai Do Minh, Christoph Wenger and Klaas Heinemann
ZEG Berlin, Berlin, Germany

Background: The INAS-FOCUS registry was a long-term, active-surveillance study investigating the cardiovascular risk of a new combined oral contraceptive (COC) containing Drospirenone/Ethinylestradiol plus metafolin (DRSP/EE+) in comparison to other COCs (oCOC). During study conduct, the FDA concluded that women taking drospirenone-containing oral contraceptives may be at increased risk for developing thromboembolism (VTE) compared to women taking oCOCs. The impact of this announcement is observed in the final study results.

Objectives: To observe the risk of VTE in users of DRSP/EE+ and DRSP/EE compared to oCOC, including levonogestrel (LNG) oral contraceptives, in North America and Eastern Europe.

Methods: INAS-FOCUS is a large, prospective, controlled, non-interventional study conducted between 2011-2019 in the US, Canada, Russia and Ukraine. Women with a new combined oral contraceptive prescription were enrolled by their prescribing physician. In the follow-up phase, women were contacted every 6 to 12 months for a maximum of 7 years and asked for information about occurrence of cardiovascular events, including VTE. Self-reported events were validated by health care professionals. Cox regression models were used to show the effect of COC-type on VTE risk. Adjustments were made for age, weight, smoking and family history of VTE.

Results: The analysis is based on 197,452 women-years (WY) of hormonal contraceptive exposure. Overall, 63 VTE were confirmed, with an incidence rate of 3.2 per 10,000WY (95% CI 2.5 - 4.1). Significant differences in VTE rates were observed in North America and Eastern Europe. The confirmed incidence of VTE in Europe was 1.3 per 10,000 WY (95% CI 0.07 - 2.4), with no difference seen between DRSP/EE and LNG users. In North America, we observed a VTE incidence of 19.8 per 10,000 WY (95% CI 8.5 - 46.3) and 25.2 per 10,000 WY (95% CI 12.8 - 49.7) in DRSP/EE+ and DRSP/EE, respectively. Incidence in LNG users was 7.9 per 10,000 WY (95% CI 3.6 - 17.3). Incidence of arteriovenous thromboembolism (ATE) was reported with similar incidence in both groups. Adjusted hazard ratio for DRSP/EE+ versus LNG in North America was 2.5 (95% CI 0.76 - 8.3).

Conclusions: We observed increased incidence of VTE in North American users of DRSP/EE+ and DRSP/EE compared to LNG users. Incidence rates were higher than previously observed. VTE incidence in Russia was unexpectedly low. The impact of the FDA black label warning in 2012 may have contributed to these unusual results.

4603 | Impact of the 2012 FDA safety communication on drosperinone containing oral contraceptives - Detection bias in the international active surveillance - Folate and oral contraceptives utilization study (INAS-FOCUS)

Clare Barnett, Anja Bauerfeind, Thai Do Minh and Klaas Heinemann
ZEG Berlin, Berlin, Germany

Background: The INAS-FOCUS registry was a long-term, active-surveillance study investigating the cardiovascular risk of a new combined oral contraceptive (COC) containing Drospirenone/Ethinylestradiol plus metafolin (DRSP/EE+) in comparison to other COCs (oCOC). In 2012 the FDA concluded that women taking drospirenone-containing oral contraceptives may be at increased risk for developing thromboembolism (VTE) compared to women taking oCOCs. The announcement changed prescriber and user behavior, impacting study results.

Objectives: To describe the impact of a safety announcement on detection and confirmation of the primary outcome of interest in an observational, post-authorization safety study.

Methods: INAS-FOCUS is a large, prospective, controlled, non-interventional study conducted between 2011-2019 in the US, Canada, Russia and Ukraine. Women with a new combined oral contraceptive prescription were enrolled by their prescribing physician. In the follow-up phase, women were contacted every 6 to 12 months for a maximum of 7 years and asked whether they had been diagnosed with a blood clot. Self-reported events were validated via source documentation. Cox regression models were used to show the effect of COC-type on VTE risk. Adjustments were made for age, weight, smoking and family history of VTE.

Results: The analysis is based on 114,081 women-years (WY) of contraceptive exposure in North America. Recruitment in North America started in November 2010. On 27 May 2011, the FDA announced a review of the risk of VTE in users of drosperinone containing COCs. Low uptake of DRSP/EE was observed in North America; 3,456 women were users of DRSP/EE, contributing 5,695 WY of observation. Self-reported VTE in this groups was high; 20 women reported a VTE during follow-up, 100% of whom sought medical attention for their symptoms. Of these, 60% (12/20) VTEs were confirmed by source documentation. In contrast, oCOC users self-reported 181 VTEs, of which only 60% sought medical attention for their symptoms. Of these 17% (31/181) were confirmed by source documentation. Incidence rates for VTE for DRSP/EE+, DRSP/EE and oCOC were 19.8 (95% CI 8.5 - 46.3), 25.2 (95% CI 12.8 - 49.7) and 4.7 (95% CI 3.3 - 6.6) per 10,000 WY, respectively.

Conclusions: We observed evidence of detection bias in users of DRSP/EE following the FDA safety communication. Users were more likely to attend their physician, and physicians were more likely to investigate symptoms, in users of DRSP containing COCs compared to users of oCOCs.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4664 | Comparative safety and effectiveness of direct oral anticoagulants and warfarin on major bleeding and thromboembolic events in atrial fibrillation: A retrospective cohort study

Ya-Ling Huang, Chia-Ling Chiang and Ching-Yao Chen
En Chu Kong Hospital, New Taipei City, Taiwan

Background: Prevention of bleeding or systemic embolism is a major concern in patients with atrial fibrillation (AF) receiving anticoagulation therapy, including direct oral anticoagulants (DOACs) and warfarin. Limited evidence has showed that Asians were prone to risk of bleeding complications when taking anticoagulants. However, the safety and effectiveness of DOACs and warfarin in AF patients remain undetermined.

Objectives: To investigate the association between risks of major bleeding and thromboembolic events with oral DOACs versus warfarin in patients with AF.

Methods: This was a regional teaching hospital-based cohort study retrieving data from patients' electronic medical records of the En Chu Kong Hospital Research Database. We identified AF patients aged over 20 years who receiving DOACs or warfarin between 2015 and 2018 and followed up them until Dec 31, 2019. The outcome of safety and effectiveness were any major bleeding and thromboembolic events, respectively. In subgroup analyses, we stratified by clinical indicators for coagulation, including international normalized ratio (INR) control, CHA_2DS_2-VASc score, and ORBIT bleeding score. Cox proportional hazard models with were used to calculate hazard ratios (HR) with 95% confidence intervals (CI), employing propensity-score based inverse-probability-of-treatment weighting to address confounding by indication.

Results: The cohort included 1,158 AF patients and was followed for a mean of 2.8 (standard deviation 0.5) years. Overall, DOACs users (n=740) were older (mean age 75.5 years) than warfarin users (n=418; mean age 72.3 years), but had the lowest INR (1.19 in DOACs and 1.73 in warfarin). For outcome of safety, the rate of any major bleeding was similar for DOACs (12.2 events per 100 person-years) and warfarin (12.0 events per 100 person-years), with a weighted HR of 0.98 (95% CI, 0.64-1.51). For outcome of effectiveness, there was no significant difference in risk of thromboembolic events compared DOACs (8.5 events per 100 person-years) to warfarin (7.3 events per 100 person-years) (weighted HR, 0.86; 95% CI, 0.52-1.40). Subgroups analyses are ongoing and will be presented at the conference.

Conclusions: In this study, there was no association between risk of any major bleeding and thromboembolic events in comparison of DOACs and warfarin among patients with AF.

4688 | A 'Real-World' study population of NOMAC-E2 users and COC-LNG users: Baseline characteristics from the multinational PRO-E2 study

Suzanne Reed[1], Carol Koro[2], Julia DiBello[2] and Klaas Heinemann[1]
[1]*Berlin Center for Epidemiology and Health Research (ZEG Berlin), Berlin, Germany;* [2]*Merck & Co., North Wales, PA*

Background: Nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg) (NOMAC-E2) is a novel monophasic oral contraceptive which is taken for 24 days followed by 4 days of placebo. It is unknown whether this regimen has an impact on cardiovascular risk, depressive disorders, hepatobiliary disorders, inflammatory bowel disease, body weight or acne.

Objectives: To describe the baseline characteristics of users of NOMAC-E2 and users of combined oral contraceptives with levonorgestrel (COC-LNG) in a study population that is representative of the actual users of the preparations.

Methods: The 'Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg)' (PRO-E2) is a large, non-interventional cohort study. New users of NOMAC-E2 or COC-LNG were recruited in Australia, Europe and Latin America by prescribing physicians. New users included starters (first-ever users) of a COC and restarters (restart COC use after a break of at least 2 months). Baseline data were captured on patient demographics, history of contraceptive use, reason(s) for prescription, medical history (including depression), mood, acne, BMI and smoking status.

Results: Interim results are based on 98,031 women (48,401 NOMAC-E2 users and 49,630 COC-LNG users) recruited between August 2014 and June 2019. Starters comprised 60.3% of NOMAC-E2 users and 61.2% of COC-LNG users. 39.7% of NOMAC-E2 users and 38.8% of COC-LNG users were restarters. NOMAC-E2 users had a higher mean age (30.9 years) than COC-LNG users (29.2 years) but a similar mean weight (NOMAC-E2: 63.3 kg; COC-LNG: 63.0 kg) and mean BMI (kg/m^2) (NOMAC-E2: 23.2; COC-LNG: 23.3). Gynecological characteristics were similar: mean age at menarche (12.8 years in each cohort), mean age at first delivery (NOMAC-E2: 24.3 years; COC-LNG: 23.6 years), mean number of live births (1.6 in each cohort) and median number of miscarriages/stillbirths/abortions (1.0 in each cohort). A total of 9.4% of NOMAC-E2 users were using a COC for non-contraceptive reasons only compared to 8.6% of COC-LNG users. The cohorts were similar with regard to cardiovascular risk factors, history of disease (including treated depression) and regular medication use. NOMAC-E2 users had a higher level of education (43.9% of NOMAC-E2 users and 35.5% of COC-LNG users achieved more than university entrance level).

Conclusions: Baseline differences were largely similar between NOMAC-E2 users and COC-LNG users in this large, prospective cohort study. Updated results will be presented at ICPE.

4733 | Face-to-face 3-year comparative effectiveness and safety of dabigatran and rivaroxaban, standard and reduced doses, for nonvalvular atrial fibrillation: A cohort study in the french nationwide claims database

Patrick Blin[1], Yves Cottin[2], Caroline Dureau-Pournin[1], Abdelilah Abouelfath[1], Régis Lassalle[1], Estelle Guiard[1], Aurélie Balestra[1], Patrick Mismetti[3], Gérard de Pouvourville[4], Cécile Droz-Perroteau[1], Jacques Bénichou[5,6] and Nicholas Moore[1,7]
[1]*Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France;* [2]*CHU de Dijon, Dijon, France;* [3]*CHU de Saint-Etienne,*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Saint-Etienne, France; [4]ESSEC, Cergy-Pontoise, France; [5]CHU de Rouen, Rouen, France; [6]INSERM U1181, Rouen, France; [7]INSERM U1219, Bordeaux, France

Background: Dabigatran (D) and rivaroxaban (R) showed better benefit-risk than vitamin K antagonists for stroke prevention in non-valvular atrial fibrillation (NVAF), but there is no direct face-to-face randomized trial comparing D to R. Our previous results and other real-life studies found similar effectiveness and better safety with D at either dose than R after 1 or 2 years of follow-up.

Objectives: To estimate the comparative effectiveness and safety of standard and reduced doses of D vs R (i.e. D150 vs. R20 and D110 vs. R15, respectively) over a 3-year follow-up in real-life setting.

Methods: All new D or R users for NVAF in 2013 were identified and followed for 3 years in the SNDS French nationwide claims database. NVAF was defined from long-term disease registration, hospital diagnoses or procedures for atrial fibrillation without valvular disease (3-year database history). D and R patients were 1:1 matched according to dose, gender, age, drug start date and high-dimensional propensity scores (hdPS) including individual stroke and bleeding risk factors (CHA_2DS_2-VASc and HAS-BLED). Hazard ratios (HR) [95% confidence interval] were estimated on treatment using Fine and Gray model for stroke and systemic embolism (SSE), clinically relevant bleeding (CRB) and acute coronary syndrome (ACS) and Cox proportional hazards model for death and a composite of death, SSE, CRB and ACS.

Results: Of the 10,847 D150, 15,532 D110, 18,829 R20 and 11,195 R15 new users for NVAF in 2013, 8,195 D150/R20 per arm, and 7,651 D110/R15 per arm were matched, i.e. 76% and 68% of patients of the smallest group (D150 and R15, respectively); with very good overlap of hdPS distributions, all standardized differences < 10% and most < 2% and a c-statistic of 0.56 and 0.57, respectively. The 3-year D vs. R HR of SSE was 0.78 [0.58-1.05] for standard dose and 0.80 [0.63-1.02] for reduced dose, 0.53 [0.42-0.66] and 0.70 [0.58-0.83] for CRB, 1.00 [0.73-1.36] and 0.85 [0.65-1.12] for ACS, 0.83 [0.65-1.07] and 0.91 [0.80-1.03] for death, 0.73 [0.64-0.84] and 0.84 [0.77-0.92] for the composite criterion, respectively.

Conclusions: This real-life nationwide cohort study confirms no significant difference of effectiveness between the two drugs for standard and reduced doses after 3 years of follow-up, but a long-term lower bleeding risk of dabigatran for both doses, as well as an overall better benefit-risk.

4808 | Five alpha-reductase inhibitors and the risk of venous thromboembolism among patients with benign prostatic hyperplasia

Henok Tadesse Ayele[1,2], Pauline Reynier[2], Laurent Azoulay[1,2,3], Robert W. Platt[1,2,4], Serge Benayoun[5] and Kristian B. Filion[1,2,6]

[1]Department of Epidemiology, Biostatistics, Occupational Health, McGill University, Montréal, QC, Canada; [2]Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montréal, QC, Canada; [3]Gerald Bronfman Department of Oncology, McGill University, Montréal, QC, Canada; [4]Department of Pediatrics, McGill University, Montreal, QC, Canada; [5]Department of Surgery, Urology Unit, Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada; [6]Department of Medicine, McGill University, Montréal, QC, Canada

Background: Although 5-alpha reductase inhibitors (5αRIs) are effective for the treatment of benign prostatic hyperplasia, their antiandrogenic effects could increase the risk of venous thromboembolism (VTE). However, few studies have examined this potential adverse drug reaction.

Objectives: To compare the rate of VTE among patients with newly diagnosed BPH prescribed 5αRIs to that in patients not prescribed 5αRIs.

Methods: We used data from the United Kingdom's Clinical Practice Research Datalink (CPRD) linked to Hospital Episodes Statistics hospitalization data and Office for National Statistics vital statistics data. Inclusion was restricted to patients aged at least 40 years with a new diagnosis of BPH recorded in the CPRD between April 1998 and March 2016. We excluded patients with a prescription for BPH drugs in the prior year, a previous diagnosis of prostate cancer, and less than one year of database history before cohort entry. We followed patients from BPH diagnosis until hospitalization for VTE or censoring due to the end of the study, a diagnosis of cancer, or death. Exposure was defined using a time-varying approach with 4 mutually-exclusive categories and a 30-day grace period: current use of 5αRIs, current use of α-blockers, current use of combination therapy (5αRIs and α-blockers), and no current use of BPH drugs. We used a time-dependent Cox proportional hazards model to estimated adjusted hazard ratios (HRs) and 95% confidence intervals for VTE for the current use of 5αRIs versus no current use of BPH drugs.

Results: We identified 94,598 patients with newly-diagnosed BPH, generating 528,616 person-years (PYs) of follow-up (median follow-up: 5.1 years with interquartile range: 2.1-9.4 years). The mean age of patients at cohort entry was 66.2 (SD: 10.4) years. A total of 1,255 VTE events were observed, representing an overall event rate of 2.4 (95% CI: 2.2-2.5) per 1,000 person-years (PYs). The incidence rates of VTE among 5αRIs and α-blockers users were 3.2 (95% CI: 2.6-4.0) and 2.5 (95% CI: 2.2-2.8) per 1000 PYs, respectively. Compared with no current use of BPH drugs, the current use of 5αRIs was not associated with the risk of VTE (HR: 1.04, 95% CI: 0.83-1.30). We obtained similar results when comparing the risk of VTE with the current use of 5αRIs to that with the current use of α-blockers (HR: 1.07, 95% CI: 0.84-1.35).

Conclusions: The use of 5αRIs is not associated with the increased risk of VTE among patients with BPH.

4921 | Validity of a case-identification algorithm for venous thromboembolism

Monica Bertoia[1], Sigalit Kaplan[2], Li Zhou[1], Amir Lass[3], Florence T. Wang[1] and John D. Seeger[1]

[1]Optum Epidemiology, Boston, MA;[2]Teva Pharmaceutical Industries Ltd., Netanya, Israel[3]Theramex, London, United Kingdom

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: A study was conducted to examine the risk of venous thromboembolism (VTE) associated with extended as compared to traditional 28-day cycle combined oral contraceptives (COCs). In the context of this safety study, a case-identification algorithm was constructed to identify VTE events in a health insurance claims database.

Objectives: To develop and validate a claims-based VTE identification algorithm.

Methods: The occurrence of VTE events were identified within a cohort study of women receiving an extended or 28-day cycle COC between 01 January 2006 and 30 June 2017 in the Optum Research Database. The VTE cases included deep venous thrombosis (DVT) and/or pulmonary embolism (PE). Identification algorithms for DVT and PE were based on both International Classification of Diseases (ICD) 9th and 10th revision codes. Pulmonary embolism was defined as an inpatient diagnosis of PE in the primary position. Deep venous thrombosis was defined as an inpatient diagnosis in the primary position or an outpatient diagnosis in any position in conjunction with an anticoagulant or alteplase dispensing or administration within 30 days. Medical records were sought for a sample of patients identified using the VTE case identification algorithm and records obtained were reviewed independently by two clinicians blinded to exposure who reached consensus in the case of discrepant reviews. The validity of the algorithm was assessed by the positive predictive value (PPV), defined as the proportion of algorithm-identified VTE that were confirmed as true VTE following medical record review. Analyses stratified by coding era (ICD-9 vs ICD-10) were performed.

Results: Medical records were sought for 123 women with algorithm-identified VTE. Medical records were retrieved for 89 (72.4%) of the women. Sixty-eight of the 89 women were confirmed as having VTE yielding a PPV of 76% (95% confidence interval 66 to 85%). The PPV was not different in the ICD-9 coding era relative to ICD-10.

Conclusions: This claims-based VTE algorithm performed well with 76% of cases identified by the algorithm confirmed as true cases. This positive predictive value is similar to that of other published, validated, claims-based VTE algorithms.

5106 | Cardiovascular risk with concomitant use of stimulants and atypical antipsychotics in US children and adolescents

Chengchen Zhang[1], O'Mareen Spence[1], Gloria Reeves[2] and Susan dosReis[1]

[1]University of Maryland School of Pharmacy, Baltimore, MD;[2]University of Maryland School of Medicine, Baltimore, MD

Background: Stimulants, widely used as the first-line treatment for pediatric attention deficit/hyperactivity disorder, are increasingly prescribed along with atypical antipsychotics (AAPs) to children and adolescents in the US. Cardiovascular safety concerns are associated with each therapeutic class, but the cardiovascular risk of concomitant use of stimulants and AAPs is not known.

Objectives: To determine if concomitant use of stimulants and AAPs is associated with increased cardiovascular risk in children and adolescents.

Methods: A retrospective cohort with a new user design was implemented with the IQVIA™ Adjudicated Health Plan Claims data from 2006-2015. The study cohort was commercially insured youth aged 5-18 years old who newly initiated a stimulant medication. The date of stimulant initiation was the index date. Eligible participants had continuous insurance coverage and no stimulant or AAP use in the 6-months prior to the index date. We operationalized stimulant/AAP concomitant use as a time-dependent measure (current/past/no use). Current concomitant use was further defined by cumulative days (≤30,30-90, ≥90) and average daily risperidone equivalent AAP dose (0, ≤1mg, 1-2mg, ≥2mg). The study outcome was a composite measure of cardiovascular event (e.g., myocardial infarction, stroke, ischemic heart disease, cardiac arrest, etc.) Individuals were followed until a cardiovascular event, loss of insurance coverage, September 2015, age of 18 or stimulant discontinuation. A disease risk score was used to adjust for observed confounders (i.e., previous cardiovascular conditions, psychiatric diagnoses, metabolic disorders, etc.). A time-varying Cox proportional hazard model estimated cardiovascular risk.

Results: During follow-up [median follow-up days = 546 (IQR: 717)] of 59157 new stimulant users, 2056 (3.5%) experienced a cardiovascular event. Compared with no concomitant use, current concomitant use was associated with a higher risk of a cardiovascular event at all AAP dose levels [HR: ≤1mg: 2.39 (1.56, 3.65); 1-2mg: 2.47 (1.31, 4.66); ≥2mg: 3.78 (1.68, 8.53)], and past concomitant use was associated with a 62% [HR: 1.62 (1.16, 2.27)] increased risk of a cardiovascular event. Cumulative concomitant days was not associated with increased cardiovascular risk.

Conclusions: Concomitant use of stimulants and AAPs is associated with increased cardiovascular risk among children and adolescent newly initiating a stimulant. AAP dose intensifies the risk.

Safety End Points -> Diabetes

2591 | Sodium-glucose Co-transporter 2 inhibitors and the risk of diabetic ketoacidosis: A multicenter international cohort study

Antonios Douros[1,2,3], Lisa M. Lix[4], Michael Fralick[5], Sophie Dell'Aniello[6], Baiju R. Shah[5], Paul E. Ronksley[7], Éric Tremblay[8], Nianping Hu[9], Silvia Alessi-Severini[4], Anat Fisher[10], Shawn C. Bugden[11], Pierre Ernst[1,2], Kristian B. Filion[1,2] and the CNODES Investigators[12]

[1]Department of Medicine, McGill University, Montreal, QC, Canada; [2]Department of Epidemiology, McGill University, Montreal, QC, Canada; [3]Charité – Universitätsmedizin Berlin, Berlin, Germany; [4]University of Manitoba, Winnipeg, MB, Canada; [5]University of Toronto, Toronto, ON, Canada; [6]Lady Davis Institute, Montreal, QC, Canada; [7]University of Calgary, Calgary, AB, Canada; [8]Institut National d'Excellence en Santé et en Services Sociaux, Quebec City, QC, Canada; [9]The Health Quality Council, Saskatoon, SK, Canada; [10]University of British Columbia, Vancouver, BC, Canada; [11]Memorial University of Newfoundland, St John's, NL, Canada; [12]Canadian Network for Observational Drug Effect Studies (CNODES) Investigators, Montreal, QC, Canada

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: There are ongoing concerns that sodium-glucose cotransporter 2 (SGLT2) inhibitors could increase the risk of diabetic ketoacidosis (DKA), a potentially fatal diabetic complication.

Objectives: To assess whether the use of SGLT2 inhibitors, compared with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors, is associated with an increased risk of DKA in patients with type 2 diabetes.

Methods: We conducted a population-based international cohort study using electronic healthcare databases from seven Canadian provinces and the United Kingdom. The study cohort included 903,016 patients with type 2 diabetes using an SGLT2 inhibitor or a DPP-4 inhibitor between January 2013 and June 2018. Using a prevalent new-user design, we matched incident new users of SGLT2 inhibitors to incident new users of DPP-4 inhibitors and prevalent new users of SGLT2 inhibitors (patients switching to an SGLT2 inhibitor from a DPP-4 inhibitor) to patients using DPP-4 inhibitors for the same amount of time. Overall, 208,757 users of SGLT2 inhibitors were matched to 208,757 users of DPP-4 inhibitors on level of antidiabetic therapy, time on DPP-4 inhibitors (for prevalent new users), calendar time, and time-conditional propensity scores. Cox proportional hazards models estimated hazard ratios with 95% confidence intervals of DKA comparing the use of SGLT2 inhibitors to the use of DPP-4 inhibitors. Secondary analyses stratified by molecule, age, sex, and prior insulin use. Site-specific hazard ratios were pooled using random-effects meta-analytic models.

Results: A total of 521 patients were diagnosed with DKA during 370,454 person-years of follow-up (incidence rate, 1.4 per 1,000 person-years). Compared with the use of DPP-4 inhibitors, the use of SGLT2 inhibitors was associated with an increased risk of DKA (hazard ratio, 2.85; 95% confidence interval, 1.99 to 4.08). Molecule-specific hazard ratios (95% confidence intervals) were 1.86 (1.11 to 3.10) for dapagliflozin, 2.52 (1.23 to 5.14) for empagliflozin, and 3.58 (2.13 to 6.03) for canagliflozin. Age, sex, and prior insulin use did not modify the association.

Conclusions: SGLT2 inhibitors were associated with an almost threefold increased risk of DKA, with molecule-specific analyses suggesting a class effect.

3800 | Risk of clinically relevant hyperglycemia with metoprolol compared to carvedilol in older adults with heart failure and diabetes

Chintan Dave, Brian Strom, Fred Kobylarz, Daniel Horton, Tobias Gerhard, Chin-Lin Tseng, Ilja Dejanovic, Abner Nyandege and Soko Setoguchi

Rutgers University, New Brunswick, NJ

Background: Although prior literature suggests that metoprolol may worsen glucose control compared to carvedilol, whether this has clinical relevance among older adults with diabetes and heart failure remains an open question.

Objectives: We aimed to assess whether initiation of metoprolol compared to carvedilol is associated with an increase in the risk of clinically relevant hyperglycemia in older adults with diabetes and heart failure.

Methods: This was a retrospective cohort study utilizing data sourced from a 50% national sample of Medicare fee-for-service claims of patients with Part D prescription drug coverage (2007-2017). Among patients with diabetes and heart failure we identified initiators of metoprolol or carvedilol, which were 1:1 propensity score matched on >90 variables. The primary outcome was initiation of a new oral or injectable antidiabetic medication (proxy for uncontrolled diabetes); secondary outcomes included initiation of insulin and severe hyperglycemic event (composite of emergency room visits or hospitalizations related to hyperglycemia). Adjusted hazard ratios (AHR) and 95% confidence intervals (CI) were estimated.

Results: Among 25,341 propensity score-matched pairs (mean [SD] age 77.6 [8.0] year; male (39.7%)), there were 8,564 [incidence rate per 100 person-years (IR) = 33.4] episodes of antidiabetic medication initiation among metoprolol users (exposure arm) compared to 8,958 [IR = 33.4] among carvedilol users (control arm) compared to corresponding to an adjusted HR [aHR] of 0.98 (95% CI: 0.95, 1.01). Similarly, metoprolol was not associated with a significant increase in the risk of secondary outcomes including insulin initiation: aHR of 0.96 (95% CI: 0.91, 1.01)) and severe hyperglycemic events: aHR of 0.95 (95% CI: 0.91, 0.99).

Conclusions: In this large and representative study of older adults with heart failure and diabetes sourced from routine clinical care in the US, initiation of metoprolol compared to carvedilol was not associated with an increase in the risk of clinically relevant hyperglycemia.

3833 | Risk of sodium—Glucose cotransporter—2 inhibitor on the incidence of urinary tract infection among diabetic patients in Japan: A nationwide cohort study

Yoshinori Takeuchi[1], Hiraku Kumamaru[2], Yasuhiro Hagiwara[1], Hiroki Matsui[3], Hideo Yasunaga[3], Hiroaki Miyata[2] and Yutaka Matsuyama[1]

[1]*Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;*
[2]*Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;*
[3]*Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*

Background: Some studies have reported an increased risk of urinary tract infection (UTI) among diabetic patients using sodium-glucose cotransporter-2 inhibitors (SGLT2i), although the association remains controversial.

Objectives: To evaluate the risk of UTI for SGLT2i use compared to biguanides and dipeptidyl peptidase-4 inhibitors (DPP4i) use among diabetic patients through population-based cohort study.

Methods: Design: A cohort study using a nationwide administrative claims database in Japan.

Setting: We selected patients aged 40 and above with prescriptions of SGLT2i, DPP4i, or biguanides between April 2014 and March 2015 from the database. For computational ease, we randomly sampled 12% of them and identified new users of the three drugs, defining new use as the first prescription of any study drugs after 365 days of no-use. We excluded patients with previous diagnoses of UTI.

Exposures: Initiation of SGLT2i, DPP4i or biguanides

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Main outcome measures: Incidence of UTI, defined as a recorded prescription of any antibiotics within 7 days of UTI diagnosis.

Statistical analysis: We estimated conditional hazard ratios (HRs) by the multivariable Cox regression model adjusting for the following baseline covariates for each patient: sex, age, medication history, and medical history. We also estimated a marginal HRs by the inverse probability of treatment weighted Cox regression model. The probabilities of receiving treatment were estimated by the generalized logistic regression model, including these baseline covariates. Robust variance estimators were employed to account for weighting.

Results: We identified 2466, 102,670, and 18,139 initiators of SGLT2i, DPP4i, and biguanides, respectively, reflecting dominant use of DPP4i as a first-line antidiabetic drug in Japan during the study period. We observed 2949 UTI events over 56,847.6 person-years of observation in biguanide users (incidence rate, IR: 0.041/person year), 365 events over 7588.4 person-years in SGLT2i users (IR: 0.048/person-year) and 16930 events over 303,095.0 person-years in DPP4i patients (IR: 0.055/person-year). Relative hazard compared to biguanide use were conditional HR: 1.30 [95% confidence interval, CI 1.24-1.36], marginal HR: 1.37 [95%CI 1.31-1.43]) for SGLT2i users, and conditional HR: 0.99 [95%CI 0.97-1.00], marginal HR: 0.99 [95% CI 0.97-1.01]) for DPP4i users.

Conclusions: The incidence of UTI was significantly increased in SGLT2i users compared with biguanide users. The risk of DPP4i was like that of biguanide.

3981 | the association between digoxin and development of diabetes: A danish nationwide new user, active comparator cohort study

Lars Christian Lund, Anton Pottegård and Jesper Hallas
University of Southern Denmark, Odense, Denmark

Background: Drug-induced diabetes is underreported and may contribute to the globally increasing prevalence of diabetes. A recent hypothesis-generating study found exposure to digoxin to be associated with an increased risk of diabetes. The literature on this putative association is, however, sparse and equivocal.

Objectives: To conduct an active comparator, new user cohort study on the potential link between digoxin and diabetes.

Methods: The study compared the 1-year rate of diabetes among new-users of digoxin to new users of verapamil, another drug used for similar indications. Data were obtained from the Danish nationwide health registries during 1996-2018. Individuals with prior diabetes or heart failure were excluded from the analysis. Digoxin and verapamil users were matched using high-dimensional propensity scores in a 1:1 ratio and followed according to the intention to treat (ITT) principle, i.e. individuals stayed in the cohort they were assigned to at study entry. We estimated incidence rate differences (IRD), incidence rate ratios (IRR) and the number needed to treat for one additional patient to be harmed (NNTH). Multiple sensitivity analyses were performed: We obtained risk estimates for varying durations of follow up and conducted an on-treatment analysis, where individuals were censored upon discontinuation of treatment. The cohorts were stratified into terciles based on the disease risk score and stratified estimates were obtained. Lastly, metoprolol was used as an active comparator instead of verapamil.

Results: 79,640 individuals were included, contributing 73,742 person years of follow-up and 1608 cases of incident diabetes. The IRR associating digoxin use to diabetes was 2.63 (95% CI: 2.63-2.94), corresponding to an IRD of 20 cases/1000 person years and a NNTH of 49 (44-55). Varying the length of follow up did not change the IRR substantially. The lowest IRR, 1.71 (95% CI: 1.29-2.29), was obtained for one month of follow up. Performing an on-treatment analysis yielded a slightly higher IRR of 3.32 (95% CI: 2.78-3.76). When stratifying on the disease risk score, the IRD was higher in the high-risk group (24 cases/1000 person years) than in the low-risk group (16 cases/1000 person years). Using metoprolol as an active comparator, an IRR of 1.88 (95% CI: 1.74-2.03) and a NNTH of 74 (66-85) were obtained.

Conclusions: Digoxin use is associated with an increased risk of developing diabetes. This association was found in both low and high diabetes risk groups, with use of verapamil and metoprolol as an active comparator, and with an ITT or on-treatment analysis.

3982 | Risk of venous thromboembolism amongst initiators of SGLT-2 inhibitors compared to other glucose-lowering agents

Chandrasekar Gopalakrishnan, Rishi J. Desai, Seoyoung C. Kim and Elisabetta Patorno
Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background: The comparative safety of frequently used second-line agents to treat type 2 diabetes (T2D) with respect to the risk of venous thromboembolism (VTE) in routine care is unknown. It has been hypothesized that the diuretic effect of SGLT-2 inhibitors (SGLT-2i) may have an unintended impact on VTE risk by increasing blood viscosity

Objectives: To assess the comparative safety of SGLT-2i for the risk of VTE compared to frequently used second-line agents to treat T2D

Methods: Using Optum Clinformatics, a large US commercial health insurance database, we identified two pair-wise 1:1 propensity score (PS)-matched cohorts of adult patients ≥18 years with T2D and no history of VTE who initiated a SGLT-2i or a comparator, i.e., a GLP-1 receptor agonist [GLP-1 RA (n=59,712 pairs)], or a DPP-4 inhibitor [DPP-4i (n=50,178 pairs)] between April 2013 and March 2019, and compared the risk of an incident hospitalization with a primary diagnosis of VTE (i.e., deep vein thrombosis or pulmonary embolism). The PS was estimated using over 100 baseline characteristics, including common risk factors for VTE (such as fractures, major surgery, long-term hospitalizations, mobility impairments), baseline comorbidities (such as cardiovascular disease and diabetes complications), medication history, healthcare utilization measures and a validated claims-based frailty score. All baseline characteristics were assessed in the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

365 days prior to and including the day of initiation of a study drug. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Patients were followed up until treatment discontinuation of the index drug (treatment gap >60 days), switch to a comparator, disenrollment or occurrence of an outcome event. We also performed subgroup analyses by age, frailty and history of cardiovascular disease and a sensitivity analyses that varied the definition of treatment discontinuation (treatment gap >7 days)

Results: After PS-matching, baseline patient characteristics were well balanced between exposure groups (all standardized differences <0.1). Mean age was 58 years and mean follow-up was 0.8 years. SGLT-2i had a similar risk of VTE compared to GLP-1 RA [HR (95% CI) = 1.01 (0.70, 1.46)] and DPP-4i [HR (95% CI) = 0.99 (0.66, 1.51)], with incidence rates ranging between 1.1 and 1.3 events per 1,000 person-years. Results were robust across subgroup and sensitivity analyses

Conclusions: In this large population-based study of adult patients with T2D, SGLT-2i had a similar risk of VTE compared to GLP-1 RA and DPP-4i, with reassuringly low absolute rates overall

4203 | Lack of insulin secretagogue deprescribing and risk of severe hypoglycemia following bariatric surgery

Scott M. Vouri[1,2], Jiajing Chen[3], Jayme Sparkman[4], Joshua D. Brown[1,2,2], Hui Shao[1], Arghavan Salles[5] and Scott T. Micek[6]
[1]University of Florida College of Pharmacy, Gainesville, FL; [2]University of Florida, Gainesville, FL; [3]Mercy – Performance Solutions, St. Louis, MO; [4]Washington University School of Medicine, St. Louis, MO; [5]Stanford University School of Medicine, Stanford, CA; [6]St. Louis College of Pharmacy, St. Louis, MO

Background: There is little guidance on antidiabetes medication (ADM) deprescribing following bariatric surgery. The recommendation to deprescribe insulin secretagogues (i.e., sulfonylurea and meglitinide) following bariatric surgery is based solely on expert opinion and is otherwise not broadly followed.

Objectives: To assess the association of the lack of insulin secretagogues deprescribing and risk for severe hypoglycemia following bariatric surgery among patients with Type 2 diabetes mellitus (T2DM).

Methods: We identified T2DM patients taking an insulin secretagogue within 6 months of bariatric surgery using claims data of a nationally representative sample patients with diabetes mellitus (2007-2014). We identified severe hypoglycemia, requiring an emergency department (ED) or hospital visit, using validated ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes. We modeled deprescribing of insulin secretagogues as a time-varying exposure allowing patients re-initiate therapy. All other antidiabetic medication (ADM) classes were modeled similarly.

Results: Among the 40,520 patients with T2DM who underwent bariatric surgery, 8,650 patients were taking an insulin secretagogue at the time of bariatric surgery. The most common type of bariatric surgery procedure was Roux-en-Y Gastric Bypass (46%). The mean (SD) age was 52.0 (10.2) years old and 63.4% of patients were females. The crude incidence rate of severe hypoglycemia associated with a lack of insulin secretagogue deprescribing was 62.6 (95% CI 53.3-73.5) episodes per 1000 patient-years compared to insulin secretagogue deprescribing which resulted in 24.7 (95% CI 20.8-29.3) episodes per 1000 patient years (p<0.0001). After adjusting for bariatric surgery type, baseline characteristics, comorbid conditions, and other ADM utilization, patients who were not deprescribed their insulin secretagogue were 77% more likely to experience severe hypoglycemia following bariatric surgery (HR 1.77, 95% CI 1.73-1.81) compared to patients who were deprescribed.

Conclusions: Lack of insulin secretagogue deprescribing following bariatric surgery is associated with an increased risk of severe hypoglycemia. Our results further inform the recommendation based on expert opinion and can help provide more guidance to clinicians who manage patients who underwent bariatric surgery.

4246 | Use of low-dose quetiapine and the risk of diabetes: A nation-wide cohort study using a high-dimensional propensity score

Mikkel Højlund[1,2], Lars C Lund[1], Kjeld Andersen[3,4], Christoph U. Correll[5,6] and Jesper Hallas[1]
[1]University of Southern Denmark, Odense, Denmark; [2]Mental Health Services in Region of Southern Denmark, Aabenraa, Denmark; [3]University of Southern Denmark, Odense, Denmark; [4]Mental Health Services Region of Southern Denmark, Odense, Denmark; [5]The Zucker Hillside Hospital/ Zucker School of Medicine at Hofstra/Northwell, Glen Oaks, NY; [6]Charité Universitätsmedizin, Berlin, Germany

Background: Quetiapine is associated with metabolic disturbances when used in high doses for treatment of schizophrenia. The use of low-dose quetiapine for other psychiatric conditions has become increasingly common due to its sedative-hypnotic and anxiolytic properties. It is not known to what degree low doses of quetiapine is associated with an increased metabolic risk.

Objectives: To investigate the association between use of low-dose quetiapine and incident diabetes.

Methods: We conducted a nation-wide, active comparator, new user cohort study of low-dose quetiapine and the risk of diabetes using benzodiazepine-related drugs (BZRDs) and selective serotonin-reuptake inhibitors (SSRIs) as active comparators. Users of quetiapine and comparator drugs were identified in the Danish National Prescription Registry and matched 1:1 using a high-dimensional propensity score. Cases of incident diabetes were identified by first use of antidiabetic medications, first diagnosis of diabetes, or first HbA1c-measurement of more than or equal to 48 mmol/mol. We computed incidence rate ratios (IRR) using both intention-to-treat and on-treatment approaches.

Results: We identified 76,735 users of low-dose quetiapine in the Danish population between 1998 and 2018. From these, we were able to match 29,869 with BZRD-users and 19,844 with SSRI-users. Comparing

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the unmatched cohorts, we found a slightly increased risk of diabetes after 5 years both in comparison with BZRDs (IRR=1.06, 95%CI: 1.00-1.13) and SSRIs (IRR=1.19, 95%CI: 1.10-1.27). However, this difference was not present after matching (IRR-BZRD=0.82, 95%CI: 0.75-0.89 and IRR-SSRI=1.03, 95%CI: 0.93-1.14). Moreover, the on-treatment analyses found a reduced risk of diabetes versus BZRDs (IRR 0.58, 95%CI: 0.42-0.80) but an increased risk versus SSRIs (IRR=1.76, 95%CI: 1.27-2.40). Supplementary on-treatment analysis identified an increased risk of diabetes with BZRDs versus SSRIs (IRR 1.87, 95%CI: 1.72-2.04).

Conclusions: We did not find a substantially increased risk of diabetes among low-dose quetiapine-users, neither in comparison with BZRD-users nor with SSRI-users. The observed pattern is suggestive of a potential diabetogenic effect of BZRD, which needs to be investigated further.

4409 | Assessing fit-for-purpose: Surrogate endpoints and clinically important outcomes in Japanese real-world data source in type-2 diabetes

Jocelyn Ruoyi Wang, Amanda Patrick, Pattra Mattox and Ashley Jaksa
Aetion Inc., Boston, MA

Background: Regulatory and payer decision-makers are increasingly relying on real-world evidence (RWE) to compliment traditionally used randomized-controlled trials (RCT). One challenge of using real-world data to generate RWE is ensuring the data is fit for use and has all the requested data to answer the research question and define the populations, exposure measurements, outcomes, confounders. In type-2 diabetes (T2D), phase 3 trials often use glycemic control as a surrogate endpoint for preventing microvascular complications, but the availability of these key study parameters within real-world data sources remains unexamined.

Objectives: To assess the availability of surrogate endpoints and clinical outcome measurements for type 2 diabetes in a Japanese administrative database.

Methods: Newly-diagnosed T2D patients were identified using ICD-10 diagnostic codes in the Japanese Medical Data Center (JMDC) claims database during 2011-2018. Patients <18 or without continuous enrollment during one-year baseline and one-year follow-up were excluded. Surrogate endpoints (glycemic control, glycated hemoglobin [HbA1c], fasting plasma glucose [FPG]) were assessed at baseline and at one-year follow-up. Patients were followed for direct clinical endpoints (e.g., microvascular complications identified using ICD-10 codes) until death, outcome occurrence, disenrollment, or the end-of-data.

Results: Among 51,559 patients, 62.1% and 60.7% of patients had at least one baseline record of HbA1c and FPG level, respectively. The median change in HbA1c was -0.10 %; FPG median change was -4.00 mg/dL. Baseline and follow-up HbA1c values were missing for 37.9% and 41.7% of T2D patients, respectively. Similar missingness was observed for baseline and follow-up FPG. The commonly reported microvascular complications were identifiable within the dataset. The risk (per 1000 patients) of microvascular complications ranged from 128.0 (neuropathy) to 322.6 (nephropathy).

Conclusions: Several potential longitudinal databases for RWE exist in Japan including JMDC. Our analysis showed the availability of key variables for diagnosis, procedures, laboratory values, and clinical outcomes required to evaluate real-world studies in a T2D population. Despite some incompleteness, the laboratory values recorded in this database were considered high-quality to allow effectiveness evaluations of antiglycemic agents. More broadly, JMDC may also allow the exploration of potential surrogate endpoints for other chronic conditions.

4587 | Use of sodium-glucose co-transporter-2-inhibitors and risk of lower limb amputation

Nikki Werkman[1], Yannick Nielen[1], Joop van den Berg[1,2], Niels Ejskjaer[3], Johan Røikjer[3], Nicolaas Schaper[1], Olaf Klungel[4], Peter Vestergaard[3], Frank de Vries[1,4] and Annemariek Driessen[1]
[1]Maastricht University Medical Centre+, Maastricht, Netherlands; [2]VieCuri Medical Center, Venlo, Netherlands; [3]Aalborg University Hospital, Aalborg, Denmark; [4]Utrecht Institute of Pharmaceutical Sciences, Utrecht, Netherlands

Background: A trial indicated that patients with type 2 diabetes mellitus (T2DM) using the sodium-glucose co-transporter-2-inhibitor (SGLT2-I) canagliflozin had a greater risk of lower limb amputations (LLAs). LLAs are associated with high burden and costs, and a 5-year mortality rate of 62%. Studies evaluating the association between SGLT2-I use and LLA have produced conflicting results and no underlying mechanism has been studied.

Objectives: The aim of the current study was to investigate the association between the use of SGLT2-Is versus other anti-diabetic drugs and the risk of LLA. In addition, we explored hypovolemia as a potential underlying mechanism.

Methods: A cohort study was conducted using data from the Clinical Practice Research Datalink (CPRD) GOLD between January 2013 and October 2019. The study population (N=51,847) consisted of individuals over 18 years of age with T2DM and at least one prescription of a non-insulin anti-diabetic drug (new users). Drug exposure was determined time-dependently using 30-day intervals and cumulative dose exposure was calculated at each current SGLT2-I use interval. Continuous duration of use was determined allowing a gap of 60 days between the estimated end date of a prescription and the start of the next prescription. Concomitant diuretic use was determined to assess the role of hypovolemia. Cox proportional hazard models were used to estimate the hazard ratio (HR) for LLA, comparing current SGLT2-I use to current sulfonylurea derivative (SU) use. Analyses were adjusted for T2DM duration, comorbidities and concomitant drug use.

Results: We identified 10,966 SGLT2-I users during a median follow-up time of 2.9 years. SGLT2-I use was not associated with an increased risk of LLA compared to SU use (adjusted HR 0.72 (95% confidence interval (CI) 0.38-1.34)). In addition, we did not find a

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

dose-response relationship, as the risk of LLA did not increase with increasing cumulative dose exposure. The adjusted HR for the highest cumulative dose group (>145.8 g canagliflozin equivalents) was 0.96 (95%CI 0.33-2.77). The risk of LLA did not increase with increasing continuous duration of use (adjusted HR for ≥2.0 years 1.11 (95% CI 0.43-2.93)). Furthermore, concomitant diuretic use was not associated with an increased risk of LLA in current SGLT2-I use compared to current SU use.

Conclusions: The results of the current study indicate that SGLT2-I use is not associated with an increased risk of LLA compared to SU use. The findings suggest that hypovolemia might not be the underlying mechanism for the previously found increased risk of LLA.

4706 | Glucagon like peptide-1 receptor agonists and the risk of anaphylactic reactions among patients with type 2 diabetes

Richeek Pradhan[1], Elisabetta Patorno[2], Sebastian Schneeweiss[2], Hui Yin[3], Helen Tesfaye[2], Ajinkya Pawar[2], Christina Santella[1], Christel Renoux[1], Oriana Yu[4] and Laurent Azoulay[1]

[1]McGill University, Montreal, QC, Canada; [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [3]Lady Davis Institute, Montreal, QC, Canada; [4]McGill University, Montreal, QC, Canada

Background: Glucagon like protein-1 receptor agonists (GLP-1 RAs) are drugs used in the treatment of type 2 diabetes that showed cardiovascular benefits in recent randomized controlled trials. However, recent case reports and a pharmacovigilance analysis have reported that animal-based, exentin-4 GLP-1 RAs, may be associated with an increased risk of anaphylactic reactions. To date, the association between exendin-4 and human-based GLP-1 RAs and this potentially fatal adverse event has not been investigated in the real-world setting.

Objectives: To determine whether use of exentin-4 and human-based GLP-1 RAs, when compared with dipeptidyl peptidase-4 inhibitors (DPP-4Is), is associated with an increased risk of anaphylactic reactions among patients with type 2 diabetes.

Methods: This was a large cohort study involving databases from the UK (CPRD) and the US (MarketScan, Optum, Medicare). We identified all patients newly prescribed exendin-4 GLP-1 RAs (exenatide, lixisenatide) or human-based GLP-1 RAs (liraglutide, semaglutide, dulaglutide, albiglutide) and compared them with patients newly prescribed DPP-4Is between 2007 and 2019. For the primary analysis, patients were followed using an as-treated approach, while an intention-to-treat approach was used in a secondary analysis. Propensity score fine stratification was used to control for confounding and Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for anaphylactic reactions, separately for exendin-4 and human-based GLP-1 RAs. Estimates across databases were meta-analyzed using a random effects model.

Results: Overall, a total of 121,499 exendin-4 GLP-1 RA and 197,121 human-based GLP-1 RA users were compared with 1,697,511 and 1,465,355 DPP-4I users, respectively. In the as-treated approach, use of exendin-4-based GLP-1 RAs was not associated with an increased risk of anaphylactic reactions, compared with use of DPP-4Is (28 vs 28 per 100,000 person-years, respectively; HR: 1.04, 95% CI: 0.73-1.47). Similarly, no association was observed with human-based GLP-1 RAs (36 vs 30 per 100,000 person-years, respectively; HR: 1.14, 95% CI: 0.88-1.47). These findings remained consistent in the intention-to-treat approach (exendin-4 GLP-1 RAs, HR: 1.03, 95% CI: 0.80- 1.31; human-based GLP-1 RAs, HR: 0.98, 95% CI: 0.81- 1.17).

Conclusions: The results of this large cohort study indicate that compared with use of DPP-4Is, use of exendin-4-based GLP-1 RAs and human-based GLP-1 RAs are not associated with an increased risk of anaphylactic reactions.

4879 | Risk of serious hypoglycemia of angiotensin converting enzyme inhibitors used concomitantly with insulin secretagogues or metformin

Young Hee Nam[1], Colleen M. Brensinger[2], Warren B. Bilker[2], Charles E. Leonard[2] and Sean Hennessy[2]

[1]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Serious hypoglycemia is one of the major adverse events that can be caused by insulin secretagogues (sulfonylureas and meglitinides). Prior studies suggested that angiotensin converting enzyme inhibitors (ACEIs) also might increase this risk; however, the risk of ACEIs used with insulin secretagogues has remained unclear.

Objectives: To investigate the risk of serious hypoglycemia of ACEIs (as precipitant drugs) used concomitantly with insulin secretagogues (as object drugs) or metformin (as a negative control object drug)

Methods: Design - Bidirectional self-controlled case series. **Study setting and population** - Adults who experienced serious hypoglycemia while receiving glimepiride, glipizide, glyburide, nateglinide, repaglinide, or metformin, identified in five US states' Medicaid claims data constituting ~40% of enrollees nationwide, supplemented with Medicare claims for dual-enrollees, from 1999-2011. **Exposure of interest** - Active prescription for ACEIs (benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril) during observation time (a period covered by an object drug prescription). **Outcome measure** - Serious hypoglycemia, ascertained by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) discharge diagnosis codes appearing in principal position in hospital inpatient claims or any-position in emergency department claims (positive predictive value ~78-89%). **Statistical analysis** - We calculated confounder-adjusted rate ratios (RRs) of outcome occurrence during precipitant-exposed time versus precipitant-unexposed time, using conditional Poisson regression, for ACEIs overall and individual ACEIs.

Results: We identified 56,347 persons experiencing serious hypoglycemia contributing to 43,268 person-years of observation. ACEIs as a drug class were associated with an elevated rate of hypoglycemia when used with glimepiride (RR: 1.23; 95% confidence interval [CI]:

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

1.11, 1.37), and a reduced rate when used with nateglinide (RR: 0.73; CI: 0.56, 0.96). The highest RR was observed in enalapril used with repaglinide (RR: 2.14; CI: 1.48, 3.10).

Conclusions: We found an association between serious hypoglycemia and certain combinations of ACEIs and insulin secretagogues. The magnitude of association varied depending on object-precipitant combinations. Underlying mechanisms also seemed to vary across object-precipitant drugs, including pharmacokinetic interactions, ACEI-mediated increase in insulin sensitivity, and potentially other mechanisms unknown.

5084 | Real-world evidence of inhaled corticosteroids and type ii diabetes manifestation

Yasser Albogami[1,2], Yu-Jung Wei[1], Michael J. Daniels[3], Kenneth Cusi[4] and Almut G. Winterstein[1]

[1]Department of Pharmaceutical Outcomes & Policy, University of Florida, Gainesville, FL; [2]Clinical Pharmacy Department, King Saud University, Riyadh, Saudi Arabia; [3]Department of Statistics, University of Florida, Gainesville, FL; [4]College of Medicine, University of Florida, Gainesville, FL

Background: The clinical literature is replete with divergent conclusions regarding inhaled corticosteroid (ICS) and type II diabetes manifestation (T2DM). Adjustment for unmeasured confounders using active comparators and linked subsample survey data, and consideration of surveillance bias might better approximate clinical trial results, which show no ICS diabetogenic risk.

Objectives: To evaluate the diabetogenic risk of ICS in asthma patients using real-world data.

Methods: We identified ~3.5 million adult asthma patients with no history of diabetes in IBM MarketScan Commercial Claims data from 2005-2017. Patients were categorized into new users of low-dose ICS or non-ICS anti-inflammatory agents, which comprised leukotriene antagonists and theophylline. We defined the outcome as the initiation of any hypoglycemic agent. In analysis 1, we estimated the hazard ratio (HR) comparing the risk of T2DM between low-dose ICS and non-ICS users in an as-treated framework. Analysis 2 included a comparison between low-dose ICS durations using non-ICS as the reference. We applied marginal structural model in analysis 3 to evaluate whether high doses of ICS are associated with T2DM compared to low dose. In each analysis, we adjusted for potential confounders using inverse probability of treatment weights. We further attempted to adjust for obesity and tobacco use using linked survey data from a subsample to perform multiple imputation of unmeasured confounders. Finally, sensitivity analyses including, high-dimensional propensity score, adjustments for outcome latency and surveillance bias, were conducted to test the robustness of the study results.

Results: The study sample comprised 104,198 low-dose ICS and 59,172 non-ICS new users, respectively. The study groups exhibited similar characteristics including comorbidities. The incidence rate of T2DM was 10.6 and 12.6 per 1000 person-time for low-dose ICS and non-ICS users, respectively. After adjusting for confounders, the HR was 0.83 (95%CI 0.66-1.03). One-year exposure to low-dose ICS compared to non-ICS yielded HR of 0.75 (95%CI 0.60-0.93) while more than a year of exposure showed HR of 0.67 (95%CI 0.21-2.01). A dose-response of an ICS diabetogenic effect was observed (high-dose vs. low-dose: HR 1.62 (95%CI 1.21-2.16); moderate-dose vs. low-dose: HR 1.23 (95%CI 1.03-1.46)). The study estimates remained consistent in various sensitivity analyses.

Conclusions: Low dose ICS did not show diabetogenic effects regardless of evaluated exposure duration. However, we noted a dose-response effect, suggesting caution when escalating ICS dose in clinical practice.

Safety End Points -> Neurological/Mental Health

56 | The association between initiation of gabapentinoids and lower-extremity oedema treated with loop-diuretics: A symmetry analysis

Daniel P. Henriksen and Jesper Hallas

Department of Public Health, University of Southern Denmark, Odense, Denmark

Background: Based on pooled data from trials, as well as case-reports, an association between gabapentinoids (gabapentin and pregabalin) with lower-extremity oedema could exist. The adverse effect could lead to prescribing loop-diuretics - a so-called prescription cascade. However, this association has not been quantified on a population-based level.

Objectives: To assess the association between initiation of gabapentinoids and lower-extremity oedema treated with loop-diuretics, in a self-controlled design.

Methods: A symmetry analysis was employed on all adults living on the island of Funen (pop: 493 000 in 2016) who filled in their first prescription of a gabapentinoid in the period of 2000-2016 and initiated a loop-diuretic (furosemide or bumetanide) three months prior to or after this date. Patients with a diagnosis of heart failure or chronic kidney disease were excluded from further analysis. A symmetrical distribution of prescriptions before and after gabapentinoid-initiation is expected if no association between gabapentinoids and loop-diuretics exist (i.e. a sequence ratio (SR) of 1.0). The symmetry analysis design is robust to confounders that are stable over time. Sensitivity analyses were performed in regards to the observation window time (one month, six months, and one year).

Results: A total of 672 patients filled in their first-ever prescription of both a gabapentinoid and loop-diuretics within a 3-month interval; 383 patients filled their prescription of gabapentinoids prior to their prescription of loop-diuretics, and 245 patients redeemed their prescriptions in the opposite order (SR 1.56, 95%CI 1.34-1.84). Younger age (below 65 years) was associated with a slightly increased SR compared to older age ($SR_{younger}$: 1.74, 95%CI 1.38-2.24 versus SR_{older}: 1.43, 95%CI 1.16-1.79). When restricting the time window to 30 days and 180 days prior to and after gabapentinoid-initiation, the SRs were

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

also increased ($SR_{30\ days}$: 1.68, 95%CI 1.32-2.18, $SR_{180\ days}$: 1.52, 95% CI 1.35-1.73).

Conclusions: We found an increased risk of treatment with loop-diuretics after initiating gabapentinoids. The results align with evidence from pooled RCTs and case reports and could be due to a prescription cascade.

3731 | Falls and fractures in patients treated for Parkinson's disease-related psychosis: Comparing an established class to a more recently introduced treatment

J. Bradley Layton[1], Joan Forns[2], Colleen Dempsey[3], Mary Ellen Turner[3], Jennifer Bartsch[1], Mary S Anthony[1], Mary E. Ritchey[1] and George Demos[4]

[1]RTI Health Solutions, Research Triangle Park, NC; [2]RTI Health Solutions, Barcelona, Spain; [3]ACADIA Pharmaceuticals, Princeton, NJ; [4]ACADIA Pharmaceuticals, San Diego, CA

Background: Patients with Parkinson's disease psychosis (PDP) are at increased risk for falls. PDP is commonly treated with atypical antipsychotics (AAP), although United States (US) labeling for AAP includes a warning of falls. Pimavanserin is an AAP approved by the US FDA for treatment of hallucinations and delusions associated with PDP.

Objectives: To compare the risk of falls/fractures among patients diagnosed with PDP treated with pimavanserin as compared to AAP.

Methods: We identified a cohort of patients aged ≥ 40 years initiating pimavanserin or another AAP (clozapine, quetiapine, risperidone, olanzapine, aripiprazole, brexpiprazole) following diagnosis of both PD and psychosis in US commercial and supplementary Medicare claims (2015-2018). Falls and fractures were identified through diagnosis and procedure coding. Patients initiating AAP were 2:1 matched with patients initiating pimavanserin using propensity scores, and the incidence rates (IR) of falls/fractures were compared with incidence rate ratios (IRR) and 95% confidence intervals (CI).

Results: We identified 56 eligible patients initiating pimavanserin and 607 initiating another AAP. Pimavanserin initiators were younger (mean, 75 vs. 79 years, respectively) and had lower prevalences of many comorbidities and falls/fracture risk factors than initiators of another AAP, including use of ambulance/life support (55% vs 77%), heart failure (32% vs. 46%), stroke/brain injury (48% vs. 58%), paralysis (5% vs. 15%), and delirium (77% vs. 84%). However, patients taking pimavanserin had more indicators of PD- and PDP-related symptoms and treatment than patients taking another AAP, including dementia (96% vs. 90%), anticholinesterase inhibitors use (54% vs. 42%), and PD medications (96% vs. 75%). The crude IRs (cases/100 person-years) (95% CI) for falls/fractures were: pimavanserin, 20.1 (5.5-51.4); AAP, 45.8 (37.8-54.9). Matching retained 42 patients taking pimavanserin and 84 patients taking another AAP, although many covariates remained imbalanced. The resulting matched IRR (95% CI) was 0.43 (0.08-1.49).

Conclusions: Sample sizes were too small to draw conclusions about the comparative risk of falls/fractures in users of pimavanserin versus another AAP. There were systematic differences between treatment groups, and pimavanserin initiators had greater PDP-specific care and treatment. This is an example of treatment dynamics where differences between the newly introduced drug and the established class are not adequately addressed through confounding adjustment.

3872 | Risk of seizure in people with autism spectrum disorder using antipsychotic medication: A population based study

Basmah Alfageh, Tian-Tian Ma, Frank M. C. Besag, Kenneth K. C. Man, Ian C. K. Wong and Ruth Brauer

University College London, London, United Kingdom

Background: In individuals affected by autism spectrum disorder (ASD), antipsychotic medications are commonly prescribed. Both first and second generation antipsychotics can potentially increase the risk of seizures. There are many case reports regarding antipsychotic induced seizures, but no analytical study thus far has investigated the strength of this association.

Objectives: To examine the association between antipsychotics use and risk of incident seizure in individuals with ASD.

Methods: This is a retrospective cohort study using The Health Improvement Network (THIN) as data source. The medical records of a cohort of individuals with recorded ASD from Jan 1996 to Sep 2017 was extracted. Exposure was defined as a receipt of at least one prescription for antipsychotics. The comparison group comprised individuals on psychotropic medication other than antipsychotics. Patients were followed up from the first day of medication prescription (index date) until developing the outcome or until the first of the following dates: the last day of the prescription, the last date of data collection, the transfer out date, death date; whichever came first. Patients with a history of seizures were excluded. Propensity score fine stratification weighting with 50 strata was applied. Standardized mean differences (SMD) were estimated to examine the balance of covariate distribution between both groups. Hazard ratios (HR) of incident seizure were estimated using Cox proportional hazard model.

Results: A total of 17,744 individuals with autism in receipt of prescriptions for any type of psychotropic medication were identified; 1583 of them had a history of seizures and were excluded. The risk of incident seizure was compared between 4426 participants exposed to antipsychotics and 11735 participants in the comparison group. The mean age of the participants was 20.84 ± 13.43 years and 23.9 % of the total cohort were females. The mean follow-up period for the exposed group was 3.08 ± 3.48 years, and 2.28 ± 2.70 years for the comparison group. In the PS weighted model, all covariates were balanced between the two study groups with SMD less than 0.1. 333 individuals had a record of incident seizure during follow-up. The adjusted model showed evidence of a lower risk of seizures in individuals with autism prescribed antipsychotics (HR 0.67, 95% CI 0.53-0.84).

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusions: This large cohort study found no evidence of an increased risk of seizures in individuals with autism exposed to antipsychotic agents. Further studies using different source of data are needed to support these findings.

4110 | Evidence of fluoroquinolone-induced acute neurological dysfunction in large adult population

Darcy E. Ellis[1], Qing Liu[2], Theoklis E. Zaoutis[1], Athena F. Zuppa[3], Allison W. Willis[1], Rebecca A. Hubbard[1] and Sean Hennessy[1]
[1]*University of Pennsylvania, Philadelphia, PA;* [2]*University of Pennsylvania, Philadelphia, PA;* [3]*Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Fluoroquinolones (FQs), one of the most commonly prescribed antibiotic classes, have been inconsistently associated with central nervous system (CNS) adverse events, which highlights the need for epidemiologic studies of the neurological safety of FQs.
Objectives: To evaluate the safety of FQs with regard to risk of diagnosed CNS dysfunction.
Methods: *Design:* Propensity score-matched inception cohort study which used claims data from a commercially insured adult population (OptumInsight). *Setting:* Our study included adults aged 18 years and older who were prescribed a FQ or comparator antibiotic between 2004 and 2015 for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, or acute bronchitis. *Exposures:* The exposures of interest included all U.S. approved oral FQ antibiotics, versus amoxicillin, amoxicillin plus clavulanic acid, azithromycin, and cefixime as the comparator group. *Outcomes:* Time from prescription to CNS dysfunction, defined as an ICD-9 code for seizures/convulsions, intracranial hypertension, psychosis/delirium, or altered mental status/encephalopathy. Patients were censored at the earlier of 120 days after antibiotic fill or disenrollment from the health plan. *Statistical analysis:* Cox proportional hazards models were estimated using propensity scores fitted using the variables age, sex, epilepsy, hereditary peripheral neuropathy, renal dysfunction, diabetes, gabapentinoid use, statin use, isoniazid use, and chemotherapy use, to match FQ and comparator antibiotic users.
Results: After propensity score matching, our cohort contained 647,876 individuals exposed to an FQ antibiotic matched 1:1 with a comparator. Forty-eight percent (n=308,998) of the FQ-exposed were prescribed an antibiotic for acute bronchitis, 44% (n=287,098) for acute bacterial sinusitis, and 8% (n=51,780) for acute bacterial exacerbation of chronic bronchitis. Matching produced balance (standardized mean difference < 0.1) on all variables included in the propensity score. The hazard ratio associated with FQ exposure was 1.30 (95% confidence interval 1.25-1.35), which was statistically significant (p-value<0.05).
Conclusions: After controlling for potential confounders through propensity score matching, we found a statistically significant association between FQ antibiotic use and development of CNS dysfunction in the adult population.

4263 | Do interruptions to the continuity of methadone maintenance treatment (MMT) in specialist addiction settings increase the risk of drug-related poisoning (DRP) deaths? A retrospective cohort study

Grainne Cousins[1], Louise Durand[1], Denis O'Driscoll[2], Fiona Boland[3], Eamon Keenan[4], Benedict Ryan[1], Joe Barry[5], Kathleen Bennett[6], Tom Fahey[7] and Tom Fahey[7]
[1]*Royal College of Surgeons in Ireland, Dublin, Ireland;* [2]*HSE Addiction Services, Dublin, Ireland;* [3]*Royal College of Surgeons in Ireland, Dublin, Ireland;* [4]*HSE National Social Inclusion Office, Dublin, Ireland;* [5]*Trinity College Dublin, Dublin, Ireland;* [6]*Royal College of Surgeons in Ireland, Dublin, Ireland;* [7]*Royal College of Surgeons in Ireland, Dublin, Ireland*

Background: Despite evidence supporting the benefits of opioid substitution treatment (OST), a recent UK study of deaths among patients in receipt of OST identified an elevated risk of mortality in the month following transfer of patients to an alternative treatment provider for continuation of OST.
Objectives: To examine risk of mortality associated with interruptions to the continuity of methadone maintenance treatment (MMT) in opioid dependent individuals attending specialist addiction services.
Methods: Retrospective cohort study using addiction services and primary care dispensing records, national methadone treatment register and national drug related death index (NDRDI). A total of 2,899 people prescribed and dispensed methadone in specialist addiction services in Dublin, Ireland between January 2010 and December 2015. Person-time in five exposure groups was determined: weeks 1-4 following transfer between treatment providers; weeks 1-4 out of treatment; weeks 5-52 out of treatment; weeks 1-4 of treatment initiation; and weeks 5+ of continuous treatment (reference category). The primary outcome was drug related poisoning (DRP) deaths, secondary outcome: all-cause mortality (ACM). Mortality rates calculated by dividing number of deaths (DRP; ACM) in exposure groups by person-years (PY) exposure. Unadjusted and adjusted Poisson regression (covariates age, sex, incarceration, methadone dose and co-morbidities) estimated differences in mortality rates.
Results: 154 ACM deaths (1.14 per 100 PY, 95% CI 0.96-1.32), 55 (35.7%) identified as DRP deaths (0.41 per 100 PY, 95% CI 0.30-0.52). No deaths were observed in the first month following transfer between treatment providers. The risk of DRP mortality was highest in weeks 1-4 out of treatment (1.29 DRP per 100 PY; ARR 4.04, 95% CI 1.43-11.43, p=0.009) and weeks 1-4 of treatment initiation (1.11 DRP per 100 PY; ARR 3.4, 95% CI 1.2-9.64, p =0.02). Similarly, risk of ACM was highest in weeks 1-4 out of treatment (9.32 ACM per 100 PY; ARR 11.78, 95% CI 7.73-17.94, p<0.001), weeks 1-4 of treatment initiation (4.17 ACM per 100 PY; ARR 5.11, 95% CI 2.95-8.83, p<0.001) and weeks 5-52 off treatment (ARR 2.04, 95% CI 1.2-3.47, p=0.009).
Conclusions: Interruptions to the continuity of MMT by treatment provider do not appear to be periods of risk for DRP or ACM deaths. Risk of DRP or ACM deaths appears to be greatest during the first four weeks of treatment initiation/re-initiation and after treatment cessation.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4280 | Lack of association between proton pump inhibitor intake and brain aging: A population based cross-sectional study

Nayeon Ahn[1,2], Stefan Frenzel[3], Katharina Wittfeld[3,4], Henry Völzke[5], Markus M. Lerch[6], Jean-Francois Chenot[5], Ulf Schminke[7], Michael Nolde[1,2], Ute Amann[1,2], Christa Meisinger[1,2], Jakob Linseisen[1,2], Sebastian E Baumeister[1,2], Hans-Jörgen Grabe[3,4] and Ina-Maria Rückert-Eheberg[1,2]

[1]*Chair of Epidemiology of the LMU Munich at UNIKA-T, Augsburg, Augsburg, Germany;* [2]*Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany;* [3]*Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany;* [4]*German Center for Neurodegenerative Diseases (DZNE), Greifswald, Germany;* [5]*Institute of Community Medicine, University Medicine Greifswald, Greifswald, Germany;* [6]*Department of Medicine A, University Medicine Greifswald, Greifswald, Germany;* [7]*Department of Neurology, University Medicine Greifswald, Greifswald, Germany*

Background: Much attention in the scientific community has been paid to suspected associations of the intake of proton pump inhibitors (PPIs) with dementia or cognitive decline. However, no consensus has been established yet.

Objectives: This study aimed to investigate correlations between PPI-intake and brain aging in the general population. For the primary analysis, we examined brain volumes as proxies to indicate dementia and estimated brain age as a derived outcome of 169 brain regions and the ventricular system. In the secondary analysis, we modelled the association of PPI-intake with verbal memory tests.

Methods: From two surveys of the Study of Health in Pomerania (SHIP) conducted in Greifswald, Germany, 2,653 individuals (39.3%) underwent brain MRI and were included in the primary analysis: They were divided into two groups according to PPI-intake and compared with regard to brain volumes (gray matter, white matter, total brain, and hippocampus) and estimated brain age. Linear regression models were computed and adjusted for age, sex, intracranial volume, height, brain lesion or vascular risk factor, education, income, smoking, alcohol consumption, total cholesterol/HDL-cholesterol ratio, glycated hemoglobin, systolic blood pressure, body mass index, study cohort effect, and use of a selection of other drug groups. To account for selective participation in the MRI exam, inverse probability weighting was applied. In the secondary analysis, cognitive function was evaluated by the Verbal Learning and Memory Test (VLMT) and the Nuremberg Age Inventory (NAI) and put in relation to PPI-intake irrespective of participation in the MRI scan (n=5,711).

Results: No significant associations were found between PPI-intake and brain volumes or estimated brain age in adjusted linear regression models, with 0.8ml larger total brain volume (95% CI: -6.5 to 8.1 ml, p=0.831), 0.006ml smaller hippocampus (95% CI: -0.1 to 0.1 ml, p=0.919), and a 0.67 years older brain (95%CI: -0.50 to 1.84 years, p=0.259) in PPI users (n=170, 6.4%). Of two verbal memory assessments, VLMT showed a significant negative correlation with PPI intake, presenting a 1.09 lower score (95% CI: -2.04 to -0.14, p= 0.025) in immediate recall (score range: 0-45 points) and a 0.72 lower score (95% CI: -1.22 to -0.22, p=0.005) in delayed recall (score range: 0-15 points). NAI was not associated with PPI use.

Conclusions: In our study, PPI-intake was not associated with brain aging as assessed by MRI examination. However, since plausible effects of PPIs on brain physiology have been proposed, further studies and longitudinal analyses are warranted.

4388 | Trends in age- and sex-specific rates of suicide and suicide by drug poisoning in the United States: 1999-2017

Dinci Pennap, Scott Swain and Andrew Mosholder

FDA, Silver Spring, MD

Background: U.S. Mortality rates from suicide have increased over roughly the same period as opioid-related mortality. An assessment of patterns and trends of drug- and opioid-related suicide could inform pharmacoepidemiology studies of suicide-related outcomes.

Objectives: To assess total suicide rates, suicides by drug poisonings, and opioid-related suicide poisonings as a proportion of total suicides, by age-group and gender.

Methods: We assessed annual suicide rates, suicide drug poisonings, and suicide by opioid poisoning, among individuals ≥15 years old using mortality data from the Centers for Disease Control and Prevention's Wide-ranging ONline Data for Epidemiologic Research from 1999-2017. Suicide was defined as all underlying causes of death with suicidal intent, suicide by drug poisoning was defined as any intentional poisoning by drugs, medicaments or biological substances [International Classification of Diseases, Tenth Revision (ICD 10) codes T36.0 - T50.0] and opioid-related suicide was defined as intentional poisoning by opium (T40.0), heroin (T40.1), methadone (T40.3), other opioids (T40.2), or other synthetic narcotics (T40.4). Annual mortality rates per 100,000 population were age-adjusted to the 2000 U.S. population and calculated overall and by sex and age-group (15-24, 25-64, and ≥65 years old).

Results: Age-adjusted suicide rates per 100,000 population rose steadily during the study period, from 13.2 in 1999 to 17.6 in 2017. Males consistently had approximately a 4-fold higher suicide rate compared to females. Suicide by drug poisoning increased from 1.5 to 2.0 per 100,000, with similar rates in males and females. Adjusted rates of opioid-related suicide ranged from 0.3-0.7 per 100,000 and accounted for 19.5% of drug poisoning suicides in 1999 compared to 35.1% in 2017. Opioid suicides represented 2.2% of suicides in 1999 and 4.1% in 2017; by gender, the proportion of all suicides due to opioids increased from 5.7% in 1999 to 10.3% in 2017 among females and from 1.4% to 2.4% among males. Gender differences were particularly pronounced among individuals ≥65 years old; across the study period, the proportion of suicides due to opioids increased from 3.9% to 15.4% among females and from 0.7% to 2.0% among males.

Conclusions: Opioid-related suicides nearly doubled during the past 2 decades. However, the increase in suicides in the overall U.S. population during the same span are not accounted for by

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

increases in intentional opioid poisoning or intentional drug poisoning. Event rates varied considerably by age and gender.

4561 | A synthetic control arm from observational data to estimate the background incidence rate of an adverse event (Pneumonia) in alzheimers disease subjects

Innocent Ngwa and Christian Mueller. F
Hoffmann La Roche, Basel, Switzerland

Background: Proactively identifying adverse events(AE) in Alzheimer's Disease (AD) clinical trials is challenging due to the blinded nature of the studies and the large number of background medical events occurring in older subjects over long trial durations. An accurate incidence estimate of an AE in non-treated AD subjects and prognostic factors affecting that AE incidence may help contextualize unexpected drug-related safety findings during clinical trials without compromising blinding.

Objectives: To estimate the background incidence proportion of an AE (pneumonia) and generate a synthetic control arm to explore prognostic factors that affect the incidence of Pneumonia in AD subjects.

Methods: A retrospective case-control study used Pharmetrics US claims data from 01/01/2014 to 31/12/2018 and high dimensional propensity scoring matching mild to severe cognitive AD patients aged 50-89 years to controls. The inclusion and exclusion criteria were matched to a selected phase 3 clinical trial in AD. Supplementary inclusion criteria included: at least two diagnoses of AD using ICD9/ICD10 within 90 days and at least 90 days of continuous enrollment in the database prior to the index date. Patients with a history of immune-related diseases were excluded. The following symptomatic (non-disease modifying) treatments were allowed in the AD cohort; Memantine, Galantamine, Donepezil or Rivastigmine. A negative binomial regression model was designed to estimate the expected count of pneumonia as a function of the AD diagnosis, propensity score, patient age at index, gender, disease history, and Charlson Comorbidity Index (CCI).

Results: 31,107 AD patients (62.55% females; mean age 75.7 [SD 8.3] years) were identified. Within 5 years of AD diagnosis, 4692 patients were diagnosed with pneumonia. The incidence rate (95% CI) of pneumonia in AD patients was 113.07 (109.84 - 116.31) per 1000 patient-years.

Increasing age (IRR 1.06) and male gender (IRR 1.5) and CCI (IRR 1.25) were associated with an increased risk of pneumonia in AD patients.

Conclusions: Incidence rates analysis and the use of synthetic control arms from observational data may help estimate the background incidence rate of AEs and potential prognostic factors in AD patients. This may be beneficial in identifying unexpected drug-related safety findings during a blinded trial thus preventing undue patient harm.

4978 | Real-world comparative risk of rhabdomyolysis with cholinesterase inhibitors for Alzheimer's disease

Pamela B. Landsman-Blumberg
TriNetX, Cambridge, MA

Background: The Pharmacovigilance Databases of the United States and Canada showed that rhabdomyolysis was reported more often in patients using donepezil compared with other cholinesterase inhibitors (odds ratio [OR] 11.00, 95% confidence interval [CI] 10.39-27.41). A recent analysis using linked claims data from Ontario, Canada also found a higher risk among user of donepezil, however to a much smaller degree.

Objectives: This study evaluates the 30-day risk of rhabdomyolysis following the initiation of donepezil vs other cholinesterase inhibitors in the US.

Methods: A retrospective analysis of the 30-day risk of rhabdomyolysis (ICD10 M62.82, T79.6) after receipt of a cholinesterase inhibitor prescription was conducted using TriNetX Dataworks, a federated network of EMR data from health care organizations across the US. Adults aged 66 years or older who initiated treatment with donepezil, rivastigmine, or galantamine and had at least 1 encounter > 180-days pre and between 30- and 90-days post-index were selected. Those with multiple prescriptions for the same agent within 180 days prior to and 30 days following the identified cholinesterase inhibitor were excluded. Eighty three covariates, similar to those in the Canadian claims data analysis, were included in the model to produce the propensity scores (PS): demographics, comorbidities, concomitant medications, and encounter types in the 180-days prior to index treatment. Comparison of donepezil to rivastigmine or galantamine was measured by ORs and their 95% CIs. ORs were measured both before and following 1:1 PS Greedy matching.

Results: Donepezil (n=75,003) and rivastigmine/galatamine (n=13,448) were matched 1:1 resulting in 13,439 patients in each cohort for the adjusted analyses. The average age of the overall population was 77.6 years at index, 56.0% was female, 79.3% were white, and 8.9% black. Before matching donepezil was associated with higher odds of a rhabdomyolysis encounter compared to rivastigmine or galantamine (37 events or 0.049% vs 16 events or 0.119%; odds ratio 0.41, 95% CI 0.23-0.74). Post-matching there was no difference in the odds of rhabdomyolysis (10 events or 0.074% vs 16 events or 0.119%; odds ratio 0.63, 95% CI 0.28-1.38) between the cholinesterase inhibitors.

Conclusions: Contrary to both pharmacovigilance case reports and a population-based claims database from Canada, donepezil was not associated with a higher 30-day risk of rhabdomyolysis compared with initiating rivastigmine or galantamine in the US EMR analysis.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5009 | Potentially inappropriate medication use in combination with opioids among older dental patients

Jifang Zhou[1], Gregory Calip[2], Susan Rowan[3], Jessina McGregor[4], Rosanne Perez[5], Charlesnika Evans[6], Walid Gellad[7] and Katie Suda[7]
[1]*University of Illinois at Chicago, Chicago, IL;* [2]*University of Illinois at Chicago, Chicago, IL;* [3]*University of Illinois at Chicago, Chicago, IL;* [4]*Oregon State University, Corvalis, OR;* [5]*University of Illinois at Chicago, Chicago, IL;* [6]*Northwestern University Feinberg, Chicago, IL;* [7]*University of Pittsburgh, Pittsburgh, PA*

Background: Opioid analgesic medications are frequently prescribed in dental settings. Yet for older patients, who are commonly on multiple medications for comorbid conditions, this introduces an added risk of severe adverse effects attributable to the concomitant use of opioids.

Objectives: To evaluate the prevalence of inappropriate opioid prescribing as defined by Beers® Criteria and risks of 30-day emergency room (ER) visits and all-cause hospitalization among commercially-insured dental patients ages 65 years and older.

Methods: *1. Design, Setting and Participants* Retrospective cohort study of patients ages 65 years and older receiving opioids on the day of their dental visit in the Truven Health MarketScan® databases between 2011 and 2015. *2. Exposure* Combined use of opioids with potentially inappropriate medications per the Beers Criteria, including benzodiazepines, gabapentin, pregabalin and/or two central nerve system-active drugs. *3. Main outcome measures* All-cause acute care utilization over the 30-day period after dental encounters. *4. Statistical analysis* Multivariable modified Poisson regression models were used to estimate relative risks (RR) and 95% confidence intervals (CI) with adjustment for age, sex, comorbidity, mental health disorders, recent hospitalization and ER visits during the 3-month period prior to dental visits and opioid formulation and dose.

Results: In a cohort of 40,800 older dental patient-visits where opioids were prescribed (mean age 71.6 [SD 6.6] years; 45.0% female), the prevalence of potentially inappropriate mediations in combination with opioids per Beers Criteria was 10.4%. A total of 947 all-cause acute care events were observed in the 30 days post-dental visit. Patients with opioids prescribed at dental visits with potentially inappropriate Beers Criteria medications had higher rates of acute care use (3.3% vs. 2.2%, p<0.001) and was associated with an increased risk of all-cause acute care utilization (adjusted RR 1.23; 95% CI 1.02-1.48). A suggestion of a dose-response with increasing oral morphine equivalents prescribed was observed (P<0.0001).

Conclusions: A non-trivial number of older patients receiving opioids at dental visits were also using psychotropic medications, and this medication combination should be avoided according to the American Geriatric Society Beers® Criteria. Dental practitioners deserve access and resources for comprehensive medication reconciliation to minimize the risks of adverse events when prescribing opiate analgesics.

Safety End Points -> Other

43 | Combined oral contraceptive utilization and uterine fibroid incidence in a novel cohort

Sarah R. Hoffman[1], Jennifer S. Smith[1], Michele Jonsson Funk[1], Michael G. Hudgens[1], Charles Poole[1], Wanda K. Nicholson[2], Donna D. Baird[3] and Quaker E. Harmon[3]
[1]*UNC Gillings School of Global Public Health, Chapel Hill, NC;* [2]*UNC School of Medicine, Chapel Hill, NC;* [3]*National Institute of Environmental Health Sciences (NIEHS), Durham, NC*

Background: To date, published studies regarding the association between combined oral contraceptive (COC) use and uterine fibroid (UF) development have lacked prospective imaging with ultrasound to examine incidence of UFs. To address this limitation, the Study of Environment, Lifestyle, and Fibroids prospectively followed fibroid-free, African-American women (the group with the highest disease burden in the U.S.) to identify incident cases.

Objectives: We examined associations between COC use and the 40-month cumulative risk of UF among women who were fibroid-free at baseline ultrasound.

Methods: History of hormonal contraceptive (HC) use (including age at first use, duration of and time since last use) was collected via telephone interview at enrollment. UF identification was performed using transvaginal ultrasonography at baseline, and 20 and 40-months of follow-up. Inverse probability (IP) weights were constructed for all exposures and censoring (hysterectomy, loss to follow-up). The covariate set for estimating IP weights included: age, age at menarche, Depo-Provera, implant and hormonal IUD use, time since last birth, parity, BMI, and education. Censoring weights also included the COC exposure of interest, income, employment, smoking, and history of heavy menstrual bleeding. Weighted risk ratios (wRR) and 95% confidence intervals (CI) were estimated using the robust sandwich estimator.

Results: Participants were from a community sample in Detroit, Michigan Area, aged 23-35, with no prior diagnosis of UF. Of the 1,308 participants in the analysis sample, 70% had used COCs and 17% developed UF by 40 months. A total of 198 women were censored: 11 (<1%) underwent hysterectomy and 187 (14%) were lost to follow-up. There was an inverse association between ever use of COCs and cumulative UF incidence (wRR: 0.78; 95% CI: 0.60, 1.00). Among ever users of COCs, age at first use ≥17 yrs was associated with an elevated risk of UF (wRR: 1.25; 95% CI: 0.89, 1.76). Among women who had used COCs, wRRs for durations of 1-<2 yrs, 2-<5 yrs, and ≥5 yrs were 1.49 (95% CI: 0.94, 2.38), 1.10 (95% CI: 0.69, 1.74), and 1.30 (95% CI: 0.83, 2.04) comparing each to <1 yr of use. Comparing each level of time since last use to current use, wRRs were 1.23 (95% CI: 0.72, 2.10) for 1-2 yrs, 0.96 (95% CI: 0.50, 1.85) for 3-<5 years, and 0.87 (95% CI: 0.55, 1.37) for ≥5 yrs.

Conclusions: This first prospective, ultrasound-based study to examine COCs as a risk factor for UF showed no consistent patterns of association to suggest either risk or protection. Given the high

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

prevalence of both COC use and UF, larger replication studies are warranted.

48 | Risk of cataract in primary immune thrombocytopenia adult patients treated with eltrombopag

Margaux Lafaurie[1,2,3], Bérangere Baricault[1,3], Vincent Soler[4], Myriam Cassagne[4], Laurent Sailler[5,2,3], Maryse Lapeyre-Mestre[1,2,3], Agnès Sommet[1,2,3] and Guillaume Moulis[5,2,3]

[1]Clinical Pharmacology Department, University Hospital Center, Toulouse, France; [2]UMR 1027 INSERM - Université de Toulouse, Toulouse, France; [3]CIC 1436, University Hospital Center, Toulouse, France; [4]Department of Ophthalmology, University Hospital Center, Toulouse, France; [5]Department of Internal Medicine, University Hospital Center, Toulouse, France

Background: In preclinical studies, eltrombopag (ELT), a thrombopoietin receptor agonist, has been associated to a dose and time-dependent increased incidence of cataract in mice and rats. In the extension study, 9,3% of the patients developed or worsened cataract over a median duration of exposure of 2.4 years. However, about 80% had at least an additional risk factor. Real-life studies are lacking.

Objectives: We aimed to assess the risk of cataract with ELT in the real-life practice in a nationwide cohort of primary ITP adults.

Methods: The population was the FAITH cohort which is the cohort of all incident primary ITP adult patients in France from June 2010 to June 2017. This cohort was identified within the national health insurance database using a validated algorithm. A nested case-control study was conducted. Cases were patients who had a surgery for cataract after ITP onset. Up to 5 controls for each case were matched on age, sex, and duration of disease. Exposure to ELT was searched within out-hospital dispensing data between ITP onset to index date. We used 2 definitions: i)"ever exposed" compared with "never exposed"; ii) cumulative exposure quantified by the numbers of Defined Daily Doses DDDs, categorized as follows "never exposed", 1-364 DDDs and ≥365 DDDs. Covariables were the presence of diabetes mellitus, cumulative exposure to corticosteroids, and the presence of ophthalmological risk factors for cataract. Conditional logistic regression models were used to compute adjusted odds ratios (aOR) and their 95% confidence intervals (CI).

Results: The cohort included 8,464 incident primary ITP adults. During the follow-up (31,448 patient-years), 1,089 patients were exposed to ELT, including 310 with a cumulative exposure ≥365 DDDs. Overall, 573 patients had a surgery of cataract; incidence: 1.91/100 person-years (95% CI: 1.76-2.07) and 1.51/100 person-years (95%CI: 1.17-1.96) in the "ever exposed" to ELT subgroup. The 573 cases were matched with 2,638 controls. Fifty-seven (9.9%) cases and 285 (10.8%) controls were "ever exposed" to ELT; 14 (2.4%) a,d 64 (2.4%) had a cumulative exposure ≥ 365 DDDs, respectively. Cases were more frequently exposed to corticosteroids, with a higher cumulative exposure, and had more ophthalmological risk factors. In the "ever/never" exposed analysis, the aOR for ELT was 0.82 (95% CI: 0.60-1.12). The aOR was 0.81 (95% CI: 0.57-1.14) in the 1-364 DDDs group, and 0.86 (95% CI: 0.48-1.56) in the 365 DDDs group, as compared with the "never exposed" group, respectively.

Conclusions: This nationwide study did not find an increased risk of cataract in primary ITP patients treated with ELT.

101 | Sex differences in hospital admissions related to adverse drug reactions

Linda C. Hendriksen[1,2], Paul D. van der Linden[2], Ron M.C. Herings[3], Bruno H. Stricker[1] and Loes E. Visser[1,4]

[1]Erasmus Medical Center, Rotterdam, Netherlands; [2]Tergooi Hospital, Hilversum, Netherlands; [3]PHARMO Institute, Utrecht, Netherlands; [4]Haga Teaching Hospital, The Hague, Netherlands

Background: Adverse drug reactions (ADRs) are a major health concern and are responsible for approximately 5% of all acute hospital admissions. Women are 1.5-1.7 times more likely to develop ADRs than men. Differences in ADR-related admissions between women and men have been described before in studies on spontaneous ADR reports and in an earlier study where adjusting for potential confounders was not possible due to its ecological design.

Objectives: The main objective of this study was to investigate whether there are sex differences in ADR-related hospital admissions and examine whether women or men are more prone to develop particular drug-ADR combinations.

Methods: Patients were selected from the PHARMO Database Network, consisting of over four million residents of the Netherlands with an average follow-up of ten years. ADR-related hospital admissions between 2005 and 2017 were identified using hospital discharge codes indicating an ADR of a drug group used at a therapeutic dose, conform the ICD 9 and 10 coding system. Patients aged ≥ 16 years who had a dispensing of the relevant drug within three months before the hospital admission were included. Drug-ADR combinations with at least 50 hospital admissions for women or men were examined, excluding sex-specific ADRs. Age-adjusted odds ratios (OR) with 95% CIs for drug-ADR combinations for women versus men were calculated with respect to the number of female and male users.

Results: There were a total of 18,469 hospital admissions involving women (0.35% of the total number of admissions) and 14,678 admissions involving men (0.35% of the total number of admissions) due to an ADR. ORs were calculated for 48 drug-ADR combinations. There were 10 combinations with a statistically significantly higher risk in women versus men and 8 in men versus women. The most substantial differences were seen in ADRs due to anticoagulants and diuretics. Anticoagulants showed a lower risk of hospital admissions with persistent haematuria (OR 0.31; 95% CI 0.21, 0.45) haemoptysis (OR 0.47, 95% CI 0.30, 0.74) or subdural haemorrhage (OR 0.61; 95% CI 0.42, 0.88) in women than in men and a higher risk of rectal bleeding in women (OR 1.48; 95% CI 1.04, 2.11) than in men. Also, there was a higher risk of hospital admission in women using thiazide diuretics

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

causing hypokalaemia (OR 3.03; 95% CI 1.58, 5.79) and hyponatraemia (OR 3.33, 95% CI 2.31, 4.81) than in men.

Conclusions: Sex differences exist for ADR-related hospital admissions due to anticoagulants and diuretics. Further research into the mechanisms of and potential confounders for these observed differences can contribute to the development of sex-specific guidelines.

106 | Development and validation of a machine learning algorithm to identify anaphylaxis in US administrative claims data

Daniel C. Beachler[1], Devon H. Taylor[1], Mary S. Anthony[2], Ruihua Yin[1], Ling Li[1], Catherine W. Saltus[2], Lin Li[3], Alka Shaunik[3], Kathleen E. Walsh[4], Stephan Lanes[1], Kenneth J. Rothman[2], Catherine Johannes[2], Vanita Aroda[5], Warner Carr[6], Pinkus Goldberg[7], Andrew Accardi[8], J. Shane O'Shura[9], Kristen Sharma[3], Juhaeri Juhaeri[3] and Chuntao Wu[3]

[1]HealthCore, Inc., Wilmington, DE; [2]RTI Health Solutions, Research Triangle Park, NC; [3]Sanofi, Bridgewater, NJ; [4]Cincinnati Children's Hospital, Cincinnati, OH; [5]Harvard, Cambridge, MA; [6]Allergy & Asthma Associates of Southern California, Mission Viejo, CA; [7]Allergy Partners of Central Indiana, Indianapolis, IN; [8]Scripps Health and SMHE, Encinitas, CA; [9]Lower Bucks Hospital, Bristol, PA

Background: Outcome misclassification is a potential threat to the validity of safety studies using administrative claims databases, particularly for outcomes such as anaphylaxis, which have been previously defined by conventional algorithms with poor positive predictive values (PPVs).

Objectives: Use medical record adjudication and machine learning predictive modeling methods to develop and validate an algorithm to identify anaphylaxis among adults with type 2 diabetes (T2D).

Methods: A conventional screening algorithm to identify potential anaphylaxis cases that prioritized sensitivity was developed based on previous literature and consisted of diagnosis codes for anaphylaxis (ICD-10 CM: T78.2, T88.6, T80.5) or other signs and symptoms suggestive of the condition. This algorithm was applied to adults (≥18) with claims for T2D in the HealthCore Integrated Research Database (HIRD) from 2016-2018. Clinical experts adjudicated anaphylaxis case status from redacted medical records. We used the confirmed case status to develop predictive models that utilized least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation that identified predictors in estimating the probability of confirmed anaphylaxis. Multiple models were evaluated, and in the best performing model we selected a probability threshold based on performance characteristics (i.e. PPV, sensitivity and specificity) and classified individuals above the probability threshold as cases.

Results: Clinical adjudicators reviewed medical records from 272 patients with sufficient information identified by the anaphylaxis screening algorithm, which had an estimated PPV of 65% (95% CI: 60%-71%). The predictive model had a c-statistic=0.95. The model's probability threshold of 0.60 excluded 89% (84/94) of false positives identified by the screening algorithm, which subsequently resulted in a PPV of 94% (95%CI: 91%-98%). The model excluded very few true positives (15 of 178), yielding a sensitivity of 92% (95%CI: 87%-96%).

Conclusions: Medical record review of the potential cases identified by the screening algorithm confirmed previous literature which note a limited performance of conventional algorithms for anaphylaxis. Machine learning techniques yielded an algorithm that achieved a substantially higher PPV for clinically confirmed anaphylaxis while retaining a similar number of cases (true positives) as the conventional screening algorithm. This new algorithm could be considered in future safety studies using claims data to reduce potential outcome misclassification.

118 | Assessment of awareness & knowledge on HIV/AIDS among people in Warangal region

Sanjay Vishwanath

Talla Padmavathi College of Pharmacy, Warangal, India

Background: Many of the people are infected with the pandemic disease HIV either knowingly or unknowingly. Irrespective of the living place (Urban/Rural), HIV is spreading enormously. One of the most important reasons for this wide spread is lack of knowledge and general awareness about the disease and its ways of transmission. In our study we have assessed the awareness levels of different kinds of people in Warangal region and a step is taken to improve their awareness (by providing pamphlets and presentations) regarding the ways of transmission of HIV/AIDS.

Objectives: To assess the awareness & knowledge on HIV/AIDS among people in Warangal region.

Methods: Design & Setting: It was a cross-sectional and observational study, which was carried out at different places including schools (for 9th & 10th Classes), colleges (healthcare & non-healthcare), offices, villages. The participants were given with a *HIV/AIDS Awareness questionnaire* and their awareness levels were assessed. The questionnaire included questions about the disease and its transmission, symptoms, treatment and prevention. This method is followed at all study places. MAIN OUTCOME MEASURES: After the completion of the study, the entire study subjects are categorized into following categories based on their awareness levels on HIV/AIDS. Very Poor: 0-25% of knowledge; Poor: 25-50% of knowledge; Good: 50-75% of knowledge; Better: 75-95% of knowledge; Best: above 95% of knowledge.

Results: It is seen that majority of population in the study i.e. 342 members are having 50-75 % of knowledge; 298 members of population are having 25-50 % knowledge; 217 members of population are having below 25% of knowledge; 191 members of population are having 75-95% of knowledge and only 67 members in the study are having knowledge of above 95% on HIV/AIDS.

Conclusions: In our entire study subjects, 53% of subjects are having Good knowledge (>50%) on HIV/AIDS.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

121 | Real-world safety of palbociclib in breast cancer patients in the United States

Daniel C. Beachler[1], Cynthia de Luise[2], Aziza Jamal-Allial[1], Ruihua Yin[1], Devon H. Taylor[1] and Stephan Lanes[1]
[1]*HealthCore Inc., Wilmington, DE;* [2]*Pfizer Inc., New York, NY*

Background: Palbociclib (palb) received FDA approval in 2015 for advanced stage HR+/HER2- breast cancer and is now a standard of care.
Objectives: Provide real-world safety information on palb.
Methods: We conducted a new user cohort study of breast cancer patients initiating palb and/or fulvestrant (fulv) from 02/01/2015 to 09/31/2017 using data from the HealthCore Integrated Research Database (HIRD), a longitudinal claims database from commercial health plan members in the US. The fulv monotherapy cohort was historical, comprising patients initiating fulv from 01/01/2011 to 01/31/2015. Propensity score matching and Cox proportional hazard regression were used to compare incidence rates between groups during therapy for 42 safety codes of interest (including acute liver injury (ALI)) which were defined via ICD-9/10 code algorithms. For ALI, additional analyses, medical record validation and preparation of case narratives for cases confirmed by hepatology experts were conducted, and a contemporaneous comparator group of new users of fulv monotherapy examined from 02/01/2015 to 09/31/2017 was added.
Results: There were 2,445 patients initiating palb including 566 new users of palb + fulv. ICD-9/10 codes of interest were identified for the palb + fulv cohort, including neutropenia, anemia, interstitial lung disease/pneumonitis, and serious infections (incidence rates >20 per 100 person-years). Compared to historical fulv new users, new users of palb + fulv had more claims for neutropenia, leukopenia, anemia, stomatitis and mucositis, and ALI (Hazard Ratios (HRs)>1.6), whereas other claims, e.g., serious infections, and QT prolongation were similar between groups (HRs<1.4). Using several algorithms to identify ALI, an elevated hazard ratio of ALI in new users of palb + fulv was observed compared to the historical fulv new users after control for additional ALI risk factors (e.g., primary ALI algorithm: HR=3.0, 95% CI=1.1-8.4). However when new users of palb + fulv were compared to the contemporaneous fulv comparator group, no increased hazard ratio was observed, although imprecise (HR=0.5 (95% CI=0.1-2.2)). In addition, available ALI cases reviewed by a blinded hepatology expert, did not directly attribute any of these cases to palb or fulv, instead attributing the majority of them to be a consequence of liver metastases progression. Residual confounding effects cannot be excluded.
Conclusions: A large real-world study of new users of palb + fulv, suggests that the observed safety profile is generally consistent with the known safety profile of palb + fulv.

2332 | Association between non-vitamin k antagonist oral anticoagulants or warfarin and liver injury: A cohort study

Jiaxi Zhao[1], Joseph E Blais[1], Celine SL Chui[1], In-Hye Suh[1], Esa YH Chen[2], Wai-Kay Seto[1], Michael T Mok[3], Vincent KC Yan[1], Wallis CY Lau[4], Ian CK Wong[1] and Esther W Chan[1]
[1]*The University of Hong Kong, Hong Kong, Hong Kong;* [2]*Monash University, Melbourne, Australia;* [3]*University Hospital Geelong and Deakin University, Geelong, Australia;* [4]*University College London, London, United Kingdom*

Background: The risk of liver injury in patients with atrial fibrillation (AF) using non-vitamin K antagonist oral anticoagulants (NOACs) has not been previously examined using liver function tests as the primary outcome in the real-world setting.
Objectives: This study assessed the association between NOACs (dabigatran, rivaroxaban, apixaban) and warfarin and the risk of liver injury, as defined by laboratory tests.
Methods: A territory-wide population-based new-user cohort study in Hong Kong was conducted using the Clinical Data Analysis and Reporting System. Patients newly diagnosed with AF and prescribed NOACs or warfarin between 2010-2016 were identified and matched with a 1:1 ratio using propensity score matching considering age, sex, health status scores, comorbidities and medication use. Risk of incident liver injury, with the same definition as milestone RCTs, defined as laboratory test values greater than 3 times the upper limit of normal of alanine aminotransferase or aspartate aminotransferase and greater than 2 times the upper limit of normal of total bilirubin, was compared between NOAC and warfarin users using Cox proportional hazards regression. An on-treatment approach was used with censoring at treatment switching or discontinuation.
Results: After matching, 13,698 patients were included (mean [SD] age 73.9 [10.6] years; 48.2% women). Covariates were well-balanced with all standardized mean differences less than 0.14. A total of 141 (2.1%) NOAC users and 232 (3.4%) warfarin users developed liver injury with median (IQR) follow-up periods of 1.05 (1.48) and 1.19 (2.45) years respectively. The hazard ratio (HR) for NOAC vs warfarin users was 0.71 (95% CI: 0.58-0.89). When comparing individual NOACs, only dabigatran (HR: 0.63; 95% CI: 0.48-0.82) was associated with a lower risk of liver injury, but not rivaroxaban (HR, 0.72; 95% CI, 0.51-1.01) or apixaban (HR, 1.13; 95% CI, 0.77-1.68). For NOACs vs warfarin, subgroup analyses suggest a similar association in men (HR, 0.69; 95% CI, 0.52-0.92) and patients under 65 years (HR, 0.38; 95% CI, 0.22-0.69) or 75 years or older (HR, 0.73; 95% CI, 0.56-0.96).
Conclusions: Among patients with AF, NOACs as a group, as well as dabigatran alone, were associated with a significantly lower risk of laboratory-based liver injury compared to warfarin. However, liver injury occurs more frequently in real-world practice than in NOAC randomized controlled trials.

2393 | Effect modification of inflammatory bowel disease on thromboembolism risk of combined oral contraceptive

Thuy Thai[1], Xi Wang[1], Phuong Pham[1] and Almut Winterstein[1,2,3]
[1]*College of Pharmacy, University of Florida, Gainesville, FL;* [2]*College of Medicine and College of Public Health and Health Professions, University of Florida, Gainesville, FL;* [3]*Center for Drug Evaluation and Safety (CoDES), University of Florida, Gainesville, FL*

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Effect modification is an important biologic phenomenon, but often neglected. Combined oral contraceptive (COC) and inflammatory bowel disease (IBD) are both risk factors of thromboembolism (TE). However, effect modification of IBD on TE risk in COC users remains unknown.

Objectives: To quantify the interaction between IBD and COC on TE risk using addictive and multiplicative scales.

Methods: We conducted two retrospective cohort studies using IBM MarketScan Claims data 2005-2017. In cohort 1, we estimated absolute risk reduction (ARR) and hazard ratio (HR) of TE among IBD patients with no previous use of hormonal contraceptive (HC) who initiated COC and who did not use any HC (IBD-COC/IBD-no HC). We mirrored the same analysis in cohort 2, but required women to have no diagnoses of IBD (no IBD-COC/no IBD-no HC). COC initiation date was the index date. No-HC users had a randomly chosen random index date within the period of 1 year enrollment and no HC initiation or censoring. We included women aged 12-48 years with ≥1 year enrollment before index date to evaluate IBD and baseline characteristics. TE was a composite outcome of ischemic stroke, acute myocardial infarction, pulmonary embolism, deep vein thrombosis, and arterial thrombosis. We excluded patients with cancer, TE event or using anticoagulants or antiplatelets prior to index. End of follow up was the earliest date of TE, end of COC use, having IBD diagnosis after index date among no-IBD women, enrollment end date, or at 6-month follow up. We adjusted for age, a variety of TE risk factors, other conditions and medications channeling HC type selection, and IBD severity in cohort 1. We used stabilized inverse probability treatment weighting and proportional hazard models. In sensitivity analyses, we varied the definition of continuous COC use and follow-up time.

Results: There were 9,787 IBD-COC, 47,409 IBD-no HC, 2,813,449 no IBD-COC and 7,331,797 no IBD-no HC women included. In the adjusted analysis, using COC resulted in an increase of 7.3 (95%CI -30.5 to 45.1) and 24.7 (95%CI 23.0-26.3) TE events per 10,000 person-years in IBD and in no-IBD women, respectively. The aHR of TE associated with COC was 1.07 (95%CI 0.70-1.64) among women with IBD and 1.92 (95%CI 1.84-2.00) among those without IBD. Sensitivity analyses provided similar results, but with a longer follow-up, aARR and aHR decreased in both cohorts.

Conclusions: We observed that use of COC did not result in excess TE risk beyond that imposed by IBD. Further studies with larger sample size are needed to confirm this interaction.

2481 | Drug-related hospital admissions following emergency department visits: Preliminary results of a cross-sectional study

Zuzana Ocovska[1], Martina Marikova[1,2] and Jiri Vlcek[1,2]

[1]*Faculty of Pharmacy in Hradec Králové, Charles University, Hradec Králové, Czech Republic;* [2]*University Hospital Hradec Králové, Hradec Králové, Czech Republic*

Background: Drug-related hospital admissions (DRA) have attracted much research attention worldwide. And yet, this topic has not been sufficiently investigated in the Czech Republic.

Objectives: To determine the prevalence and preventability of DRA, to identify the implicated medications in DRA and to examine the preventability aspects of DRA.

Methods: : This cross-sectional study examines hospital admissions following emergency department visits in the University Hospital Hradec Králové in 2018. Planned hospitalisations and visits to emergency room without inpatient hospitalisation are not included. The data are retrieved retrospectively using electronic medical records. The data are entered into an Access database. The DRA identification process draws upon the drug-related admissions adjudication guide developed by Thevelin et al.[1] Medical Dictionary for Regulatory Activities and the Anatomical Therapeutic Chemical classification system are used for classification of DRA and implicated medications. Descriptive and inferential statistics are used for statistical analyses.

Results: Out of 951 eligible hospital admissions analysed so far, 926 have been included and 154 DRA have been identified. The prevalence of DRA was 16.6% (95% CI 14.2-19.0). 118 DRA were related to treatment safety and 36 DRA were related to treatment effectiveness. Antithrombotic agents (21.2%), psycholeptics (9.3%), antiinflammatory and antirheumatic products (5.9%) and antineoplastic agents (5.9%) represented the most common medication classes involved in DRA related to treatment safety. Diuretics (25.0%), antihypertensives (22.2%), antithrombotic agents (16.7%) and drugs used in diabetes (13.9%) represented the most common medication classes involved in DRA related to treatment effectiveness. Gastrointestinal disorders and metabolism and nutrition disorders were the leading causes of DRA. The number of drugs in medication history was a predictor of DRA (OR 1.11, 95% CI 1.07-1.16). 56.5% of identified DRA were potentially preventable.

Conclusions: Measuring the scope and nature of DRA is essential for the development of risk minimization measures. The relatively high preventability observed suggests the research on preventability aspects of DRA deserves attention. *The study was supported by Charles University (Project SVV 260 417, PROGRES Q42).* [1] *Thevelin S et al. Development of a standardized chart review method to identify drug-related hospital admissions in older people. Br J Clin Pharmacol. 2018;84 (11):2600-14.*

2505 | Effect of renin-angiotensin system inhibitors on the comparative renal safety of nonsteroidal anti-inflammatory drugs and opioids in hospitalized patients

Todd A. Miano

Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Background: Nonsteroidal anti-inflammatory drugs (NSAIDS) are increasingly important alternatives to opioids for acute pain control in hospitalized patients, as health systems implement opioid minimization initiatives. Increasing NSAID use may increase acute kidney injury (AKI) rates in this vulnerable population, particularly in patients with predisposing risk factors. Conflicting data in outpatient populations

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

suggests that NSAID nephrotoxicity is magnified by renin-angiotensin system (RAS) inhibitors, but no studies have examined this question in hospitalized patients.

Objectives: To determine whether the renal safety of short term treatment with NSAIDs vs. oxycodone is altered by concomitant RAS treatment in hospitalized patients.

Methods: Retrospective, active-comparator cohort study of patients admitted to four hospitals in Philadelphia, PA. To minimize confounding by indication, NSAIDs were compared to oxycodone, and RAS inhibitors were compared to amlodipine. We tested synergistic interaction between NSAIDs and RAS by comparing the difference in AKI rate between NSAID vs. oxycodone in RAS exposed patients to the difference in AKI rate between NSAID vs. oxycodone in amlodipine exposed patients. In a secondary analysis, we restricted the cohort to patients with baseline diuretic treatment. AKI rates were adjusted for 78 baseline characteristics with inverse probability of treatment weighted Poisson regression.

Results: The analysis included 25,571 patients who received a median of 2.4 days of analgesia treatment. The overall AKI rate was 23.6 per 1000 days. The rate difference (RD) for NSAIDs vs. oxycodone in amlodipine exposed patients was 4.1 per 1000 days (CI95 -2.8, 11.1), and the rate difference for NSAID vs. oxycodone in RAS exposed patients was 5.9 per 1000 days (CI95 1.9, 10.1), resulting in an interaction estimate consistent with negligible synergy: 1.8 excess AKI events per 1000 days (CI95 -6.2, 9.9). An analysis restricted to patients treated with baseline diuretics produced a stronger, albeit non-significant interaction estimate: 9.9 excess AKI events per 1000 days (CI95 -5.05, 24.83).

Conclusions: This study did not observe synergistic nephrotoxicity with short term NSAIDs+RAS treatment in the absence of concomitant diuretics, suggesting that RAS treatment may not be a reason to choose an opioid in lieu of a NSAID. Clinically important synergistic effects of NSAID+RAS cannot be ruled out, however, in patients receiving concomitant diuretics.

2535 | Improving identification of anaphylaxis

James S. Floyd[1], David S. Carrell[2], Maralyssa Bann[3], Susan Gruber[4], Ron L. Johnson[2], Vina F. Graham[2], Cosmin A. Bejan[5], Yong Ma[6], Mayura Shinde[7], Robert Ball[8] and Jennifer C. Nelson[9]

[1]University of Washington, Seattle, WA; [2]Kaiser Permanente Washington Health Research Institute, Seattle, WA; [3]University of Washington, Seattle, WA; [4]Putnam Data Sciences, LLC, Cambridge, MA; [5]Vanderbilt University Medical Center, Nashville, TN; [6]Food and Drug Administration, Silver Spring, MD; [7]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [8]Food and Drug Administration, Silver Spring, MD; [9]Kaiser Permanente Washington Health Research Institute, Seattle, WA

Background: Anaphylaxis is an acute life-threatening illness that is often misidentified by ICD diagnostic codes. This threatens the validity of claims-based epidemiologic studies of anaphylaxis as an adverse drug event.

Objectives: (1) Conduct physician adjudication of potential ICD-10 based anaphylaxis events to identify genuine cases. (2) Improve the accuracy of claims-based anaphylaxis identification using natural language processing (NLP) of unstructured clinical notes and machine learning methods.

Methods: We obtained medical records with diagnosis codes for anaphylaxis from inpatient (IP), emergency department (ED), and outpatient (OP) encounters in an integrated healthcare system in Washington State from October 2015 to December 2018. Eligible OP events were also required to have modifier codes suggesting presence of an acute condition. Potential drug-related events (ICD-10 code T88.6) were over-sampled. Two physicians performed adjudication using established events criteria; disagreements were resolved by discussion. We also reviewed IP and ED encounters with diagnosis codes for allergic reactions and adverse drug reactions to identify further potential anaphylaxis cases.

Results: Out of 247 potential events sampled, 240 (97%) had medical records adequate for adjudication (162 ED/IP, 78 OP). The overall positive predictive value (PPV) for validated anaphylaxis events was 64.6% (95% CI 58-70%) with minimal heterogeneity by setting (ED/IP vs. OP), sex, race, or specific ICD-10 code. PPV was higher among those under age 40 (72%, 95% CI 63-79%) versus age 40 or higher (58%, 95% CI 49-66%, p=0.02). Among validated events, common causes were food (39%), medications (34%), and insect bite or sting (12%). Among false positives, 94% were considered to be another serious allergic reaction. Clinical context (timing, alternative clinical conditions, information source) was important in making the proper classifications for some cases. Adjudication of 76 encounters identified by allergy and adverse drug reaction codes yielded a single anaphylaxis event (PPV 1.3%, 95% CI 0.0-9.0%). Toward improving identification of actual anaphylaxis events, we are currently developing machine learning models using predictors from structured electronic health record (EHR) data and NLP-extracted information from the clinical notes of these 316 adjudicated cases.

Conclusions: ICD-10 diagnosis codes for anaphylaxis had moderate PPV for validated events. Many of the misclassified events were serious allergic reactions. These findings have implications for pharmacoepidemiologic studies that seek to estimate treatment-related risks of anaphylaxis using EHR data.

2559 | Second-generation antipsychotics and the risk of chronic kidney disease: A population-based case-control study

Mikkel Højlund[1,2], Lars C. Lund[1], Jonas L. E. Herping[1], Maija B. Haastrup[3], Per Damkier[3,4] and Daniel P. Henriksen[3]

[1]University of Southern Denmark, Odense, Denmark; [2]Mental Health Services Region of Southern Denmark, Aabenraa, Denmark; [3]Odense University Hospital, Odense, Denmark; [4]University of Southern Denmark, Odense, Denmark

Background: Second-generation antipsychotics (SGA) are associated with development of metabolic disturbances which can lead to cardiovascular and renal disease.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Objectives: To examine the association between use of SGAs and the risk of chronic kidney disease (CKD).

Methods: We conducted a population-based case-control study by identifying 21,434 cases of incident CKD from 2001 to 2016 in the Funen Laboratory Cohort containing more than 7.7 million creatinine samples. Cases were identified based on creatinine measurements and matched by risk-set sampling to four population controls using age, sex, and calendar year. We obtained information on drug exposure and comorbidities from the Danish National Prescription Register and the Danish National Patient Register. We calculated odds ratios (OR) for the association between SGA use and CKD using conditional logistic regression.

Results: Use of SGAs was associated with increased risk of CKD among ever-users (OR 1.24, 95%CI: 1.12-1.37) and current users (OR 1.26, 95%CI: 1.12-1.42). We found no clear evidence of dose-response-relationship. Both short duration (1-2 antipsychotic prescriptions; OR 1.22, 95%CI: 1.01-1.48), as well as long-term use (>30 prescriptions; OR 1.45, 95%CI 1.19-1.76) were associated with an increased risk of CKD. Both use of SGAs with mild and high risk of metabolic disturbances was associated with increased risk of CKD (Mild risk: OR 1.21, 95%CI: 1.06-1.39 and high risk OR 1.36, 95%CI: 1.11-1.68). Recent use of NSAIDs, prior use of lithium, hypertension, or prior AKI were not clearly associated with development of CKD in connection to SGA exposure. All SGAs, except for aripiprazole, were associated with increased risk of CKD, and the highest risk was found for clozapine (OR 1.81, 95%CI: 1.22-2.69).

Conclusions: Use of SGA is associated with a small-to-moderately increased risk of incident CKD. All investigated second-generation antipsychotics, except for aripiprazole, were associated with an increased risk of CKD.

2590 | Newer second-line glucose-lowering drugs versus thiazolidinediones and cirrhosis risk in type 2 diabetes

Jeff Y. Yang[1], Anastasia Alexopoulos[2], Andrew M. Moon[3], Hannah Kim[3], Virginia Pate[1], A. Sidney Barritt, IV[3], Til Stürmer[1] and John B. Buse[4]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Duke University, Durham, NC; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Type 2 diabetes (T2D) accelerates progression of chronic liver disease to cirrhosis. Thiazolidinediones (TZDs) have been shown to reduce hepatic steatosis and hepatocellular injury in non-alcoholic fatty liver disease. However, the impact of second-line glucose-lowering drugs (SL-GLDs) on cirrhosis risk is unknown.

Objectives: To compare cirrhosis risk with use of newer SL-GLDs vs. TZDs among patients with T2D.

Methods: We conducted a retrospective cohort study using a 20% sample of Medicare Fee-for-Service. We compared initiators of TZD vs. newer SL-GLDs - sodium-glucose co-transporter 2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitors (DPP4i), and glucagon-like peptide receptor agonists (GLP1RA) - between January 2007 (2013 for SGLT2i) and September 2015. Eligible patients had ≥2 same-drug class prescription claims, were ≥65 years old, and had ≥1 year of continuous enrollment in Parts A/B/D, with no claims for either study drug or cirrhosis/cirrhosis-related complication, prior to index date. We defined cirrhosis using outpatient and inpatient ICD-9 codes 456.1, 571.2, or 571.5 [*Lapointe et al, PLoS One 2018*, specificity 61-77%, sensitivity 98-99%]. We estimated crude incidence rates (IR), as well as adjusted hazard ratios (aHR) and 95% CI using propensity-score (PS) weighted Cox proportional hazards models controlling for demographics; comorbidities; medication use; and healthcare utilization, censoring for treatment changes.

Results: We identified 309,456 new users of the 4 study drug classes. Median follow-up ranged from 0.39-0.64 years. We observed 692, 293, and 89 cirrhosis events in the DPP4i, GLP1RA, and SGLT2i comparisons, respectively. Crude cirrhosis IRs ranged from 4.8 (95% CI 4.1-5.5) to 9.3 (95% CI 6.8-12.7) events per 1,000 person-years. Compared to new use of TZD, initiation of newer SL-GLDs was associated with increased risk of cirrhosis, with elevated aHR estimates for SGLT2i (1.72, 95% CI 1.05-2.82) and DPP4i (1.38, 95% CI 1.15-1.66); GLP1RA was the most comparable agent to TZD (1.18, 95% CI 0.85-1.64). Results were consistent across a number of a priori sensitivity (1% PS trimming, initial treatment, varying lag times, competing event analysis, PS matching) and subgroup analyses (age, sex, baseline metformin, baseline liver disease, baseline insulin).

Conclusions: TZDs were associated with lower cirrhosis risk than newer SL-GLDs except GLP1RAs, suggesting that TZDs and GLP1RAs may reduce cirrhosis risk in patients with T2D. Further study will assess the impact of different validated cirrhosis definitions on safety results.

3691 | Revision risk of lower joint replacement for non-steroidal anti-inflammatory drug users: A retrospective cohort study

Mohammad Bakhriansyah[1], Arief Lalmohamed[2], Patrick C Souverein[3], Anthonius de Boer[3,4] and Olaf H Klungel[3,5]

[1]Lambung Mangkurat University, Banjarmasin, Indonesia; [2]University Medical Centre, Utrecht, Netherlands; [3]Utrecht Institute for Pharmaceutical Science, Utrecht, Netherlands; [4]Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen, CBG), Utrecht, Netherlands; [5]University Medical Centre, Utrecht, Netherlands

Background: Only a few studies assess the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on the revision risk of lower joint replacement (LJR). Moreover, the results are conflicting.

Objectives: To assess the risk of revision LJR (i.e., hip and knee replacements) associated with NSAID use compared to non-use.

Methods: A retrospective cohort study was performed in the UK Clinical Practice Research Datalink among patients aged ≥40 years with a primary LJR between January 2000-December 2018. Patients were followed until either date of revision surgery, lost to follow-up, or end

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of study. Use of NSAIDs (either conventional NSAIDs or selective COX-2 inhibitors), as well as potential confounders was assessed time-dependently. Cox-proportional hazard analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs).

Results: At cohort entry, 155,490 patients with a primary LJR were identified. 26,946 (17.3%) and 4,646 (3.0%) patients were prescribed conventional NSAIDs and selective COX-2 inhibitors, respectively and 123,898 (79.7%) were non-users. Compared to non-use, the adjusted HRs of revision surgery for different durations of current use of conventional NSAIDs were <1 month: 2.48 (2.07-2.96), 3-6 months: 1.51 (1.16-1.96), 6-12 months: 1.67 (1.27-2.20), >12 months: 2.08 (1.69-2.56). For current use of selective COX-2 inhibitors, the HRs were <1 month: 2.85 (1.87-4.34), 1-3 month(s): 1.17 (0.69-1.98), 3-6 months: 1.20 (0.62-2.32), and >12 months: 2.07 (1.29-3.30). Recent and past use of both conventional NSAIDs and selective COX-2 inhibitors were also associated with a higher risk compared to non-use.

Conclusions: Compared to non-use, current use of conventional NSAIDs and selective COX-2 inhibitors for most durations of use were associated with a higher risk of revision of LJR. A higher risk lasted for >3 months after discontinuation. We cannot exclude that confounding by indication (severity of pain) might explain our results.

3805 | Biologic therapy and the risk of herpes zoster among patients with inflammatory bowel disease

Christina Santella[1], Alain Bitton[2], Christopher Filliter[1], Maria Vutcovici[2], Talat Bessissow[2], Peter Lakatos[2] and Paul Brassard[1]
[1]Lady Davis Institute, Montreal, QC, Canada; [2]McGill University Health Center, Montreal, QC, Canada

Background: Studies show that patients with inflammatory bowel disease (IBD) are at an increased risk of infection, including herpes zoster (HZ), which is associated with a range of complications. The contribution of specific biologic therapy to this increased risk remains uncertain.

Objectives: To determine whether use of biologics for IBD is associated with an increased risk of HZ, compared with non-use.

Methods: Using databases from the Regie de l'assurance maladie du Quebec (RAMQ), we conducted a population-based study with a nested case-control analysis. Incident cases of IBD (Crohn's disease (CD) and ulcerative colitis (UC)) were identified between 1 January 1996 and 31 December 2015. Cases of HZ were matched with up to 10 HZ-free controls randomly selected from risk sets based on year of cohort entry and duration of follow-up. The index date was set as the date of HZ diagnosis for the cases and the date resulting in the same duration of follow-up for the matched controls. The exposure of interest was current use, defined as a prescription for a biologic (anti-TNF, anti-integrin, anti-IL-12/23) dispensed within 60 days of the index date, with non-use as the reference category. Conditional logistic regression was performed to compute odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for other IBD medications and potential confounders including severity of disease.

Results: The cohort included 15,453 IBD patients. Over a mean follow-up of 5.0 years, 824 patients were diagnosed with HZ (crude incidence rate of 9.3 per 1000 person-years) and matched to 8240 controls. Compared to controls, cases were older, had a slightly higher frequency of prior immune-mediated inflammatory diseases, and a higher proportion were exposed to steroids. Overall, current use of biologics was associated with an increased risk of HZ (adjusted OR 1.5, 95% CI 1.1-2.1), compared with non-use. Furthermore, the risk was particularly increased among those aged <50 years (adjusted OR 2.1, 95% CI 1.2-3.6), especially among females (adjusted OR 2.8, 95% CI 1.3-6.2). Other the other hand, the risk attenuated among those aged ≥50 (adjusted OR 1.2, 95% CI 0.7-1.9).

Conclusions: Among patients with IBD, current exposure to biologics was associated with an increased risk of HZ, which was especially elevated among those <50 years of age. Preventive measures for HZ should be considered for younger patients initiating such therapies.

3829 | Concomitant use of dipeptidyl peptidase-4 inhibitors with statins and the risk of acute kidney injury in patients with type 2 diabetes

Antonios Douros[1,2,3], Pauline Reynier[4] and Kristian B. Filion[1,2]
[1]Department of Medicine, McGill University, Montreal, QC, Canada; [2]Department of Epidemiology, McGill University, Montreal, QC, Canada; [3]Charité – Universitätsmedizin Berlin, Berlin, Germany; [4]Lady Davis Institute, Montreal, QC, Canada

Background: Dipeptidyl peptidase-4 inhibitors (DPP-4i) and statins are commonly co-administered among patients with type 2 diabetes. While both drug classes have separately been linked to an increased risk of acute kidney injury (AKI), the nephrotoxic risk associated with their concomitant use is unknown.

Objectives: To assess the risk of AKI associated with concomitant use of DPP-4i and statins compared with DPP-4i use alone in patients with type 2 diabetes.

Methods: We conducted a population-based cohort study using the United Kingdom's Clinical Practice Research Datalink and including patients who initiated antidiabetic drugs between 2007 and 2015. We used a time-varying exposure definition, in which each person-day of follow-up was classified into one of the following three mutually-exclusive categories: 1) current concomitant use of a DPP-4i with statins; 2) current use of a DPP-4i without statins, or 3) no current use of a DPP-4i with or without statins. Time-dependent Cox proportional hazards models estimated confounder-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for AKI (defined as hospitalization with AKI or death due to AKI) associated with current concomitant use of DPP-4i and statins compared with current DPP-4i use alone. In secondary analyses, we stratified by prior chronic kidney disease (CKD), by statin potency, and by statin inhibition of P-glycoprotein (p-gp).

Results: The cohort included 87,909 patients initiating antidiabetic drugs. During 316,977 years of follow-up, 3,938 patients were

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

hospitalized with or died due to AKI (crude incidence rate, 1.2 per 100 person-years). Compared with DPP-4i use alone, concomitant use of DPP-4i and statins was not associated with an increased risk of AKI (HR, 0.87; 95% CI, 0.70 to 1.09). Results did not differ between patients with (HR, 1.00; 95% CI, 0.74 to 1.37) and without prior CKD (HR, 0.72; 95% CI, 0.53 to 0.995). Compared with concomitant use of DPP-4i and low-potency statins, concomitant use of DPP-4i and high-potency statins was not associated with an increased risk of AKI (HR, 1.01; 95% CI, 0.81 to 1.26). Similar results were obtained when comparing concomitant use of DPP-4i and p-gp inhibiting statins with concomitant use of DPP-4i and non-p-gp inhibiting statins (HR, 1.24; 95% CI, 0.83 to 1.84).

Conclusions: Concomitant use of DPP-4i and statins is not associated with an increased risk of AKI compared with the use of DPP-4i alone among patients with type 2 diabetes. Prior CKD and the pharmacologic intra-class heterogeneity of statins did not modify the association.

3835 | A multinational European study of anaphylaxis among recipients of intravenous Iron

Lia Gutierrez[1], Patrick Blin[2], Jochen Dress[3], Cecile Droz-Perroteau[2], Vera Ehrenstein[4], Carla Franzoni[1], Bianca Kollhorst[5], Regis Lassalle[2], Marie Linder[6], Nicholas Moore[2], Ingvild Odsbu[6], Jetty Overbeek[7], Susana Perez-Gutthann[1], Tania Schink[5], Katherine Rascher[8], Lawrence Rasouliyan[1], Jonas Reinold[5], Kenneth J Rothman[9], Nuria Saigi-Morgui[1], Mathias Schaller[8], Elisabeth Smits[7], Antje Timmer[10], Gunnar Toft[4], Gero von Gersdorff[8], Intravenous Iron Consortium[11] and Joan Fortuny[1]

[1]RTI Health Solutions, Barcelona, Spain; [2]University of Bordeaux PharmacoEpi, Bordeaux, France; [3]Information System for Health Care Data (Data Transparency), DIMDI, Cologne, Germany; [4]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; [5]Leibniz Institute for Prevention Research and Epidemiology-BIPS GmbH, Bremen, Germany; [6]Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden; [7]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands; [8]QiN-group, University of Cologne, Cologne, Germany; [9]RTI Health Solutions, Waltham, MA; [10]Carl von Ossietzky Universität Oldenburg, Oldenburg, Germany; [11]Intravenous (IV) Iron Consortium of IV Iron Manufacturing Companies, Guildford, United Kingdom

Background: Anaphylaxis (ANA) related to intravenous (IV) iron treatment is a poorly characterized safety concern in Europe. A postauthorization safety study requested by the European Medicines Agency assessed the risk of ANA in IV iron users in Europe.

Objectives: To assess the risk of ANA overall, by IV iron groups (iron non-dextrans and iron dextran), and by individual types.

Methods: A cohort study of IV iron users was conducted in 5 European countries covered by 6 health databases, including data spanning from 1999 through 2017: Denmark (Health Services Database of the Central Region), France (SNDS), Germany (GePaRD and Quality in Nephrology programme), the Netherlands (PHARMO), and Sweden (Swedish national registers). IV iron treatment was captured mainly from ambulatory drug dispensing data. Data source-specific analyses followed a common protocol with a new-user design. Risk of ANA occurring the day of or day after first, second, and third or subsequent iron treatment was estimated using beta-binomial derived combined incidence proportions (IPs) and 95% confidence intervals. To provide context, the risk of ANA was also assessed among users of IV penicillins, if available. Validation of potential ANA events was conducted in the Health Services Database of the Central Denmark Region and PHARMO by review of medical records. For GePaRD, indirect validation of the case-identification algorithm was performed in the Oldenburg Hospital.

Results: Of 304,210 first-recorded IV iron treatments, 2.1% were iron dextran. There were 231,294 first-recorded IV penicillin treatments. The overall IP of ANA at first IV iron treatment ranged from 0.41 (0.13-1.28) to 1.16 (0.20-6.68) per 10,000 treatments; at first iron non-dextrans treatment, the IP ranged from 0.43 (0.13-1.37) to 1.2 (0.21-6.72) per 10,000 treatments (IPs reported as ranges to comply with data protection rules). There were no ANA events among first iron dextran treatments. Risk by groups and types of IV iron were estimated but were limited by very low numbers. No adjusted analyses could be performed either. The IP of ANA at first IV penicillin treatment was 1.29 (0.54-3.11) per 10,000 treatments.

Conclusions: We found an IP of ANA lower than the estimated 2 to 6.8 per 10,000 first treatments (IV iron non-dextrans and iron dextrans, respectively) reported by two recent United States studies. The IP of ANA in users of penicillins was consistent with the incidences reported in the literature. Most data sources do not capture in-hospital use of IV iron, likely resulting in misclassification of repeated users as first users. This may have resulted in an underestimation of the IPs of ANA.

3888 | Adverse bleeding events among patients concomitantly treated with direct anti-coagulants and antibiotics within a Swedish nationwide cohort

Tatsuya Yagi[1], Helle Kieler[1], Johan Reutfors[1], Buster Mannheimer[2] and Marie Linder[1]

[1]Department of Medicine Solna, Centre for Pharmacoepidemiology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [2]Department of Clinical Science and Education at Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

Background: Potential drug-drug interaction between concomitant use of direct anti-coagulants (DOAC) with macrolides/fluoroquinolones and bleeding events has not been fully clarified in a Western population.

Objectives: To investigate association between adverse bleeding events and concomitant use of DOAC with antibiotic agents of macrolide/fluoroquinolone type in Sweden.

Methods: Design and setting: Cohort study using Swedish national health register data. Patients with ≥1 dispensation of rivaroxaban,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

apixaban or dabigatran for deep venous thrombosis, pulmonary embolism or atrial fibrillation (1 January 2010 - 31 December 2015) were included. Exposures: Concomitant use of DOAC with macrolides/fluoroquinolones. To assess the potential for confounding by indication of antibiotics, we also identified users of DOAC concomitant with doxycycline (controls). To minimize confounding by indication, we excluded patients with antibiotic treatment assumed to be for *H. pylori*: patients with concurrent use of amoxicillin/metronidazole and clarithromycin, with concurrent use of amoxicillin/metronidazole and levofloxacin, and with concurrent use of metronidazole and doxycycline. Outcome: Bleeding events defined as intracranial bleeding, gastrointestinal bleeding or vitreous hemorrhage. Statistical analysis: We compared the incidence of bleeding events between users of DOAC together with macrolides or fluoroquinolones vs controls. Adjusted for known confounders (diabetes, *H. pylori*, ischemic heart disease, mitral stenosis, obesity, electronic cardiac devices, sepsis, smoking, substance abuse, CYP-inhibitor/inducer, NSAIDS, antiplatelet). Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) using Cox regression were estimated.

Results: We identified 89 212 patients (mean age 70.5 years (SD 13.7), 54.6% males) fulfilling inclusion criteria. Number of patients dispensed rivaroxaban, apixaban and dabigatran was 34 306, 34 716 and 20 190. Number of patients dispensed macrolides, fluoroquinolones and doxycycline were 247, 3 191 and 3 035, respectively. In total, 492 patients had bleeding events. The aHRs (95% CI) for bleeding events were 1.84 (0.22-15.5) for macrolides, and 1.79 (0.72-4.43) for fluoroquinolones, compared to doxycycline.

Conclusions: Among DOAC users, concomitant use of macrolide or fluoroquinolone might be associated with bleeding events. Further investigation using case-time-control design and a larger study population are required to clarify the association and to adjust for other patient characteristics.

3907 | intravenous bisphosphonate use and 30-day risk of inflammatory bowel disease flare

Jeff Y. Yang[1], Bharati D. Kochar[2], Jennifer L. Lund[1] and Hans H. Herfarth[3]

[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC;* [2]*Massachusetts General Hospital, Boston, MA;* [3]*University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: In up to 30% of patients, intravenous bisphosphonates (ivBPs) can cause acute-phase reactions (APRs), marked by release of pro-inflammatory cytokines. Case series suggest that APRs may trigger flares in patients with co-existing autoimmune diseases including inflammatory bowel disease (IBD). [*Markovits et al, Inflammopharmacology 2017*] This phenomenon has not been systematically investigated in IBD patients.

Objectives: To evaluate the association between ivBP therapy and increased risk of IBD flare activity, compared with oral bisphosphonates (poBPs).

Methods: We conducted a retrospective cohort study using the IBM MarketScan® Commercial Claims and Encounters Database, between January 1, 2006 and December 31, 2017. New users of both poBPs and ivBPs were identified using National Drug Codes and Healthcare Common Procedure Codes for alendronate, ibandronate, risedronate, and zoledronic acid. Eligible patients had ≥1 prescription (Rx) claim for any study drug, were 18-64 years old, and had ≥6 months of continuous enrollment prior to index date (baseline period) with no claims for any study drug. Baseline IBD was identified using a validated algorithm requiring either 1) ≥3 International Classification of Disease (ICD)-9 or -10 codes for Crohn's disease (555.x or K50.x) or ulcerative colitis (556.x or K51.x) on different days; or 2) one ICD code for IBD and a Rx for IBD-related medication. We used propensity-score methods to control for confounders (age, sex, region, IBD subtype, Charlson Comorbidity Index, baseline IBD medication use, and healthcare utilization). Standardized mortality ratio-weighted binomial regression was used to estimate the adjusted 30-and 90-day risk difference (RD) and risk ratio (RR) for IBD flare, defined as either 1) an urgent care, emergency department, or hospital visit with 1st- or 2nd-position IBD diagnosis; or 2) systemic corticosteroid or enteral budesonide Rx in those not treated with corticosteroids in the 30-days before index date.

Results: We identified 319 eligible new users of ivBPs and 7,655 new users of poBPs. We observed 670 IBD flares (30-day pooled risk: 8.4%), though we did not observe increased risk in ivBP users (RD: 0.011, 95% CI -0.027, 0.048; RR: 1.13, 95% CI 0.75, 1.72). Results were similar for 90-day risk (RD: 0.034, 95% CI -0.022, 0.089; RR: 1.19, 95% CI 0.91, 1.56), and in female users (RD: 0.026, 95% CI -0.019, 0.072; RR: 1.35, 95% CI 0.86-2.12).

Conclusions: We found that IBD flares after ivBP and poBP initiation were rare among commercially-insured adults under 65. New use of ivBP compared to poBP was not associated with an increased flare risk.

3915 | Are indicators of difficult insertion among women with intrauterine devices associated with uterine perforation and expulsion?

Mary E. Ritchey[1], Susan Reed[2], Amy Alabaster[3], Darios Getahun[4], Jennifer Gatz[5], Catherine Saltus[6], Mary Anne Armstrong[3], Fagen Xie[4], Jinyi Wang[1], Michael Fassett[4], Giulia Chillemi[3], Jeffrey Peipert[7], Shannon Hunter[1], Laura Ichikawa[8], Alex Asiimwe[9] and Mary Anthony[1]

[1]*RTI Health Solutions, Research Triangle Park, NC;* [2]*Kaiser Permanente Washington, University of Washington, Seattle, Seattle, WA;* [3]*Kaiser Permanente Northern California, Oakland, CA;* [4]*Kaiser Permanente Southern California, Pasadena, CA;* [5]*Regenstrief Institute, Indianapolis, IN;* [6]*RTI Health Solutions, Waltham, MA;* [7]*Indiana University School of Medicine, Indianapolis, IN;* [8]*Kaiser Permanente Washington, Seattle, WA;* [9]*Bayer AG, Berlin, Germany*

Background: Approximately 16% of women who use contraception in the United States use long-acting reversible contraceptives such as an

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

intrauterine device (IUD). Outcomes such as uterine perforation and IUD expulsion might be associated with difficulty in IUD insertion.

Objectives: Assess difficult IUD insertion as a potential risk factor for uterine perforation and IUD expulsion.

Methods: A cohort of women receiving IUDs were identified from each of four sites (three Kaiser Permanente sites—Northern California, Southern California, and Washington—and Regenstrief Institute, Indiana) for assessment of exposures covered elsewhere. Structured data (National Drug Codes, International Classification of Diseases 9/10, Current Procedural Terminology) and unstructured data (clinical notes with natural language processing) were used to identify uterine perforation, IUD expulsion, and five possible indicators of difficult IUD insertion: cervical dilation, ultrasound assessment, paracervical block, misoprostol use, and provider note of difficult insertion. The proportion of women with indicators of potentially difficult insertion pooled across sites was assessed overall and by uterine perforation and IUD expulsion along with the Hazard Ratio (HR) for difficult insertion associated with each outcome.

Results: Among 326,658 women with IUD insertions, 29,777 (9.1%) had at least one indicator for a potentially difficult insertion, ranging 3.5%-16.3% across sites. The frequency of each indicator varied across sites. Women who experienced difficult insertion had a higher risk for uterine perforation and IUD expulsion (Hazard Ratio [HR] for uterine perforation: 1.38 [95% CI 1.14, 1.68]; HR for IUD expulsion: 1.16 [95% CI 1.08, 1.24]). This slightly higher proportion of uterine perforation and IUD expulsion among women with difficult insertions was seen at all sites, though there was variability in the specific indicators both across outcomes and by site.

Conclusions: The prevalence of difficult insertions was similar to published data from prospective studies (8%-9%) and was higher among women with IUD perforations and expulsions. We were able to identify indicators of difficult insertion using structured and unstructured data. Differences in prevalence exist across sites which might suggest differences in modes of data collection, patient characteristics, or clinician practice. We cannot determine the proportion of indicators that represent true difficult insertions.

3919 | Risk across postpartum timing of insertion in women with intrauterine devices

Mary E. Ritchey[1], Jennifer Gatz[2], Maqdooda Merchant[3], Michael Fassett[4], Susan Reed[5], Catherine Saltus[6], Darios Getahun[4], Jeffrey Peipert[7], Giulia Chillemi[3], Jennifer Bartsch[1], Theresa Im[4], Alex Asiimwe[8], Mary Anne Armstrong[3] and Mary Anthony[1]

[1]RTI Health Solutions, Research Triangle Park, NC; [2]Regenstrief Institute, Indianapolis, IN; [3]Kaiser Permanente Northern California, Oakland, CA; [4]Kaiser Permanente Southern California, Pasadena, CA; [5]Kaiser Permanente Washington, University of Washington, Seattle, Seattle, WA; [6]RTI Health Solutions, Waltham, MA; [7]Indiana University School of Medicine, Indianapolis, IN; [8]Bayer AG, Berlin, Germany

Background: United States obstetrics and gynecology professional organizations recommend that women consider using intrauterine devices (IUDs) beginning in the immediate postpartum (PP) time period to prevent unintended pregnancy. However, risk of uterine perforation and IUD expulsion may vary by PP timing of IUD insertion

Objectives: To assess the risk of uterine perforation and IUD expulsion according to PP timing of IUD insertion, using a finer categorization of PP timing than has been previously attempted

Methods: Women receiving IUDs were identified at each of four sites (three Kaiser Permanente sites—Northern California, Southern California, and Washington—and Regenstrief Institute, Indiana) between January 2001 and April 2018 (start date variable by site) and assessed for outcomes through June 2018. PP timing and patient/procedure characteristics were assessed at the time of insertion. PP timing was dichotomized in two ways: at 14 weeks and separately at 36 weeks. Groups were further stratified into four and five-category PP exposure groups. Risk of uterine perforation and IUD expulsion was assessed via Cox models, including confounder adjustment by propensity score overlap weighting

Results: Among 326,658 women with IUD insertions, there were 1,008 uterine perforations and 8,943 IUD expulsions in 641,427 woman-years. After adjustment, the hazard ratio (HR) for uterine perforation with insertion ≤ 14 weeks PP was 3.44 (95% confidence interval [CI], 2.70-4.40) compared with insertion > 14 weeks PP, and HR ≤ 36 weeks PP was 4.36 (95% CI, 3.45-5.51) compared with insertion > 36 weeks PP. The adjusted HRs for IUD expulsion were 0.88 (CI, 0.83-0.94) and 0.95 (CI, 0.89-1.00) for the dichotomous 14- and 36-week PP comparisons, respectively. Consideration of heterogeneity in the dichotomous categories led to a separate, prespecified four-category PP exposure variable. The adjusted HRs for uterine perforation decreased from ≤ 6 weeks, 6 to ≤ 14 weeks, and through 14 to ≤ 52 weeks compared with > 52 weeks (including no birth), respectively. The adjusted HRs for IUD expulsion were lowest at 6 to ≤ 14 weeks. Further concern of underlying heterogeneity in outcome risk led to splitting the earliest PP time period. With this split, lower rates of perforation and higher rates of expulsion were seen in IUD insertion 0-3 days PP compared with insertion 4 days to ≤ 6 weeks PP

Conclusions: Underlying heterogeneity across the PP time period could lead to differences in risk interpretation based on the categorization of exposure. Clinical considerations of interpretation should be used alongside data-driven analyses to determine categorization of exposures

3974 | Comparative risk of infection for first line csDMARD therapy in rheumatoid arthritis: A multinational cohort analysis of real world data

Meghna Jani[1], Edward Burn[2,3], James Weaver[4], Loreto Carmona[5], Katerina Chatzidionysiou[6], Ben Illigens[7,8], David Vizcaya[9], Talita Duarte-Salles[2], Patrick Ryan[4], Daniel Prieto-Alhambra[3] and RA Research Group EHDEN[3]

[1]Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, United Kingdom; [2]IDIAPJGol, Barcelona, Spain; [3]University of Oxford, Oxford, United Kingdom; [4]Janssen Research and Development, Titusville, NJ; [5]Inmusc, Madrid, Spain; [6]Karolinska Institutet, Stockholm,

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Sweden; [7]Harvard Medical School, Boston, MA; [8]Odysseus Inc, Cambridge, MA; [9]Bayer Hispania, Barcelona, Spain

Background: Infections on conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) are an important concern for rheumatoid arthritis (RA) patients, however comparative safety data have been conflicting and limited in power.

Objectives: To assess the comparative safety of serious, opportunistic and all infections (including non-serious) of first-line csDMARDs in RA

Methods: We evaluated first-line new users of methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SZ) and leflunomide (LEF) monotherapy. Data was obtained from four US databases (IQVIA US Ambulatory EMR (AMBER), Optum de-identified Clinformatics Datamart (Optum), IBM MarketScan® Medicare Supplemental Database (MDCR), and IBM MarketScan Commercial Database (CCAE)), one from Germany (IQVIA Disease Analyser Germany EMR (Germany)), and another from the UK (IQVIA UK THIN). Patients included were ≥18 years with a RA diagnosis between 2005-2019, without prior inflammatory arthritis, cancer or infection (in the preceding 30 days). Serious infections were defined as those requiring hospitalisation or resulting in death within 30 days; opportunistic infections as per published consensus. Patients were followed from 1-day following treatment initiation to the earliest of treatment discontinuation, switching, or add-on plus 14 days, or loss to follow-up. Cox proportional-hazards models for MTX against each csDMARD with large-scale propensity score stratification were performed. A large set of negative control outcomes were used to calibrate hazard ratios (cHR) to account for potential residual confounding. Estimates were pooled where homogeneity across sources was adequate (I^2<0.4).

Results: A total of 170,450 patients were included (MTX: 94,942, HCQ: 50,603, SSZ: 15,607, LEF: 9,298), with pooled incidence rates of serious, opportunistic and all infections across sources for MTX users of 33.7, 20.1 and 311.8 per 1,000 pyrs, respectively. With MTX as the referent, for all infections, the pooled cHR (with 95% CI) for SSZ was 0.72 (0.59, 0.88); HCQ, 0.96 (0.90, 1.03); and LEF, 0.73 (0.50, 1.05). The serious infection pooled cHR for SSZ was 0.74 (0.56, 0.99) and for LEF, 0.91 (0.61, 1.37). For opportunistic infections, pooled cHR for HCQ was 1.05 (0.92, 1.19).

Conclusions: SSZ and less consistently LEF and HCQ had a lower risk of all (including non-serious) infections, compared to MTX. In the first large scale observational network study assessing comparative risk of infection with csDMARDs, there was no consistent difference between groups for serious and opportunistic infections.

4074 | Real-world evidence (RWE) study to access motor vehicle accidents data: Real-world data landscaping and feasibility

Hu Li[1], Michael Phinney[2], Rashna Khanna[3], Sonja M Bragg[1], Tammy Clemmer[2] and Eva Oakkar[2]

[1]Eli Lilly and Company, Indianapolis, IN; [2]IQVIA, New York City, NY;[3]Lilly UK, Erl Wood, United Kingdom

Background: Motor vehicle accidents (MVA) are a major public safety concern, particularly in the context of prescription drugs. FDA guidance issued in 2017 recommends evaluating the potential for driving impairment with all psychoactive drugs using "tiered approaches". The FDA recently approved a centrally-penetrant, novel 5HT1F receptor antagonist, lasmiditan, for the acute treatment of migraine. To our knowledge, the background rate of MVA in people with migraine is not available to date.

Objectives: To conduct a feasibility study of linking existing United States MVA data sources and migraine-related clinical databases for future research capability in assessing the MVA background rate of various populations (e.g., people with migraine using acute migraine prescription or non-prescription medications, people with migraine without any migraine medication, or general US population).

Methods: A targeted English language literature search was conducted and subject matter experts (SMEs) were consulted to identify migraine and MVA data sources. The identified data sources were then investigated using a qualitative questionnaire. Identified data sources were weighted for partnership potential across three categories: collaboration, use access, and research capability. Collected information was consolidated into standardized summaries with an RWE road map.

Results: Fifteen clinical databases including patients with migraine and sixty MVA-related data sources were identified and contacted. Nine migraine-related clinical data and patient care networks and seven MVA data sources were open to partnership with private parties. The detailed assessments on each data source will be presented, along with advantages and limitations of potential approaches to link MVA and clinical databases. Based on the initial outreach and limitations of existing data sources, there is potential to conduct a 12-month prospective survey and link to state DMV data sources for car crash validation using probabilistic linkage techniques.

Conclusions: There are limited real-world data sources for MVA outcomes that are open to access for research. Also, the number of people with migraine that can be linked across these data sources to prescription data and electronic medical records may be sparse. Future research investigating medication effects on driving impairments using secondary data sources is possible but will be challenging.

4122 | Factors associated with serious vehicular accidents: A real-life study

Nicholas Moore[1], Karelle Forest[2], Guillaume Valdenaire[3], Jean-Paul Lorendeau[4], Patricia Sagaspe[5], Benjamin Contrand[6], Charlotte Durand-Teissier[2], Dunia Sakr[1], Cedric Gil-Jardiné[7], Sebastien Boutreux[4], Emmanuel Lagarde[6], Helene Peyrouzet[2], Regis Lassalle[1], Pierre Philip[8] and Pierre-Olivier Girodet[2]

[1]University of Bordeaux, Bordeaux, France; [2]CHU de Bordeaux, Bordeaux, France; [3]CHU de Bordeaux, Bordeaux, France; [4]CH de Perigueux, Perigueux, France; [5]Unviersity of Bordeaux, Bordeaux, France; [6]University of Bordeaux, Bordeaux, France; [7]CHU de Bordeaux, Bordeaux, France; [8]University of Bordeaux, Bordeaux, France

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Background: Many factors have been associated with accidents and their severity or responsibility, among which sleepiness, alcohol, and use of medicinal drugs. Medicinal drugs deemed at risk have been attributed colored pictograms to indicate the risk of accident. Various public campaigns have warned about the risks of sleepiness, alcohol and the use of such drugs

Objectives: Identify risk factors associated with serious vehicular accident, including drugs with a pictogram warning.

Methods: Subjects with serious and non-serious accidents arriving in the emergency room of a general academic urban hospital and a more rural local hospital were interviewed to identify factors associated with the serious/non-serious nature of the accident

Results: Between 18/10/2016 - 26/12/2018, 6212 drivers were admitted to the emergency rooms of the Bordeaux and Perigueux public hospitals. 1200 of these (741 non-serious accidents, 459 serious, hospitalized at least 24 hours) were interviewed. In 207 serious accidents a police report ascertained the driver's responsibility in the accident. Compared to non-serious, serious accidents were associated in multivariate analysis with male sex (OR 1.89, 95% confidence interval [1.36 - 2.64], age above 60 (3.64 [2.21 - 6.00]), driving on local roads (3.34 [2.34 - 4.76]), driving a motorcycle (3.39 [2.29 - 5.00]), having drunk alcohol within 6 hours before the accident (2.89 [1.85 - 4.51]), and using a drug with a pictogram during the 24 hours previous to the accident (1.57 [1.06 - 2.32]). Overall, 87% of drivers with non-serious accidents and 83% with serious accidents knew of the pictograms and their meaning. In univariate analyses the risk of an accident being serious increased with the pictogram, from 1.27 for the use of any drug to 2.2 [1.25-.89] for level 3 pictograms drugs used within 24 hours before the accident. Among the 207 drivers with a police report, 106 responsible and 101 not responsible, responsibility was associated with age below 40, driving in overcast or rainy weather 2.62 [1.29 - 5.33], driving on local roads (3.89 [1.90 - 7.95]), and use of at least one pictogram drug in the week previous to the accident (3.12 [1.31 - 7.41]). Behavioral sleepiness as measured by the Epworth sleepiness scale did not predict accidents.

Conclusions: The known risks of alcohol and pictogram drugs, of riding motorcycles and using local roads were confirmed

4319 | Time to biologic treatment and to total colectomy associated with diagnostic delay in ulcerative colitis: Analysis of an Italian regional administrative healthcare database

Sara Ferraro[1], Claudia Bartolini[2], Lorenzo Bertani[3], Irma Convertino[1], Ersilia Lucenteforte[4], Francesco Costa[3], Giulia Valdiserra[1], Emiliano Cappello[1], Corrado Blandizzi[1,5], Rosa Gini[2] and Marco Tuccori[5,1]

[1]*Unit of Pharmacology and Pharmacovigilance, Clinical and Experimental Medicine, University of Pisa, Pisa, Italy;* [2]*Tuscan Regional Healthcare Agency, Florence, Italy;* [3]*IBD Unit, General Surgery and Gastroenterology, Pisa University Hospital, Pisa, Italy;* [4]*Unit of Medical Statistics, Clinical and Experimental Medicine, University of Pisa, Pisa, Italy;* [5]*Unit of Adverse Drug Reactions Monitoring, University Hospital of Pisa, Pisa, Italy*

Background: Diagnostic delay (DD) in Ulcerative colitis (UC) is mainly documented in studies based on disease registries, and may lead to disease complications and increased rate of surgery.

Objectives: To quantify potential DD in a real-world cohort of UC patients, and to assess whether DD is associated with adverse clinical outcomes.

Methods: This is a retrospective cohort study. Data was retrieved from administrative healthcare databases of Tuscany, an Italian region. We included patients with a first record of a diagnosis of UC or a first record of dispensation of oral mesalazine from 6/1/2011 to 6/30/2016 (index date, ID). Patients < 18 years old at ID or with look-back period < 5 years or follow-up period < 3 years were excluded. Patients with less than 2.4 mg/day average dose of mesalazine, calculated in the first year after ID, were excluded from the cohort. Patients were classified as exposed to DD when at least 1 Emergency Department admission or hospitalization for gastrointestinal causes were recorded in the look-back period, excluding the 6 months preceding ID. Patients without any record of interest in the look-back period or with a record of interest in the 6 months preceding ID were defined as not-exposed to DD. We investigated time from ID to the date of first prescription of a biologic drug (BIO) and to total colectomy (TCOL). Hazard ratio (HZ) was estimated using Cox models adjusted for age and gender.

Results: The overall cohort included 3,951 patients. Females were 1,655 (41.9%). Mean age was 53.5 (standard deviation: 16.7). Patients exposed to DD were 1,640 (41.5%) with a median delay time of 534 days, and those not-exposed were 2,311 (58.5%). Out of the whole cohort, 286 patients had the first prescription of BIO and 54 had a TCOL with an average time of 2.86 and 2.98 years, respectively. Among patients non-exposed to DD, cases of BIO and TCOL were 160 (6.9%) and 30 (1.3%), and among exposed ones were 126 (7.7%) and 24 (1.5%), respectively. The HZ was 1.13 (confidence interval, CI, 95%: 0.89-1.43) for BIO, and 1.17 (CI 95% 0.68-2.00) for TCOL.

Conclusions: A non-significant risk of biologic therapy and surgery is reported for UC patients with suspected DD compared with UC patients timely diagnosed. Further studies using other databases are needed to investigate UC patients' outcomes related to DD.

4475 | Incidence of thromboembolic events among prothrombin complex concentrate (Human)-treated patients: A review of the literature and meta-analysis

Nicole Baker, Brahm Goldstein, Haley Kaplowitz and Jinesh Shah

CSL Behring, King of Prussia, PA

Background: Kcentra, Prothrombin Complex Concentrate (Human) [PCC] approved by FDA in 2013, is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding or need for an urgent surgery or invasive procedure. In two Phase IIIb

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

clinical studies of subjects with acute major bleeding and subjects with the need for urgent surgery or invasive procedures, the proportion of patients with thromboembolic events (TEE) among the PCC-treated subjects during the 45 day follow-up period was 8.7% and 4.5%, respectively. The incidence of TEEs in the post-marketing setting has not been well established.

Objectives: To estimate the incidence of TEEs among PCC-treated patients reported in observational studies in the literature.

Methods: A review of the published literature was conducted to identify observational studies of patients treated with PCC for VKA reversal that reported the incidence of TEEs. Results from the literature were analyzed using a Bayesian meta-analysis. Uncertainty in the mean rates and between-study heterogeneity were accounted for and a non-informative prior was used on each parameter. The meta-analysis was conducted separately for studies with follow-up during the hospitalization or within 7 days (short-term follow-up) and follow-up that ended between 14 and 90 days (long-term follow-up).

Results: Eighteen publications provided estimates of the incidence of TEEs among PCC-treated patients. The overall incidence of TEEs among PCC-treated patients ranged from 0% to 19%. The meta-analysis resulted in an estimated TEE rate of 3.8% (95% Bayesian Credible Interval [BCI]: 2.2%, 5.7%) and 8.6% (95% BCI: 2.4%, 19.5%) among studies with short-term follow-up (n=13) and long-term follow-up (n=5), respectively.

Conclusions: The incidence of TEEs among PCC-treated patients reported in observational studies in the literature support the safety of PCC in the post-marketing setting.

4496 | Validity of hospital ICD-10-GM-codes to identify anaphylaxis

Dominik de Sordi[1], Sanny Kappen[1], Fabian Otto-Sobotka[1], Lia Gutierrez[2], Joan Fortuny[2], Jonas Reinold[3], Tania Schink[3] and Antje Timmer[1]

[1]Carl von Ossietzky University, Oldenburg, Germany; [2]RTI Health Solutions, Barcelona, Spain; [3]Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany

Background: Anaphylaxis (ANA) is defined as a severe acute hypersensitivity reaction. It may occur as a potentially life threatening adverse event of drug treatment. In the context of a post authorization safety study (PASS) information on the validity of algorithms to define anaphylaxis based on ICD-10-GM codes was needed.

Objectives: Primary aim was to assess the positive predictive value (PPV) of ICD-10-GM based algorithms to define ANA in the context of a European multinational PASS on the safety of iv iron. In addition, we identified missed cases to estimate negative predictive values (NPV), sensitivity (Se) and specificity (Sp).

Methods: A cross-sectional approach was applied based on routine data from a German academic hospital (2004 to 2019). Potential cases were identified from the hospital administration system, selecting all cases with any type of specific ANA diagnosis (T78.2, T80.5, T88.6). A random sample of patients with non-specific ANA-related codes (T78.4, T88.7, Y57.9) was also selected to identify any additional cases not identified by using specific codes. Case validation was based on clinical expert chart review by two independent raters and applied internationally consented clinical criteria for diagnosis of ANA. PPV for two ICD-10-based algorithms are presented. Algorithm I looked for any ANA-specific code in hospital or emergency room stays. Algorithm II restricted the search to primary discharge diagnoses only. PPV, NPV, Se and Sp are presented with 95% CI. Sensitivity analyses modified assumptions on non-evaluable cases and case verification criteria.

Results: Of 344 cases available for chart review, 69 (30) patients fulfilled algorithm I (II). ANA was confirmed in overall 76 cases, of these 43 (23) in the cases identified using algorithm I (II). This resulted in the following for algorithm I: PPV 62.3% (49.8-73.7); NPV 88.0% (83.6-91.6); Se 62.3% (49.8-73.7); Sp 90.3% (86.1-93.6). Corresponding figures for algorithm II were PPV 76.7% (57.7-90.1); NPV 83.1% (78.5 - 87.1); Se 30.3% (20.3-41.9); Sp 97.4% (94.7-98.9). Sensitivity analyses showed a maximum increase in PPV to 68.1% (80.0%).

Conclusions: PPV was best if specific ANA diagnoses were restricted to primary discharge diagnoses but this resulted in a low number of cases. Expanding to any type of specific diagnoses doubled the number of identified cases and showed an acceptable PPV. Interpretation of NPV, Se and Sp is limited due to the sampling procedure. Screening for missed cases among those with non-specific ANA codes may be helpful to increase the number of cases only if additional verification procedures can be applied.

4523 | Risk of thromboembolic events associated with concomitant use of oral hormonal contraceptives and selective serotonin reuptake inhibitors

Phuong Pham[1], Yasser Albogami[1,2], Brian Cicali[1], Patrick Squires[1], Amir Sarayani[1], Thuy Thai[1], Victoria Reams[1], Kiyon Rhew[3], Amie Gooddin[1], Stephan Schmidt[1], Almut G. Winterstein[1] and Joshua Brown[1]

[1]University of Florida, Gainesville, FL; [2]King Saud University, Riyadh, Saudi Arabia; [3]Dongduk Women's University, Seoul, Republic of Korea

Background: Several selective serotonin reuptake inhibitors (SSRIs) are CYP450 inhibitors or substrates which could affect the metabolism of hormonal contraceptive agents (HCAs). Little information exists regarding the risk of thromboembolism among women taking HCAs and SSRIs concomitantly.

Objectives: Our study evaluated the risk of thromboembolic events associated with the concomitant use of HCAs and SSRIs.

Methods: This retrospective cohort study utilized IBM MarketScan commercial claims data (2005-2015). Women newly used oral HCAs aged 12 to 48 years with a diagnosis of depression within 12 months before or after HCA initiation were selected. The index date was the first day of concomitant use of HCAs and SSRIs. We required

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

12-month continuous enrolment pre-index to assess baseline characteristics. We excluded women with prior thromboembolic events, anticoagulant use, or cancer during the pre-index period and those with pregnancy or with a delivery within 3 months before the index date. Exposure groups were defined based on concomitant use of HCAs and five SSRIs: fluoxetine, paroxetine, sertraline, citalopram and escitalopram. The composite safety outcome included stroke, acute myocardial infarction, pulmonary embolism, deep vein thrombosis, or arterial thrombosis. Patients were followed until an event, a 7-day gap in concomitant use, SSRI switch, pregnancy, hospitalization, end of study period, end of enrolment, or 365 days, whichever came first. A Cox proportional hazard regression with stabilized inverse probability of treatment weighting was used to compare the risk of thromboembolism (TE) among SSRIs with concomitant use of HCAs, adjusting for the time from initiating HCAs to index date to control for changing hazards of HCAs over time.

Results: The adjusted hazard ratio (HR) for each SSRI-HCAs combination were: fluoxetine versus paroxetine HR= 0.24 (0.08-0.74), fluoxetine versus sertraline HR=0.31 (0.14-0.70), fluoxetine versus citalopram/escitalopram HR=0.31 (0.14-0.69), paroxetine versus sertraline HR= 1.28 (0.50-3.25), paroxetine versus citalopram/escitalopram HR= 1.29 (0.52-3.20), and sertraline versus citalopram/escitalopram HR=1.01 (0.61-1.68). Sensitivity analyses changing allowable exposure gaps provided consistent findings.

Conclusions: In this study, women in childbearing age with concomitant use of HCAs and fluoxetine had lower risk of thromboembolic events compared to those with concomitant use of HCAs with other SSRIs. Other combinations showed similar risk, but confidence intervals were wide.

4600 | Analysis renal dysfunction incidence caused by acyclovir injection in a regional teaching hospital in Taiwan

Suhan Hsu, Chia-Hui Lin and Yea-Jou Lou

Department of Pharmacy, YangMin Branch Taipei City Hospital, Taipei, Taiwan, Taiwan

Background: Literatures had reported only a few cases of renal failure caused by acyclovir injection and lack of Asia reports.

Objectives: To determine the rate of acyclovir induced renal dysfunction.

Methods: This study is a retrospective pilot study with chart review, which included patients who received acyclovir for in-hospital injection (IV acyclovir) during 2018-2019. Exclusion criteria are poor renal function at baseline, no renal function records, and use IV acyclovir less than one day. The study outcome was the number of cases with renal dysfunction, including diagnosis of acute renal failure (AKI) or whether the event of renal dysfunction occurred after the use of IV acyclovir. The incidence of renal dysfunction was analyzed by excel 2010.

Results: During 2018-2019 study period, a total of 70 patients used IV acyclovir. After screening by exclusion criteria, 57 patients were finally entered into the analysis. Analysis of 57 cases, 56% were female (N = 32) and 44% were male (N = 25), with an average age of 69 ± 2.23 years old. All of them have herpes-related diagnosis. There are 22.8% (N = 13) of patients whose renal function was abnormal but all had been adjusted acyclovir dosage by patient renal function. 5 cases (8.7%) developed renal dysfunction after IV acyclovir, 2 of whom had clinical diagnosis of AKI and 3 had clinical symptoms without diagnosis. 1 of 5 cases had concurrently used other medicine that are likely to cause renal dysfunction, but the other 4 were not. After finishing IV acyclovir therapy, all 5 cases' renal function returned to normal. None of them had severe complications. 4 patients with normal renal function receive 0.9% normal saline hydration during IV acyclovir used.

Conclusions: The pilot study shows that there are clinical cases of suspected renal dysfunction caused by acyclovir. The incidence rate obtained from the study is higher than that mentioned in the literature, but the severity is not as high as previous reported. Although every effort has been made to eliminate the possible causes of renal dysfunction in the study, there are still many possible causes that cannot be ruled out. More studies are expected to understand IV acyclovir related renal dysfunction to improve medication safety.

4654 | Risk of acute liver injury with protease inhibitor-based antiviral therapy for hepatitis C

Jessie Torgersen[1], Craig W. Newcomb[1], Dena M. Carbonari[1], Christopher T. Rentsch[2,3], Lesley S. Park[4], Rajni Mehta[5,3], Kathryn D'Addeo[5,3], Tamar Taddei[5,3], Amy C. Justice[5,6,3] and Vincent Lo Re, III[1]

[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]VA Connecticut Healthcare System, West Haven, CT; [4]Stanford University, Palo Alto, CA; [5]Yale University School of Medicine, New Haven, CT; [6]Yale University School of Public Health, New Haven, CT

Background: Spontaneous adverse event reports have identified acute liver injury in hepatitis C virus (HCV)-infected initiators of protease inhibitor (PI)-based direct-acting antivirals (DAAs), predominately among people with decompensated cirrhosis. While cytochrome P450 impairment in cirrhosis may result in toxic levels of PIs, no comparative analyses have been performed to evaluate whether initiators of PI-based DAA have higher rates of acute liver injury than those treated with a non-PI-based DAA by cirrhosis status.

Objectives: To compare rates of acute liver injury with PI- versus non-PI-based DAA, accounting for baseline cirrhosis status.

Methods: We evaluated incidence rates of three acute liver injury outcomes among HCV-infected initiators of PI-based (i.e., elbasvir/grazoprevir, glecaprevir/pibrentasvir, paritaprevir/ritonavir/ombitasvir +/- dasabuvir) and non-PI-based (i.e., sofosbuvir/ledipasvir, sofosbuvir/velpatasvir) DAA therapy in the Veteran Birth Cohort between January 1, 2014 and September 30, 2017. The outcomes included incident: 1) alanine aminotransferase (ALT) >200 U/L, 2)

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

severe hepatic dysfunction (defined as international normalized ratio ≥1.5 and total bilirubin >2 times upper limit of normal), and 3) hepatic decompensation (defined by ICD-9 and ICD-10 diagnoses) during or within 30 days following DAA treatment initiation. Results were stratified by baseline Fibrosis-4 Index for Hepatic Fibrosis (FIB-4) strata. Logistic regression was used to create propensity scores for PI-based versus non-PI-based DAA using date of treatment along with baseline clinical and demographic variables. Propensity score-adjusted hazards ratios (HR) were calculated.

Results: 13,403 HCV-infected patients initiated PI-based DAA, while 47,133 started non-PI-based DAA. Unadjusted incidence rates of ALT >200 U/L were higher for PI than non-PI initiators (22.6 vs. 5.4 per 1,000 person-years [py]), but there were no differences in rates of either severe hepatic dysfunction (6.3 vs. 6.3 per 1,000 py) or hepatic decompensation (4.7 vs. 6.9 per 1,000 py). PI-based DAA had higher risk of ALT >200 U/L among both FIB-4 strata (FIB-4 ≤3.25: HR: 5.1; 95% CI: 3.5-7.2; FIB-4 >3.25: HR: 3.1; 95% CI: 1.4-7.0); however; no differences were observed for other acute liver injury outcomes in either FIB-4 strata.

Conclusions: Risk of incident ALT elevations was increased among PI-based versus non-PI-based DAA initiators, but there were no significant differences in risk of severe hepatic dysfunction or hepatic decompensation between the groups.

4655 | Fracture incidence on tenofovir disoproxil fumarate: A south African cohort analysis

Johannes P. Mouton, Karen Cohen and Gary Maartens
University of Cape Town, Cape Town, South Africa

Background: Antiretrovirals (ARVs), specifically tenofovir disoproxil fumarate (TDF), efavirenz (EFV) and protease inhibitors (PIs), have been implicated in bone mineral density loss which may cause fractures. The incidence of fractures in African cohorts of people living with HIV (PLWH) and the influence of ARVs is not well known.

Objectives: To determine the incidence of fractures in a cohort of PLWH newly started on ARVs. To describe the difference in fracture incidence between users and non-users of TDF.

Methods: We conducted a cohort analysis of privately insured adult (>= 18 y) PLWH managed under the Aid for AIDS (AfA) disease management program who newly commenced ARVs between Jan 2011 and Sep 2018. We excluded persons with ARV exposure before AfA enrolment. Outcome was first fracture identified from ICD10 codes submitted with insurance claims. We determined time-updated TDF exposure from claims. We used generalized estimation equations with Poisson regression to determine the incidence rate ratio (IRR) among TDF users and non-users. In these models we adjusted for 1) demographic and clinical covariates: age, sex, chronic kidney disease, alcohol-related hospitalisations, chronic obstructive airways disease (COPD, proxy for smoking), malignancies and highest decile of corticosteroid use; 2) time-updated HIV covariates (CD4 count, viral load and backbone ARV, classified as EFV, nevirapine, PI or other); and 3) time-updated exposure to oestrogens, testosterone or bisphosphonates.

Results: We identified 912 fractures among 92,940 persons (53,468 (58%) female, median age 38 years, follow-up 244,503 person-years (PY)). Incidence was 3.7 per 1,000 PY. Adjusted IRR for ever versus never TDF use was 1.27 (95% CI 1.00 to 1.61). Adjusted IRRs for duration of exposure to TDF were, versus no exposure, 1.21 (0.95 to 1.55) for 0 to 2 years, 1.28 (0.99 to 1.67) for 2 to 4 years, 1.44 (1.07 to 1.92) for 4 to 6 years, and 1.78 (1.18 to 2.68) for 6 to 7.75 years. Adjusted IRRs were significant for the following covariates: male sex 1.45 (1.26 to 1.66), alcohol-related hospitalisations 3.56 (2.50 to 5.05), COPD 3.15 (2.05 to 4.85), testosterone use 4.40 (1.41 to 13.7) and viral load 0.91 (0.86 to 0.96) per log unit increase. There was no association with backbone ARV.

Conclusions: In this cohort of mostly young, female, African PLWH traditional fracture risk factors including alcohol use and smoking showed a strong association with fractures. TDF use was associated with fracture incidence with an increasing incidence with longer duration of exposure. The associations with male sex and suppressed viral load require further exploration.

4703 | Impact of metabolic profiles on drug safety in routine care in Germany: Results from the EMPAR study

Steffen Heß[1], Michael Steffens[2], Jochen Fracowiak[2], Tatjana Hübner[2], Daria Langner[3], Marco Garling[4], Felix Falkenberg[4], Christoph Roethlein[5], Willy Gomm[5], Roland Linder[4], Julia Stingl[6] and Britta Hänisch[5]
[1]Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany; [2]Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany; [3]Techniker Krankenkasse, Hamburg, Germany; [4]Techniker Krankenkasse, Hamburg, Germany; [5]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [6]University Hospital of RWTH Aachen, Aachen, Germany

Background: The individual response to drug treatment and the occurrence of adverse drug reactions (ADRs) can be affected by genetic variability in metabolic profiles. However, the magnitude of the effect within a real world setting is largely unknown and needs to be determined in order to assess the clinical utility of pharmacogenetic testing in routine care.

Objectives: The EMPAR project is designed to determine the effect of metabolic profiles on drug safety in routine care in Germany.

Methods: EMPAR is a cohort study focusing on users of drugs which are considered to be influenced by pharmacogenetic variants. Study participants are insured by the Techniker Krankenkasse, have at least one prescriptions of a pharmacogenetically relevant drug and provide DNA samples for the analyses of metabolic profiles. Patient groups involved in the study comprise users of anticoagulants, statins, as well as patients who received an ICD-10 Y57.9 diagnosis of ADRs. One of the objectives of EMPAR is to study how the risk of ADRs after use of a pharmacogenetically relevant drug can be influenced by the

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patient's individual metabolic profile. The enzymes of interest comprise e.g. cytochrome p450 enzymes, such as the enzymes CYP2C9, CYP2C19 and CYP3A4 whose encoding genes are determined from DNA samples. The occurrence of ADRs in routine care data are compared amongst groups of varying metabolic profiles. In further pharmacoepidemiological analyses, we study parameters which correlate with ADRs, health care utilization, and economic outcomes.

Results: So far, we determined the metabolic profiles of 7668 users of pharmacogenetically relevant drugs and combined it with clinically relevant information from routine care data. Thus, we are able to show differences in the occurrence of severe ADRs, such as bleeding and thromboembolic events for anticoagulants, depending on the combination of the type of drug and individual metabolic profiles.

Conclusions: With the EMPAR study, we are the first to examine the effect of metabolic profiles on drug safety with German routine care data. The results provide insights into the clinical utility of pharmacogenetic testing in routine care.

4761 | The risk of muscular events among new users of different statins: An observational cohort study

Alexandra M. Mueller[1,2], Evangelia Liakoni[3], Cornelia Schneider[1,2], Theresa Burkard[1,2], Susan S Jick[4,5], Stephan Krähenbühl[6,7], Julia Spoendlin[1,2] and Christoph R. Meier[1,2,4]

[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [3]Clinical Pharmacology and Toxicology, Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [4]Boston Collaborative Drug Surveillance Program, Lexington, MA; [5]Boston University School of Public Health, Boston, MA; [6]Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Basel, Switzerland[7]Department of Biomedicine, University of Basel, Basel, Switzerland

Background: Statins are effective drugs for the prevention of cardiovascular disease, but they frequently cause adverse muscular events. Hydrophilic statins (pravastatin, rosuvastatin) may cause less muscular events than lipophilic statins (e.g. simvastatin, atorvastatin) due to low passive diffusion into muscle cells.

Objectives: We aimed to compare the risk of muscular events between different hydrophilic and lipophilic statins at comparable lipid-lowering doses.

Methods: We conducted an observational cohort study using data from the UK-based Clinical Practice Research Datalink. We identified all new statin users to perform the following pairwise comparisons: (1) pravastatin 20-40 mg vs simvastatin 10-20 mg, (2) rosuvastatin 5-40 mg vs atorvastatin 10-80 mg, and (3) simvastatin 40-80 mg vs atorvastatin 10-20 mg. For each comparison, we conducted propensity score (PS) matching accounting for 40 baseline covariates. The primary endpoint was a first record of a muscular event (i.e. myopathy, myalgia, myositis, rhabdomyolysis) during a maximum follow-up of 1 year. Patients were censored if they stopped or switched the initially prescribed statin. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) for the comparative risks of muscular events.

Results: The PS-matched cohorts consisted of (1) 9'703, (2) 7'032, and (3) 37'743 pairs of new statin users. After PS-matching, the incidence rate (IR, per 1000 person-years) of muscular events was 10.8 in pravastatin users and 12.5 in simvastatin users. In the PS-matched cohort of rosuvastatin vs atorvastatin, IRs of muscular events were 17.8 and 15.2, respectively, and in the PS-matched cohort of simvastatin vs atorvastatin, 16.5 and 12.4. Low-intensity statin therapy with pravastatin (hydrophilic) was associated with a lower risk of muscular events than low-intensity statin therapy with the lipophilic simvastatin (HR 0.86 [95% CI 0.64-1.16]). Comparing statins for the moderate- to high-intensity statin therapy yielded a HR of 1.17 (95% CI 0.88-1.56) for rosuvastatin (hydrophilic) when compared to equivalent doses of atorvastatin (lipophilic) and a HR of 1.33 (95% CI 1.16-1.53) for simvastatin compared to atorvastatin.

Conclusions: Our results do not suggest a systematically lower risk of muscular events for hydrophilic statins when compared to lipophilic statins at comparable lipid-lowering doses. Hydrophilic or lipophilic properties of statins do not seem to predict the risk of muscular events.

4801 | Rapid cycle analytics to obtain descriptive insight into drug utilisation and background disease rates: building on the sentinel modular programs

Jolyon Fairburn-Beech[1], Jiajun Wen[2], Rachel Williams[3], John Logie[1], Marianne Cunnington[1] and Andrew Bate[1]

[1]GlaxoSmithKline, London, United Kingdom; [2]John Hopkins University, Baltimore, MD; [3]GlaxoSmithKline, Philadelphia, PA

Background: Innovation in digital technologies, data access and advanced analytics is rapidly changing the possibilities for pharmacovigilance and contextualisation of emerging clinical safety data. Opportunities now exist to harness multiple approaches to implement rapid cycle analytics. FDA's Sentinel data network proved an early example of mapping data from disparate sources to a common data model, enabling rapid analytics and hypothesis driven safety studies. However, increasingly pan-regional data are required. The emergence of new analytic tools and alternative common data models provides an opportunity to explore and compare alternative rapid cycle analytic capabilities.

Objectives: To evaluate alternative approaches to rapid cycle, descriptive analytics to support contextualisation of observed events, using the existing Sentinel modular programs as a guide.

Methods: We selected descriptive analyses that could be deployed using existing rapid analytic tools including incidence and prevalence, drug utilisation, treatment patterns, comorbidities and concomitant medications. All analyses were compared with existing Sentinel modules 1, 2, 5 and 6 as provided in July 2019; analyses was conducted in

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the Instant Health Data Tool (IHD). We created a cohort of new users of *belimumab* between 2011 and 2018 from the IBM® MarketScan® Research database and compared quantitative difference in outputs as well as qualitatively evaluating the analytical implementation.

Results: We were able to replicate the functionality of the Sentinel modules within IHD but with increased flexibility. In our cohort of 3,486 belimumab initiators, analysis output was consistent between Sentinel and our custom-built modules. Proportion of new users and demographics were similar between Sentinel and IHD (1.73% vs 1.29% of SLE patients, 93% female, mean age 44.1 v 44.4 years). Background rates of common comorbidities were also similar; prevalence of prior kidney disease, a common lupus comorbidity, was found to be 13.8% using the Sentinel modules vs 13.3% with the customised approach.

Conclusions: We evaluated a suite of descriptive analyses against the Sentinel programs and showed similar insights can be gained without the need to build internal Sentinel capabilities. All comparisons were conducted using the IHD tool but could be replicated in other tools or in alternative common data models or data sources.

4878 | Healthcare utilization of prescribing long-term opioids in HIV patients who initiated art: A retrospective cohort study

GYeon Oh[1,2], Erin L. Abner[1,3,4], David W. Fardo[3,4], Patricia R. Freeman[5,6] and Daniela C. Moga[1,3,5,6]

[1]*University of Kentucky, Lexington, KY;* [2]*University of Kentucky, Lexington, KY;* [3]*University of Kentucky, Lexington, KY;* [4]*University of Kentucky, Lexington, KY;* [5]*University of Kentucky, Lexington, KY;* [6]*University of Kentucky, Lexington, KY*

Background: Chronic pain is common among patients diagnosed with HIV, with about half receiving opioid prescriptions. The potential effect of opioids on immune function, combined with their misuse potential, calls for a thorough investigation of benefits and risks opioid prescribing, especially long-term (LT) use in vulnerable populations.

Objectives: To examine the healthcare utilization associated with LT opioid use in HIV patients, compared to a group of HIV patients with no LT opioid use.

Methods: Using Medicaid data (2002-2009) from four US states [Kentucky, Maryland, North Carolina, and Washington], we conducted a retrospective cohort study to examine healthcare utilization of LT opioid use in HIV patients initiating combined antiretroviral therapy (cART). LT opioid use was defined as 90 days of continuous use over a six-month period, accepting < 32 days gap (index date). Among HIV diagnosed beneficiaries, incidence density sampling was used to select the unexposed group (1:5 ratio), matched on year of starting cART. Follow-up extended from the index date to the end of the study, or the time of LT opioid use initiation for those in the unexposed group. Zero-inflated negative binomial and Cox proportional hazard regressions were used to examine the risk of emergency department (ED) visits and HIV-related hospitalization. We estimated adjusted rate ratios (aRR) and hazard ratios (aHR) with 95% confidence intervals (CI). Confounders (demographics, comorbidities, other medications) were selected using causal diagrams and were measured six-months prior to the start date of LT opioid use.

Results: Among 9,601 eligible patients, 1,000 were identified as LT opioid users [mean (SD) age: 43.5 (7.6) years; 53.2% male], and 5,000 were selected for the unexposed group [mean (SD) age: 41.9 (9.9) years; 53.7% male]. The median follow-up time was 662.5 and 540 days for the exposed and unexposed groups, respectively. Overall rates of ED visit [5.8 vs. 3.3 per 1,000 person-days] and HIV-related hospitalization [1.7 vs. 0.8 per 1,000 person-days] were higher in the exposed group compared to the unexposed group. LT opioid use in the HIV patients was associated with increased risk of ED visit [aRR (95% CI): 1.3 (1.2-1.5); aHR (95% CI): 1.1 (1.0-1.2)] and HIV-related hospitalization [aRR (95% CI): 1.3 (1.1-1.6); aHR (95% CI): 1.3 (1.1-1.4)].

Conclusions: LT opioid use was associated with increased healthcare utilization in HIV-diagnosed Medicaid beneficiaries. Further studies are needed to determine whether this association is causal.

4881 | Comparative safety of antibiotic therapy for outpatient treatment of urinary tract infections

Anne Butler, Michael Durkin, Yinjiao Ma, Matthew Keller, William Powderly and Margaret Olsen

Washington University, St. Louis, MO

Background: Urinary tract infection (UTI) is one of the most common indications for antibiotic prescriptions in otherwise healthy women, yet the comparative safety of antibiotics for empirical therapy is not well-established.

Objectives: To evaluate the safety of guideline-recommended antibiotic regimens for the treatment of outpatient uncomplicated UTI among premenopausal women in the US.

Methods: Using the IBM® MarketScan® Commercial Database (2006-2015), we identified healthy, non-pregnant, commercially-insured women aged 18-44 who received a new outpatient diagnosis of UTI plus a same-day antibiotic prescription with activity against common uropathogens. Patients were followed for outcomes with varying follow-up periods: 3 days (anaphylaxis), 14 days (acute renal failure, skin rash, urticaria/hives, nausea/vomiting, abdominal pain), 30 days (vaginitis/vulvovaginal candidiasis, non-C. difficile diarrhea), and 90 days (C. difficile diarrhea, pneumonia, tendinopathy, retinal detachment). Patients were censored for hospitalization, disenrollment, end of study, or subsequent antibiotic prescription (except for treatment of C. difficile or pneumonia). We estimated propensity score-weighted hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazards models.

Results: Of 1,140,602 eligible women, the distribution of antibiotic receipt was fluoroquinolones (44%), trimethoprim-sulfamethoxazole (TMP/SMX) (28%), nitrofurantoin (24%), narrow-spectrum B-Lactam/B-Lactamase inhibitor combinations ("B-Lactams") (3%), broad-spectrum B-Lactams (1%), and amoxicillin/ampicillin (1%). Of two first-line agents, we observed higher risk of outcomes among

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TMP/SMX vs. nitrofurantoin initiators: acute renal failure (HR 2.46, 95% CI 1.46-4.14), skin rash (HR 2.43, 95% CI 2.13-2.77), urticaria (HR 1.35, 95% CI 1.18-1.56), nausea/vomiting (HR 1.19, 95% CI 1.10-1.29) and abdominal pain (HR 1.14, 95% CI 1.09-1.19). Compared to nitrofurantoin, non-first-line agents (fluoroquinolones, broad-, and/or narrow-spectrum B-Lactams) were associated with higher risk of acute renal failure, skin rash, nausea/vomiting, abdominal pain, vaginitis/vulvovaginal candidiasis, diarrhea (C. difficile & non-C. difficile), pneumonia, and tendinopathy.

Conclusions: The risk of adverse drug events differs widely by antibiotic agent, with substantial differences in first-line agents. Understanding the safety of antibiotic therapy is critical to prevent suboptimal antibiotic prescribing, reduce adverse events, and ultimately combat antibiotic resistance.

5068 | A universal method to obtain prediction intervals for prevalence and rate parameters estimated from meta-analyses

Tibor Schuster and Araceli Gonzalez Reyes
McGill University, Montreal, QC, Canada

Background: Pooling prevalence and rate estimates from epidemiological studies using meta-analysis (MA) methods is a common and useful approach for synthesizing real-world evidence. Recently, prediction intervals (PIs) have emerged as a valuable measurement of between study (or between population) heterogeneity, but their calculation remains problematic when applied to proportions or rates, and can easily yield misleading results using conventional estimation approaches.

Objectives: We aimed to provide a universal method to calculate PIs that provide valid coverage regardless the underlying parameter distribution and the heterogeneity of included study sizes.

Methods: We conducted a systematic literature review and meta-analysis of observational studies reporting the prevalence or rate of exposure to drug-drug interactions among non-elderly community-dwelling outpatient adults. Prevalence and event rate estimates were pooled to obtain 95% PIs using two recommended methods: (1) Inverse-variance estimation, using Freeman-Tukey double arcsine transformation, (2) generalized linear mixed modeling (GLMM). In addition, we employed Monte-Carlo sampling from binomial & exponential distributions, emulating 10,000 meta analyses with the equivalent effect and sample size distribution as the original MA (parametric bootstrapping). PIs were compared to those obtained using currently recommended methods.

Results: Our systematic literature review identified 12 eligible studies (out of 5449 identified studies) with high heterogeneity in study size, prevalence proportions, and event rates. The smallest study included 52 participants and 104 person-months of follow-up, while the largest studies had 652753 participants and 12.7 million person-months of follow-up. PIs for pooled prevalence estimates using the inverse variance method, GLMM, and parametric bootstrapping were, respectively: 0.07 to 0.40, 0.01 to 0.84, and 0.01 to 0.80. Event rates per 1000 person-months of follow-up were 8.87 to 68.7, 0.51 to 792.23, and 0.57 to 152.07.

Conclusions: The heterogeneity of obtained PIs depending on the method chosen underscores the need for a robust method to compute PIs. The recommended inverse-variance with Freeman-Tukey double arcsine transformation leads to artificially narrow PIs for both prevalence estimates, as previously reported, as well as for event rates. Our results suggest that the use of GLMM for pooling event rates appears vulnerable to inflation of standard errors and associated PI widths.

Vaccines

37 | Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease

J. Bradley Layton[1], Leah J. McGrath[2], John M. Sahrmann[3], Yinjiao Ma[3], Vikas R. Dharnidharka[4], Caroline O'Neil[3], David J. Weber[5] and Anne M. Butler[3,6]
[1]RTI Health Solutions, Research Triangle Park, NC; [2]NoviSci, Durham, NC; [3]Washington University School of Medicine, St Louis, MO; [4]Washington University School of Medicine, St Louis, MO; [5]University of North Carolina at Chapel Hill, Chapel Hill, NC; [6]Washington University School of Medicine, St Louis, MO

Background: High-dose influenza vaccine (HDV) is an option for patients with end-stage renal disease (ESRD), though the safety of HDV has not been evaluated in this population.

Objectives: The objective of this study was to estimate the relative occurrence of adverse reactions in patients with ESRD following vaccination with HDV compared with standard-dose influenza vaccine (SDV).

Methods: Using data from the United States Renal Data System, patients with ESRD aged ≥ 65 years were identified on the date of influenza vaccination during yearly influenza seasons (2010-2016). In each outcome-specific analysis, patients were followed from vaccination to observe serious (anaphylaxis, angioedema, seizure, encephalopathy, Guillain-Barré syndrome, and short-term mortality) and milder (urticaria/hives, rash, pain in limb, cellulitis, myalgia/myositis, fever, nausea and vomiting, diarrhea, and syncope) events. Propensity score-weighted hazard ratios (HR) and 95% confidence intervals (CI) comparing recipients of HDV to SDV were estimated with Cox proportional hazards models.

Results: Of 520,876 vaccinated patients (mean age = 74.7, standard deviation = 7.0; 63% white race), 7.4% received HDV. Crude incidence rates of serious events were low. HRs were inestimable for anaphylaxis, angioedema, and Guillain-Barré syndrome due to too few cases, and HRs for seizure, encephalopathy, and mortality were null. HRs for some minor events were increased in the HDV group: rash (HR = 1.86; 95% CI: 1.34-2.57), diarrhea (HR = 1.26; 95% CI: 1.07-1.50), pain in limb (HR = 1.23; 95% CI: 1.12-1.34), and myalgia/myositis (HR = 1.16; 95% CI: 1.04-1.30). This pattern was consistent in subgroup and sensitivity analyses.

Conclusions: HDV recipients had increased risks of several minor events, while the risks of severe events were generally low and similar between the treatment groups, consistent with clinical trials findings

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

in the general population of older adults. The risk-benefit tradeoff of HDV versus SDV use in patients with ESRD should be carefully considered given these safety data, increases in national use of HDV, and high comorbidity burden in this population.

2339 | Equality analysis on three doses coverage of DPT vaccine among children aged 12-59 months in China

Xiaoli Liu, Lin Zeng, Xiaoxiao Wang, Lin Zhuo, Hua Zhang, Nan Li, Liyuan Tao, Yanyan Shi, Yiming Zhao and Hongling Chu
Peking University Third Hospital, Beijing, China

Background: Diphtheria pertussis tetanus (DPT) vaccine is one of the important vaccines in children's routine immunization. Three full doses of DPT vaccine are the best way to control pertussis, diphtheria and neonatal tetanus. There are relatively few studies on the vaccination coverage of DPT vaccine in China, and research on disparities in coverage is scarce.
Objectives: To understand three doses coverage of DPT vaccine and socio-economic inequality distribution among children aged 12~59 months in 20 counties in 10 provinces of China.
Methods: In China, using three-stage probability proportion to size sampling, 2,892 children aged 12-59 months with an immunization card were selected from 20 counties across 10 counties in 2016. Some socio-economic characteristics were obtained from face-to-face questionnaire survey and copies of vaccination certificates. We performed two-level logistic regression models to identify the determinants and computed the concentration index to evaluate socioeconomic inequality of three doses coverage of DPT vaccine.
Results: In 2016, the overall three doses coverage of DPT vaccine among children aged 12-59 months in the surveyed areas of China was 77.6%. The concentration index value was 0.0376 (P<0.001). In 2016, having a second or higher birth order (adjust OR: 1.38; 95%CI: 1.12-1.70), being born at home (adjust OR: 1.61; 95%CI: 1.04-2.49), having a minority caregiver (adjust OR: 1.36; 95%CI: 1.01-1.84) were significantly related with higher risk of unvaccinated three doses coverage of DPT vaccine.
Conclusions: The socioeconomic inequality in three doses coverage of DPT vaccine still existed in 2016. To improve inequality in three doses coverage, the government should pay more attention to the disadvantaged groups, especially the children who were ethnic minorities, had a second or higher birth order and were delivered at home.

2341 | Vaccination coverage and its determinants of Japanese encephalitis vaccine among children aged 12-59 months in rural counties of China in 2016

Xiaoli Liu, Lin Zhuo, Xiaoxiao Wang, Lin Zeng, Nan Li, Hua Zhang, Yanyan Shi, Liyuan Tao, Hongling Chu and Yiming Zhao
Peking University Third Hospital, Beijing, China

Background: Japanese encephalitis (JE) is caused by the JE virus, a flavivirus transmitted by mosquitoes. The majority of JE virus infections are asymptomatic, with about 0.2-0.4% of the infected individuals developing encephalitis. The vaccination of children with JE vaccine is considered to be the most effective means for prevention of JE virus infection. The Chinese Ministry of Health integrated JE vaccine into the National Immunization Program (NIP), providing free vaccinations for children under 7 years old in the whole country. However, there are still some outbreaks of JE in some parts of China, especially in rural areas. This study attempted to estimate the first dose coverage of JE vaccine in 2016 among children aged 12-59 months in rural areas of China and identify the factors hindering high vaccination coverage in those areas.
Objectives: To understand the first dose coverage of JE Vaccine and its determinants of vaccination coverage among children aged 12-59 months in rural counties of China.
Methods: In 2016, using three-stage probability proportion to size sampling, 2235 children aged 12-59 months with an immunization card, which is the record of children's vaccination and every child should be in accordance with national regulations to establish the immunization card and receive vaccination in China, were selected from 14 rural counties of China in 2016. Some socio-demographic and socio-economic characteristics were acquired from face-to-face questionnaire survey and copies of the immunization cards. We used multivariate logistic regression models to identify the determinants of the first dose coverage of JE Vaccine.
Results: In 2016, the first dose coverage of JE Vaccine among children aged 12-59 months in rural areas of China was 88.5%. The adjusted analysis showed that the children who were born at home (adjusted OR: 2.44; 95%CI: 1.12-5.30) or in households with the lowest per capita income (adjusted OR: 2.70; 95%CI: 1.35-5.39) were significantly related with unvaccinated coverage of the first dose of JE Vaccine.
Conclusions: The first dose coverage of JE Vaccine was still at a relatively low level in 14 rural counties of China. To improve the coverage of Japanese Encephalitis Vaccine, the government should pay more attention to the disadvantaged groups, especially the children who were delivered at home, or from households with the lowest per capita income.

2342 | Variation in influenza vaccination among residents of predominantly white and black long-term care facilities

Elliott Bosco[1], Kevin W. McConeghy[1,2], Patience Moyo[1], Barbara Bardenheier[1], Yoojin Lee[1], Jessica Ogarek[1], Robertus van Aalst[3,4], Ayman Chit[5,4], Vincent Mor[1,2], Stefan Gravenstein[1,2,6] and Andrew R. Zullo[1,2]
[1]Brown University School of Public Health, Providence, RI; [2]Providence Veterans Affairs Medical Center, Providence, RI; [3]University of Groningen, Groningen, Netherlands; [4]Sanofi Pasteur, Swiftwater, PA; [5]University of Toronto, Toronto, ON, Canada; [6]Warren Alpert School of Medicine at Brown University, Providence, RI

Background: Annual assessment and provision of influenza vaccination is both guideline-recommended and legally required for older

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

adults in long-term care facilities (LTCFs). Disparities in vaccination between white and black LTCF residents have been documented, but data are older, not nationally representative, and do not differentiate within versus between LTCF disparities or short-stay versus long-stay residents.

Objectives: To compare the vaccination coverage of white and black residents in LTCFs serving predominantly white or black residents, stratified by short-stay and long-stay status. We hypothesized that vaccination coverage would be lower in black-predominant LTCFs, while differences between white and black residents would be largest in white-predominant LTCFs.

Methods: We conducted a retrospective cohort study using 2013-2014 Medicare claims linked to Minimum Data Set (MDS) assessments and LTCF data from LTCFocus. Short-stay (<100 days) and long-stay (100+ days) LTCF residents were identified during influenza season (October-March). Residents were stratified by race and residence in a predominantly white or black LTCF (≥70% residents white or black). The outcome was LTCF influenza vaccination coverage, the proportion of residents vaccinated as defined by the MDS.

Results: We included 805,321 short-stay (14,252 LTCFs) and 750,404 long-stay residents (14,488 LTCFs). Overall, average influenza vaccination coverage was higher for white short-stay residents [Mean (95% CI): 61.4 (61.0, 61.8)] than black residents [52.6 (51.8, 53.4)], and higher for white long-stay residents [78.0 (77.8, 78.3)] than black residents [72.9 (72.2, 73.5)]. Average short-stay vaccination coverage was higher for white residents [64.1 (63.7, 64.5)] than black residents [55.3 (54.2, 56.4)] in predominantly-white LTCFs, but similar among white [43.6 (39.1, 48.2)] and black residents [43.8 (41.0, 46.6)] in predominantly-black LTCFs. Average long-stay vaccination coverage was higher for white residents [79.8 (79.5, 80.0)] than black residents [74.8 (74.0, 75.7)] in predominantly-white LTCFs, but similar among white [67.9 (64.5, 71.3)] and black residents [66.6 (64.6, 68.7)] in predominantly-black LTCFs.

Conclusions: Vaccination coverage for white and black residents was lowest in black-predominant LTCFs. Differences between white and black residents were largest in white-predominant LTCFs. Efforts to improve influenza vaccination in LTCFs should further investigate reasons (e.g., LTCF quality) for differences in vaccination across and within LTCFs. Funding: Sanofi Pasteur.

2369 | Post-licensure observational safety study after meningococcal B Vaccine (4CMenB) vaccination in routine UK care

Gillian C Hall[1], Ian Douglas[2], Paul T Heath[3], Prab Prabhakar[4], Dominique Rosillon[5], Javeed Khan[6] and Victoria Abbing-Karahagopian[7]

[1]Gillian Hall Epidemiology Ltd, London, United Kingdom; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]St George's University Hospitals NHS Foundation Trust, London, United Kingdom; [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [5]GSK, Wavre, Belgium; [6]IQVIA, London, United Kingdom; [7]GSK, Amsterdam, Netherlands

Background: 4CMenB vaccine was added to other vaccinations given at 2, 4 and 12-13 months of age in the UK National Immunisation Program (NIP) in September 2015.

Objectives: To assess the safety of 4CMenB vaccination within the UK NIP with regards to three primary (seizures, febrile seizures (FS) and Kawasaki disease (KD)) and three secondary (Acute disseminated encephalomyelitis, Guillain-Barré syndrome and anaphylaxis) outcomes as a post-authorisation safety study.

Methods: The study population included children permanently registered at a listed practice in THIN UK de-identified primary healthcare database when aged between 1 and 18 months, from 1st May 2015 to 31st December 2018 (seizures) or to May 2018 (other outcomes), and who received at least one 4CMenB vaccination during this observation period. Outcomes were identified from THIN using Read codes and unstructured text either directly (any seizure and FS) or after case adjudication (other outcomes). Incidence estimates and self-controlled case series (SCCS) analyses used outcome specific risk periods after any 4CMenB exposure. The primary SCCS included only the first event for each outcome, and adjusted for age, year and season comparing incidence in the risk period with that in a control period. A separate pre-exposure period was included in the SCCS analysis.

Results: Four KD cases in a 1-28 day risk period and 23 FS in a 0-6 day risk period were identified after 194,929 4CMenB doses in 89,259 children. Forty-three seizures were identified in a 0-6 day risk period after 239,505 4CMenB doses given to 107,231 children. Day 0 was the day of exposure. No cases of other outcomes were identified in their risk period. The incidence rate per 1,000 person years (PY) was 9.4 (95%CI 6.8, 12.6) for seizures, 6.2 (95%CI 3.9, 9.3) for FS, and 27.3 (95%CI 7.4, 69.8) per 100,000 PY for KD. The adjusted incidence rate ratio from the SCCS were 1.43 (95%CI 1.02, 2.02) for seizures and 1.72 (95%CI 1.08, 2.75) for FS. There were insufficient KD cases for an adjusted SCCS analysis.

Conclusions: Few cases of primary outcomes and no cases of secondary outcomes were identified in risk periods after exposure to vaccinations which included 4CMenB. This exposure is associated with an increased risk of seizures and FS. It is not possible to attribute the finding specifically to one vaccination type as most 4CMenB was given with other vaccines. Increased risks are reported by some previous studies of infant vaccination. KD is rare after vaccinations which included 4CMenB and the small number of cases does not allow us to draw conclusions about any causal association.

2528 | Selecting an appropriate comparator group in vaccine cohort studies of older adults: Recombinant zoster vaccine as an example

Jennifer H. Han[1], Carla A. Talarico[1], Soowoo Back[2], Susan dosReis[3], Aziza Jamal-Allial[4], Cheryl N. McMahill-Walraven[5], Talia J. Menzen[2], Vinit P. Nair[6], Young Hee Nam[2], Josephine C. Ocran-Appiah[1], Jeffrey S. Brown[2] and Katherine W. Yih[2]

[1]GlaxoSmithKline, Rockville, MD; [2]Harvard Pilgrim Health Care Institute, Boston, MA; [3]University of Maryland School of Pharmacy, Baltimore, MD; [4]HealthCore, Inc., Watertown, MA; [5]Healthagen, part of the CVS

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Health Family of Companies, Blue Bell, PA; [6]Humana Healthcare Research, Louisville, KY

Background: Observational studies are critical for assessing effectiveness and safety of vaccines in the real-world setting. However, substantive differences between individuals who do and do not receive the vaccine can lead to a number of biases. Selection of an appropriate comparator group is an important study design consideration, especially in studies of older adults with multiple comorbidities.
Objectives: To identify the most appropriate comparator group for a cohort study assessing safety outcomes in recipients of the two-dose adjuvanted Recombinant Zoster Vaccine (RZV) aged ≥ 50 years.
Methods: Curated administrative data in the Sentinel common data model format from 4 health plan participants in the US Food and Drug Administration's Sentinel Initiative were used to select commercially-insured adults ≥ 50 years of age with medical and drug coverage from 1/2018-1/2019. The exposed group was individuals who received ≥ 1 RZV dose, an adjuvanted subunit vaccine approved in the US for the prevention of herpes zoster in people aged ≥ 50 years. Six different comparator selection algorithms were evaluated, using various combinations of receiving ≥ 1 healthcare utilization service: annual physical exam; age-appropriate screening; annual exam or screening; age-appropriate vaccination; annual exam and influenza vaccination; and outpatient encounter for chronic condition management. Demographics, healthcare-seeking behaviors, and the prevalence of comorbidities and immunosuppressive conditions for the RZV recipient group and the comparator groups were descriptively compared.
Results: 261,050 and 133,256 individuals received ≥ 1 and two doses of RZV, respectively, during the study period. The number of individuals with ≥ 1 comparator visit ranged from 1,666,326 to 6,698,184, depending on the definition. The mean age for each of the comparator groups was similar to that of RZV recipients (68 years, standard deviation, 9). However, there was substantial variation in the prevalence of some comorbidities across the six comparator groups compared to RZV recipients. Adults who received a routine annual physical exam or an age-appropriate preventive screening measure were one of the most comparable unexposed groups compared to RZV recipients.
Conclusions: Differences among potential comparator groups highlight the importance of the rigorous selection of a comparator group in cohort studies evaluating vaccine effectiveness or safety, especially in older adults who have multiple comorbidities.

2529 | A broad safety assessment of the 9-valent human papillomavirus vaccine

Katherine Yih[1], Martin Kulldorff[2], Inna Dashevsky[1] and Judith Maro[1]
[1]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: Uptake of human papillomavirus (HPV) vaccine lags behind that of other adolescent vaccines. In recent surveys of parents, safety has been cited as the top concern.
Objectives: To apply a new data-mining method to evaluate whether any of thousands of health outcomes was associated with HPV9.
Methods: We extracted data from the IBM Watson® MarketScan® Research Databases on persons 9-26 years of age who were vaccinated during 4 Nov 2016—5 Aug 2018. HPV9 was identified using CPT and NDC codes. Outcomes were identified using ICD-10-CM codes. The analysis used the hierarchical ICD-10 code structure, which consists of 21 broad categories of diagnoses, each branching into progressively more specific diagnoses. No codes were removed from the tree. Cases ascertained in the hospital or emergency department during follow-up that were not preceded by the same 3-character code in 400 days were included in analysis. We used the self-controlled tree-temporal scan statistic to detect any clustering of cases within the tree of diagnoses and, simultaneously, any temporal clustering of cases within the 1 year of follow-up. We allowed patients to contribute data even if they disenrolled < 1 year after vaccination. The multiple testing was adjusted for by Monte Carlo simulation.
Results: With 493,089 doses of HPV9 vaccine in the main analysis, there were 10 sets of statistically significant signals ($p \leq 0.05$). Four were for delivery-related outcomes, with risk windows ranging between Days 232 and 362 post-vaccination. Two represented general categories of immunization-related adverse event, e.g., "Other complications following immunization," all during Days 1-2, with attributable risks ranging from 1.0 to 1.6 cases per 100,000 vaccinees. The other 4 sets of signals were for influenza (2 sets), with risk windows starting months after vaccination, "Other injury of unspecified body region" during Days 1-71, and "Other specified post-procedural states" during Days 7-65.
Conclusions: Based on previously published work on HPV4, the signals for general immunization-related adverse events on Days 1-2 likely indicate known vaccine reactions such as injection site pain. The birth/delivery signals were due to confounding by contraindication, HPV vaccination being contraindicated during pregnancy. The influenza signals reflected time-varying confounding, related to most HPV first doses being given in August. In spite of these instances of temporal confounding, considering the broad scope of the evaluation and the high statistical power, the findings should serve to reassure those concerned about the safety of HPV9.

2541 | The influenza vaccination continuity in Korean elderly with high-risk conditions

Na-Young Jeong[1], Chulwoo Rhee[2], Joongyub Lee[3], Byung-Joo Park[4] and Nam-Kyong Choi[1]
[1]Ewha Womans University, Seoul, Republic of Korea; [2]International Vaccine Institute, Seoul, Republic of Korea; [3]Inha University Hospital, Incheon, Republic of Korea; [4]Seoul National University College of Medicine, Seoul, Republic of Korea

Background: Since different flu viruses circulate every year and change during flu season, influenza vaccination is needed every year.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

In particular, the continuity of influenza vaccination is essential to the people at high risk for complications in the case of influenza infection such as elderly and patients with specific diseases.

Objectives: To evaluate the continuity of influenza vaccination during the 2015/16 to 2017/18 flu seasons for elderly with high-risk conditions.

Methods: We used linked databases of the Korea Centers for Disease Control & Prevention's vaccination registry, which contains all National Immunization Program vaccination records, and the National Health Insurance Service claims data. The patients with high-risk conditions were defined as those who visited ≥1 in inpatient setting or ≥3 in outpatient setting for the influenza season, Sep 30 to Apr 30, and the preceding 8 months with diseases specified by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices as high-risk groups. Those who died before Apr 30, 2018 were excluded. The proportion of vaccination for each season were calculated, and the association of vaccination continuity and the types or the number of diseases were assessed by using logistic regression.

Results: A total of 1,617,546 elderly who had at least one high-risk disease and at least one flu vaccination during the three seasons were identified. Among them, 1,247,297 (77.11%) were vaccinated in all three seasons. In patients with one high-risk condition in all three seasons, people with pulmonary disease, cardiac disease, or diabetes had higher odds of vaccination continuity (Pulmonary: 1.22, 1.20-1.23; Cardiac: 1.15, 1.13-1.16; Diabetes: 1.15, 1.14-1.17), while patients with liver disease, renal disease, Immunodeficiency disease, or cancer were less likely to vaccinated successively. People with more than one high-risk condition during all flu seasons are likely to be vaccinated continuously than those with only one condition (1.06, 1.04-1.08).

Conclusions: We observed that of all high-risk elderly were vaccinated in all three seasons, which means the vaccination continuity were high. Because this study used only 3 seasons from the 2015/16 flu season, further studies using more influenza seasons are needed.

2552 | Operational considerations and challenges in use of an external comparator arm to contextualize safety data from maternal immunization trials: The South Africa epidemiology of obstetric and neonatal outcomes (SAFE ONE) study example

Vera Frajzyngier[1], Jean Le Roux[2], Shobna Sawry[2], Jeanne Louw[3], Kekane Kebonethebe[4], Lee Fairlie[2], Judith Absalon[5], Shaun Barnabas[3], Samantha Munson[6], Caroline Vika[2] and Clare Cutland[4]
[1]Pfizer, New York City, NY; [2]Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [3]Family Centre for Research with Ubuntu (FAMCRU), Stellenbosch University, Cape Town, South Africa; [4]African Leadership in Vaccinology Expertise (Alive), School of Pathology, Faculty of Health Science, University of the Witwatersrand, Johannesburg, South Africa; [5]Pfizer, Pearl River, NY; [6]Pfizer, Collegeville, PA

Background: Immunization of pregnant women to protect their infants has been shown to be safe and effective, with several vaccines undergoing clinical trials. The availability of expected rates of obstetric and neonatal outcomes in an external comparator cohort helps to contextualize safety signals observed in vaccine development programs and facilitates recognition of true safety concerns.

Objectives: To describe operational challenges and considerations encountered during a retrospective chart review study estimating the incidence of obstetric and neonatal outcomes among pregnant women and their infants at 3 clinical trial sites (and associated clinics/hospitals) in South Africa.

Methods: An electronic composite of individual birth register files from each institution in a region served as a sampling framework, with random sampling of charts proportional to the expected regional recruitment in the clinical trial. Inclusion and exclusion criteria replicated those of the vaccine trial. Data from paper-based or electronic maternity case records were abstracted onto a shared REDCap database. Outcomes were defined using Global Alignment of Immunization Safety Assessment in Pregnancy standardized definitions, and necessitated capture of detailed clinical data spanning antenatal care to post-delivery admissions.

Results: Charts for 9414 women and their newborns were abstracted. Among 10,600 files originally sampled <10% were not located initially and were replaced by subsequent files on a random number list. Potential reasons for missingness included patient referrals to other facilities, filing specific outcomes (e.g. stillbirth) in separate locations, and misfiling. Charts of patients referred to tertiary facilities and filed separately were tracked and abstracted where feasible. Neonatal charts were often systematically missing; bias mitigation necessitated obtaining data from unplanned data sources across various hospital units. Benefits of access to electronically scanned files were offset by misordered and missing pages. Complex pregnancies and/or deliveries required clinically experienced abstractors and additional quality control measures.

Conclusions: Despite careful planning and pilot testing, unanticipated challenges were encountered in the review of both electronically scanned and paper-based source documents. Lessons learned from the SAFE ONE study can inform the design of future chart review-based comparator cohorts in LMIC.

2576 | Pneumococcal vaccination coverage in individuals (16 to 59 Years) with a newly diagnosed risk condition in Germany

Arijita Deb[1], Victoria Louise Parsons[2], Bélène Podmore[2,3], Dominik Beier[4], Wolfgang Galetzka[4], Mai Duong[2], Nawab Qizilbash[2,3], Dennis Haeckl[5], Timo Boellinger[6] and Sarah Mihm[6]
[1]Merck & Co, Kenilworth, NJ; [2]OXON Epidemiology Ltd., London, United Kingdom; [3]London School of Hygiene & Tropical Medicine, London, United Kingdom; [4]InGef, Berlin, Germany; [5]WIG2 GMBH, Leipzig, Germany; [6]MSD Sharp & Dohme GmbH, Haar, Germany

Background: The German Committee on Vaccinations (STIKO) recommends pneumococcal vaccination for individuals with certain underlying medical conditions who are at increased risk of developing

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

pneumococcal disease such as those with congenital or acquired immune-deficiencies or immunosuppression, anatomical and foreign-material associated risks for pneumococcal meningitis and chronic conditions.

Objectives: This study estimated the pneumococcal vaccine coverage rate (VCR) among individuals aged between 16 to 59 years in Germany recommended to receive pneumococcal vaccination, according to the STIKO.

Methods: A retrospective cohort database analysis was conducted using the German InGef database. The study population comprised individuals aged between 16 to 59 years with at least one new at-risk (chronic conditions) or high-risk condition (immunocompromising conditions). The study cohorts were identified at time of first diagnosis in each calendar year from 2014 to 2016 and were followed up until 2017 (2 to 4 years follow-up). The underlying medical conditions were identified using International Classification of Diseases, 10th revision, German Modification (ICD-10 GM) codes, German Procedure Classification (OPS) codes and German doctor fee's schedule (EBM) codes in the InGef research database.

Results: The pneumococcal VCR among adults under 60 years with risk conditions after four years of follow-up increased slightly from 2014 to 2017 from 0.33% to 0.97%. Adults aged 50 to 59 years were more likely to be vaccinated than those aged 16 to 49 years. Adults with high-risk conditions were more likely to be vaccinated than adults with at-risk conditions (1.98% vs. 0.79% in 2017). A higher number of risk conditions increased the likelihood of vaccination. Median time to vaccination from the first diagnosis of the risk conditions was 385 days and 451 days, respectively, for adults with at-risk conditions and high-risk conditions.

Conclusions: Despite recommendations from STIKO, pneumococcal vaccination coverage remains suboptimal in vulnerable populations. Further efforts are required to raise awareness and increase immunization levels among individuals with risk conditions.

2635 | Utilization of a booster dose of influenza vaccine among adults with end-stage renal disease in the United States

Leah J. McGrath[1], J. Bradley Layton[2], John M. Sahrmann[3], Vikas R. Dharnidharka[3], Caroline A. O'Neil[3] and Anne M. Butler[3]

[1]NoviSci, Durham, NC; [2]RTI Health Solutions, Research Triangle Park, NC; [3]Washington University in St. Louis, St. Louis, MO

Background: Evidence suggests that neither the standard-dose nor high-dose influenza vaccines are effective among patients with end-stage renal disease (ESRD). A second, booster dose of standard-dose vaccine may provide better protection than a single dose, but it is unknown whether a booster dose is used in clinical practice.

Objectives: To compare baseline characteristics of patients with ESRD who receive one versus two doses of influenza vaccine in a given influenza season, overall and by influenza season.

Methods: Patients with ESRD receiving hemodialysis were identified in the United States Renal Data System during each influenza season from 2010 to 2016. Patients were eligible for multiple seasons. Standard-dose vaccines of any type were identified between August 1 and the end of the influenza season, except for the season starting in 2016, where the data ended on December 31. Baseline demographics were assessed on the date of the first vaccination date. Healthcare utilization measures were assessed during the 30 days before the first vaccination date. We compared patient characteristics of one vs. two-dose recipients using a standardized mean difference (SMD).

Results: Of 1,076,535 influenza vaccine recipients, 2.2% received at least two doses of standard-dose vaccine during a single influenza season. This proportion was similar for all influenza seasons. There was little difference between patients with one and two doses with regards to demographics. However, two-dose recipients were more likely to be dual-eligible for Medicaid than one-dose recipients (64% versus 51%; SMD = 0.26). Similarly, two-dose recipients had a higher prevalence of skilled nursing facility stays in the 30 days prior to the vaccination date (10% versus 4%, SMD = 0.26). The pattern was similar for hospitalization days. Vaccination was administered more often in the outpatient setting than in the dialysis clinic, regardless of dose. Among two-dose recipients who received the first dose in the dialysis clinic, 85% received the second dose in an alternate setting.

Conclusions: A small proportion (~2%) of vaccinated patients received two doses in one influenza season. Some patients received the second dose in a different setting from the first, perhaps in part due to an inability to transfer medical history data across health care facilities resulting in inadvertent re-vaccination, or a true perceived need for a booster dose. Investigating the effectiveness of a two-dose vaccination strategy could be possible if differences in health care utilization can be addressed in the analysis.

3759 | Influenza vaccination in adult patients with hypertension or diabetes in South Korea: A cross-sectional study

Seon-Ha Kim[1], Sangshin Park[2] and Nam-Kyong Choi[1]

[1]Ewha Womans University, Seoul, Republic of Korea; [2]University of Seoul, Seoul, Republic of Korea

Background: World Health Organization (WHO) recommended influenza coverage targets of 75% in elderly and at high-risk groups. Diabetes status is a high-risk group of developing influenza complications. Patients with hypertension who got an influenza vaccine are reduced risk of death during flu season.

Objectives: To address the coverage rate for influenza vaccination and related factors depending on hypertension or diabetes status in Korean adults.

Methods: The study population included 16,206 participants aged ≥20 years from the Korea National Health and Nutrition Examination Survey, 2016 to 2018. The health interview was a self-administered questionnaire and that gathered socioeconomic factors and health-related factors. The influenza vaccination status was estimated by the question about receiving a flu shot in the last 12 months.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Hypertension and diabetes were defined by health examination. Logistic regression analyses, adjusted for age, sex, occupational status, education level, family income, marital status, smoking status, alcohol intake, and obesity, were performed to examine the relationships between hypertension or diabetes status and vaccination.

Results: The mean age of participants was 51 years and 44% were male. The vaccination coverage rate was 43% among all adults. Significantly different coverage rate was observed in the age group divided into 20-39, 40-64, and ≥65 years (24% vs 30% vs 84%, P<.0001). For adults aged 40-64 years, the coverage rate was 37% and 39% among adults with hypertension and diabetes. Hypertension (OR=1.08, 95% CI=0.88-1.31) was not associated with vaccination in males aged 40-64 years, whereas diabetes (OR=1.18, 95 CI=0.92-1.51) was not associated with vaccination in females aged 40-64 years.

Conclusions: Over 80% of the elderly aged ≥65 were vaccinated with or without diseases. Improving influenza vaccination coverage rate for adults with hypertension and diabetes is encouraged. It is necessary to devise strategies to raise coverage in patients with hypertension and diabetes.

3923 | All-cause pneumonia among adults 2007-2018 and utility of a simple algorithm to confirm pneumonia

Amber Hsiao[1], Joan Bartlett[1], John Hansen[1], Edwin Lewis[1], Ronika Alexander-Parrish[2], Raul E Isturiz[2], Jose A Suaya[2], Bradford D. Gessner[2] and Nicola P Klein[1]

[1]*Kaiser Permanente Vaccine Study Center, Oakland, CA;* [2]*Pfizer Vaccine Medicines Development & Scientific Clinical Affairs, Collegeville, PA*

Background: Thirteen-valent pneumococcal conjugate vaccine (PCV13) has been routinely recommended for infants since 2010. In 2014, PCV13 was added to the existing recommendation for 23-valent polysaccharide vaccine (PPV23) among adults ≥65 years. We estimated the incidence of all-cause pneumonia episodes among adults ≥18 years during an 11-year period within Kaiser Permanente Northern California (KPNC). Using a simple algorithm, we also estimated the proportion of episodes that were radiographically confirmed as pneumonia.

Objectives: To describe incidence and healthcare utilization related to all-cause pneumonia.

Methods: We identified all KPNC members aged 18-64 years and ≥65 years from 2007-2018 with non-hospitalized (clinic and emergency department) and hospitalized pneumonia using ICD 9/10 diagnostic codes. We considered pneumonia diagnoses that occurred ≥30 days apart as separate episodes. We estimated incidence of hospitalized and non-hospitalized encounters with any pneumonia code. For episodes between 2012-2018, we applied a simple text string algorithm to radiologists' notes (previously validated with 85% sensitivity and 77% specificity) to classify whether chest radiographs also indicated pneumonia.

Results: Among persons aged ≥18 years in all settings, we identified 439,890 pneumonia episodes over ~29 million person-years (PY), including 160,893 hospitalized and 278,997 non-hospitalized episodes. From 2007-2018, among persons aged ≥65 years, incidence of hospitalized pneumonia went from 24.0/1,000PY (95% CI 23.5, 24.4) in 2007 to 21.9/1,000PY (21.5, 22.4) in 2011, where it mostly remained through 2018 (range 19.4/1,000PY to 22.1/1,000PY); non-hospitalized pneumonia went from 25.8/1,000PY (25.3, 26.3) in 2007 to 22.2/1,000PY (21.8, 22.6) in 2018. From 2007-2018, among persons aged 18-64 years, hospitalized pneumonia incidence was steady at 1.8/1,000PY to 1.7/1,000PY, while non-hospitalized pneumonia went from 7.5/1,000PY to 5.6/1,000PY. Regardless of age, most hospitalized pneumonia (74-81%) had a radiograph indicating pneumonia while only 46-51% of non-hospitalized pneumonia did.

Conclusions: In a setting with robust PCV13 and adult PPV23 immunization programs, the incidence of all-cause pneumonia in adults modestly declined over 11 years. Incidence depended on age and healthcare setting, however for those ≥65 years, disease burden remained high in both hospital and non-hospital settings. A simple text algorithm confirmed pneumonia in most hospitalized episodes and may be useful in the future to further refine estimated incidence of hospitalized pneumonia.

3932 | Accuracy of batch production identifiers of vaccines recorded in the clinical practice research datalink gold

François Haguinet, Olivia Mahaux and Vincent Bauchau

GSK, Wavre, Belgium

Background: Batch production identifiers (BIDs) of vaccines are unique identifiers issued by manufacturers for traceability. BIDs of vaccines are recorded in the Clinical Practice Research Datalink (CPRD), thus enabling the vaccine exposure to be detected with high accuracy (e.g. by vaccine brand). So far, this information seems to be underutilised.

Objectives: To assess the accuracy of GSK vaccines BIDs reported in CPRD.

Methods: The BIDs were reported as free text with limited standardisation in the CPRD GOLD. The assessment was performed using a cleaning procedure of the free text and pooling the records for compound vaccines which had the same CPRD BID. Each GSK vaccine product/brand has a specific four characters prefix in the BID, e.g. 'AROL' for GSK's rotavirus vaccine (*Rotarix*) and 'A69C' for GSK's measles-mumps-rubella vaccine (*Priorix*). In a first step, all potential immunisations with GSK vaccines during the year 2015 were identified based on these GSK-specific prefixes in the CPRD BIDs. The accuracy of the CPRD BIDs was then evaluated by computing the proportion of these reports matched to valid GSK BIDs. In a second step, an extended assessment was performed for *Rotarix* over the period 01-Jul-2013 to 31-Dec-2015. During this period, *Rotarix* was the only rotavirus vaccine available on the UK market, and this start date corresponds to the time when *Rotarix* was introduced into the childhood immunisation schedule in the UK. The detection of *Rotarix* vaccinations by matching with valid GSK BIDs was evaluated

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

considering the medcodes and immunisation type specific to rotavirus vaccination as reference. Both methods were expected to detect the same records of *Rotarix* vaccinations. The sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were estimated.

Results: In 2015, 91.4% of the total immunisation records (i.e. 1407457) had a BID reported. 19 GSK vaccines were represented in the immunisation records with GSK prefixes. 319584 (95.7%) of the 333815 records had a CPRD BID matching with a valid GSK BID (94.6% for *Rotarix* and 97.5% for *Priorix*). When *Rotarix* vaccinations were searched using medcodes and immunisation type as reference, the detection based on the batches had Se of 80.0%, Sp of 99.9%, PPV of 98.6% and NPV of 99.0%.

Conclusions: Our study demonstrated high accuracy of the batches reported in CPRD GOLD, opening new research perspectives for batch specific safety signal detection. The high accuracy of BIDs could improve the quality of brand-specific vaccines studies (e.g. estimation of effectiveness) in CPRD. **Funding:** GlaxoSmithKline Biologicals SA

4030 | Tolerability of MenACWY-TT vaccination in adolescents in the Netherlands

Jeanet Kemmeren[1], Leontine van Balveren[2], Agnes Kant[2] and Hester de Melker[1]

[1]*National Institute for Public Health and the Environment, Bilthoven, Netherlands;* [2]*Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, Netherlands*

Background: Since 2015 the incidence of invasive meningococcal disease due to capsular group W in the Netherlands has been increasing. Therefore, in 2018 meningococcal ACWY vaccine (MenACWY) was offered to adolescents of 14 years of age within the National Immunization Programme (NIP) in the Netherlands.

Objectives: The objective of this study was to evaluate the tolerability of a single dose of MenACWY-TT in adolescents in the Netherlands to generate data for this new target population in the NIP.

Methods: A total of 5000 adolescents were asked to participate in a questionnaire study. After registration for participation, the adolescent was asked to fill in two questionnaires about local reactions and systemic events in the week before and after vaccination, respectively. The association between the occurrence of systemic symptoms in the week before and after the vaccination was tested by using generalized mixed models (GLMM).

Results: One or more questionnaires were retuned by 139 adolescents. Any local reaction within 7 days after vaccination were reported by 55.6% of the adolescents. Pain (50%) and reduced use of the arm (21.3%) were most often reported. Any systemic events in the week after vaccination were reported by 67.6% of the participants. Of these symptoms, myalgia was the systemic event most often reported (37.0%). Adolescents who had local reactions reported system AEs more often (84.7%) than adolescents who not had local reactions (51.1%) ($p<0.001$, χ^2-test). No increased risks were found for all system adverse events in the week after vaccination compared to these risks in the week before vaccination (OR 0.95; 95%CI 0.40-2.27, GLMM).

Conclusions: After vaccination with MenACWY vaccine, most adolescents reported one or more short-term adverse events. These adverse events were mostly mild and transient, and did not occur more often in the week after compared to the week before vaccination. The response rate was low so it is hard to draw firm conclusions. However, the results did not identify any safety problems.

4072 | Where are children in the United States receiving their influenza vaccination?

Dana Gates[1], Mohammad A Al-Mamun[1], Kelly Orr[1], Steven A Cohen[2] and Aisling R Caffrey[1,3,4]

[1]*College of Pharmacy, University of Rhode Island, Kingston, RI;* [2]*College of Health Sciences, University of Rhode Island, Kingston, RI;* [3]*Providence Veterans Affairs Medical Center, Providence, RI;* [4]*School of Public Health, Brown University, Providence, RI*

Background: Since the 1990s, various states within the United States (U.S.) have passed laws allowing pharmacists to administer vaccines in an effort to increase vaccination rates. However, regulatory mandates, including minimum age requirements, as well as required vaccine protocols and/or provider prescriptions have limited access to and utilization of pharmacy-based immunization services for children in the U.S.

Objectives: The purpose of our study was to describe temporal trends in pediatric influenza vaccination by provider setting and region within the U.S.

Methods: Pediatric (<18 years of age) influenza vaccinations were captured using Current Procedural Terminology, 4th Edition (CPT®-4) procedure codes entered from July 1, 2010 to June 30, 2017 in the de-identified Optum Clinformatics™ Data Mart database. Time trends of administration rates were assessed by provider setting. Geographic variations were also assessed.

Results: In the cohort evaluated from 2010-2017, 5,384,815 influenza vaccinations were identified in the pediatric population: 3.1% in a pharmacy-based setting, 2.3% in a convenience care clinic, 0.2% in an urgent care setting, 87.6% in a primary care office, and 6.8% in another location, such as a school or other immunization center. During the study period, the mean age for pharmacy-based influenza vaccination was 12.6 ± 3.3 years. Of all children in the 13-17-year-old age group, 9.5% were immunized against influenza at a pharmacy, compared with 3.0% of the 5-12-year-old group and 0.3% of 6 months to 4-year-old group.

The States with the highest percentage of children vaccinated in a pharmacy were Arizona (7.5%), New Mexico (6.4%), and Colorado (6.4%). This is also reflected in the Western region of the U.S., where 4.7% of influenza vaccinations occurred in the pharmacy. The total number of pediatric influenza immunizations increased by 67,391 (8.5% change) from 2010 to 2017, however, it should be noted that the 2013-2014 season had the highest number of influenza

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

vaccinations overall. During the 2016-2017 influenza season, 4.0% of all influenza immunizations took place within a pharmacy, compared with the 2010-2011 season in which 1.4% of all influenza immunizations were administered in a pharmacy. This is an increase of 21,900 immunizations (68.1% change).

Conclusions: Vaccination in the pharmacy setting improves access to care through increased convenience, with longer service hours, and without the need for an appointment. According to our findings, pharmacy-based influenza immunizations are more common among older children, in the Western region, and utilization has increased over time.

4076 | Pharmacist authority to administer pediatric influenza immunizations in the United States

Dana Gates[1], Kelly Orr[1], Steven A. Cohen[2] and Aisling R. Caffrey[1,3,4]
[1]College of Pharmacy, University of Rhode Island, Kingston, RI; [2]College of Health Sciences, University of Rhode Island, Kingston, RI; [3]Providence Veterans Affairs Medical Center, Providence, RI; [4]School of Public Health, Brown University, Providence, RI

Background: Over the past decade, alternative healthcare settings have expanded access to preventive and urgent healthcare services. Historically, vaccination rates for vaccine-preventable diseases have been lower than target population health goals. Understanding the need to expand access to vaccination, most states in the United States (U.S.) have passed laws allowing pharmacists to administer vaccines to adults. However, pharmacist vaccination of children has been adopted more slowly and with greater limitations.

Objectives: As of 2009, pharmacists were approved vaccinators in all states, however, each state instituted minimum age requirements and other restrictions to pharmacy-based pediatric vaccination. Therefore, the objective of our study was to compare and contrast state regulations with respect to pharmacist administration of pediatric influenza vaccines.

Methods: State-level pediatric (0-17 years of age) influenza vaccination regulations, including minimum age requirements, required vaccine protocols, years of law passage/revision, and other regulatory mandates for pharmacy-based vaccinations, such as prescription requirements, were collected for all 50 states and the District of Columbia.

Results: According to the National Alliance of State Pharmacy Associations, as of 2019, 92% (n=47) states allow pharmacist administered pediatric influenza vaccination in some form, and 8% (n=4) do not allow pharmacy-based influenza vaccination in children under 18 years of age.

There are three main models under which pharmacists can administer pediatric influenza vaccines: prescriptions from providers (n=1, 2%), vaccination protocols (n=25, 53%), or independently (neither prescription nor protocol, n=7, 15%) as of January 2019. There are 14 states (30%) that use multiple pharmacist authorization models with varying ages per approach.

Pharmacist administered influenza vaccination is allowed for any age in 12 states via protocol alone and 3 states via pharmacist independent authority alone. There are 12 states that allow pharmacist administered influenza vaccination to any age via prescription, however, all 12 states also follow another pharmacist authorization model with varying minimum age restrictions for older children, either protocol (n=5) or independent authority (n=7).

Conclusions: Regulations permitting pediatric vaccination by pharmacists vary greatly across the U.S., as do vaccination rates. Greater access to pediatric vaccinations without arduous restrictions could help bridge gaps in the Healthy People 2020 target for pediatric influenza vaccination rates of at least 70%.

4147 | Venous thromboembolism among male recipients of the 4-valent human papillomavirus vaccine in United States insurance claims data

Kandace Amend[1], Bruce Turnbull[1], Li Zhou[1], Morgan Marks[2], Christine Velicer[2], Patricia Saddier[2] and John Seeger[1]
[1]Optum, Boston, MA;[2]Merck & Co. Inc., Kenilworth, NJ

Background: The 4-valent human papillomavirus (HPV) vaccine (4vHPV vaccine), Gardasil®, is indicated for the prevention of several HPV-related diseases in females and males. In the US, it was licensed for use in females in 2006 and males in Oct-2009. Venous thromboembolism (VTE), which is rare among adolescent males and young men, was studied as part of a post-marketing safety study of 4vHPV vaccine.

Objectives: To identify VTE outcomes among male recipients of the 4vHPV vaccine.

Methods: Using the Optum US health insurance claims database, males vaccinated with the 4vHPV vaccine were followed for the occurrence of VTE associated with an outpatient visit, emergency department visit or hospitalization within a 60-day risk period after vaccination and in a subsequent 60-day self-comparison period (14-day subsets of these risk and self-comparison periods were also used). Initial identification of a potential VTE was based on International Classification of Diseases (ICD) diagnosis codes. Medical records of potential VTE cases were reviewed and adjudicated by physicians with relevant expertise. Incidence rates (IRs) were calculated for chart-confirmed VTE outcomes as the number of events per 1,000 person-years, and relative rates (RRs) were calculated by dividing the rates in the risk period by the self-comparison period.

Results: Between Oct-2009 and Dec-2016, 114,035 males received at least one dose of the 4vHPV vaccine (with 202,737 doses administered overall). Thirty-four potential VTE events were identified during the 60-day risk (23 events) or self-comparison (11 events) periods. Medical records were obtained for 27 events (27/34 = 79%) and 16 were confirmed after adjudication: 5 VTEs were confirmed in the risk period, 2 in the self-comparison period, and 9 occurred outside of either period. The IR for chart-confirmed VTE in the 60-day risk and self-comparison period was 0.16 (95% CI 0.05-0.37) and 0.07 (95% CI

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

0.01-0.26) per 1,000 person-years, respectively. The RR for chart-confirmed VTE was 2.17 (95% CI 0.35-22.74).

Conclusions: Although numbers of cases were small, the incidence rate of VTE among 4vHPV vaccine male recipients was consistent with background rates in the study age group and there was no evidence of an increased risk of VTE. These findings are consistent with the safety profile of 4vHPV vaccine.

4181 | Selecting a comparison group for outcomes occurring on the day a vaccine is administered

Kandace Amend[1], Bruce Turnbull[1], Li Zhou[1], Morgan Marks[2], Christine Velicer[2], Patricia Saddier[2] and John Seeger[1]
[1]*Optum, Boston, MA;* [2]*Merck & Co. Inc, Kenilworth, NJ*

Background: The 4-valent human papillomavirus (HPV) vaccine (4vHPV vaccine) was licensed for use in males in Oct-2009 in the US. In post-marketing observational studies of health outcomes occurring on the day of vaccination, a suitable comparison group is needed to provide context on incidence of outcomes among vaccinees.

Objectives: To assess the impact of different comparison groups on measurement of frequency of outcomes occurring on day of 4vHPV vaccination.

Methods: Males vaccinated with 4vHPV vaccine were identified in US health insurance claims data between Oct-2009 and Dec-2016. Pre-specified events (syncope, epilepsy/convulsions, head trauma, allergic events) occurring on Day 0 (day of vaccination) were identified by diagnosis codes associated with outpatient visit, emergency room visit, or hospitalization. Outcome frequency was assessed by counts and compared against 3 groups of males: 1) matched cohort (by age and calendar time) with physician office visit that included administration of another vaccine (Td/Tdap, meningococcal, or injectable influenza); 2) matched cohort with any health care encounter; and 3) same patients at a later time point (self-comparison).

Results: Between Oct-2009 and Dec-2016, 114,035 males received at least one dose of 4vHPV vaccine (202,737 doses administered overall). For comparison group 1 (160,867 doses matched), counts of Day 0 outcomes tended to be similar between 4vHPV vaccine recipients and the comparison cohort: allergic reactions (338 vs 201); syncope (101 vs 95); epilepsy/convulsions (118 vs 154); and head trauma (196 vs 190). In comparison group 2 (202,668 doses matched), counts of Day 0 outcomes were lower among 4vHPV vaccine recipients vs comparators: allergic reaction (449 vs 1,128); syncope (126 vs 526); epilepsy/convulsions (136 vs 889); and head trauma (270 vs 1,384). In comparison group 3, counts on day of 4vHPV vaccination were higher compared to the post-vaccination self-comparison day: allergic reactions (449 vs 19); syncope (126 vs 8); epilepsy/convulsions (136 vs 8); and head trauma (270 vs 43).

Conclusions: Selection of a comparison group for assessment of health outcomes on day of vaccination can impact safety conclusions. In a healthy group of males, a concurrent control group based on receipt of another vaccine may provide a balanced comparison, whereas, a concurrent control group not based on receipt of vaccine may tend to select for those who rarely visit the doctor except for vaccinations and acute health reasons. Utilizing a self-comparison period for events occurring in a narrow time window (one day) may be too short to capture healthcare encounters.

4192 | Change-point analysis of spontaneous adverse event reporting following human papillomavirus vaccination

Seung-Hun You, Myo-Song Kim, Min-Taek Lee, Ye-Jin Kang and Sun-Young Jung
College of Pharmacy, Chung-Ang University, Seoul, Republic of Korea

Background: Detecting signals of sharp increase in temporal trends of adverse event reporting is important to notice public safety concerns and to take prompt actions, especially for the vaccines under national immunization program (NIP).

Objectives: To assess applicability of change-point analysis for signal detection of vaccine safety surveillance using spontaneous reporting database in Korea.

Methods: Among the individual case safety reports (ICSRs) reported to Korea Adverse Event Reporting System (KAERS) between 2008 and 2017, ICSRs containing vaccines were extracted. Vaccine of interest was human papillomavirus (HPV) (WHO-ATC, J07BM01-J07BM03) vaccine, which was recently included in the NIP in Korea. We assessed demographic characteristics of reported cases and characteristics of ICSRs. We defined syncope and dizziness as the target adverse events (AEs). We analyzed the number of reports based on the quarterly recognition date AEs. To derive safety signals, we used the change-point analysis approach in which cumulative sum (CUSUM) and bootstrapping techniques were iteratively used to detect the changes and to assign a confidence level to each change. The p-value of the detected change point using CUSUM was cut off at the significance level of 0.05 and it was defined as a signal.

Results: Among total of 26,293 vaccine ICSRs in KAERS database, the number of ICSRs for HPV was 2,842. Reports for cases aged 11 - 64 years old were 56.6% and the unknown 42% in HPV. Among report type, 56.8% were reported as the spontaneous report and were higher in HPV vaccine than other vaccines (P<0.01). The change-point analysis detected four significant change points in the number of reports: Q2 2013 (P=0.02), Q4 2014 (P=0.01), Q3 2016 (P<0.01), Q2 2017 (P<0.01). A significant increase in the number of reports from the first, third and fourth change point (Q2 2013, Q3 2016, Q2 2017), and a significant decrease in reports from the second change point (Q4 2014) was observed.

Conclusions: The detected change points were consistent with increased public concerns about adverse reactions of HPV through mass media, and inclusion into NIP in Korea. The change-point analysis, which focuses on detecting changes within time-series data could be used as a useful tool for signal detection within spontaneous adverse event reporting system.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4207 | Anaphylaxis following vaccination in South Korea: A large-linked database study

Hyesung Lee[1], Young June Choe[2], Ju Hwan Kim[1] and Ju-Young Shin[1]
[1]*Sungkyunkwan University (SKKU), Suwon, Republic of Korea*; [2]*Hallym University, Chuncheon, Republic of Korea*

Background: Anaphylaxis is a severe and potentially fatal systemic reaction that can be triggered by various allergens. The risk of anaphylaxis after vaccination has not been well understood in Asian population.
Objectives: We sought to assess the vaccine-specific rates in occurrence of anaphylaxis in Korea, by linking National Immunization Program database with National Health Insurance Service database to create a vaccine safety large-linked database (LLDB).
Methods: The LLDB included data for 4.3 million Korean children aged 0-9 years followed from 2008 to 2017. We included all cases that were diagnosed to have anaphylaxis and were treated with epinephrine and/or corticosteroid within 2 days of vaccination. Data on demographic information, type of vaccine, co-administered vaccines, prior history of allergy, atopy, or anaphylaxis were retrieved. We calculated the incidence of anaphylaxis after vaccination within the time window of 0-2 days.
Results: From the LLDB, we identified 137 post-vaccination anaphylaxis cases that occurred after 112,799,043 doses, resulting 1.21 (95% CI, 1.02-1.44) per million doses. Vaccine-specific rates included 2.87 (95% CI, 1.15-5.92) per million doses for Vero cell cultured inactivated Japanese encephalitis vaccine and 2.72 (95% CI, 1.59-4.36) for measles-mumps-rubella vaccine. For trivalent inactivated influenza vaccine, a total of 36 cases were reported from 14,850,886 doses, resulting rate of 2.42 (95% CI, 1.70-3.36) per 1 million doses. The rates were generally lower for Hib, PCV10, and PCV13 vaccines.
Conclusions: Anaphylaxis after vaccination is rare in South Korea, however, the vaccine providers should be prepared to treat the potentially life-threatening allergic reaction.

4233 | Prescription patterns of the inactivated influenza vaccine in private healthcare settings in South Africa

Ilse Truter
Nelson Mandela University, Port Elizabeth, South Africa

Background: Vaccination is one of the most cost-effective healthcare interventions. A previous study conducted in pharmacies has shown that approximately 50% of vaccines dispensed in community pharmacies in South Africa are for the influenza vaccine.
Objectives: The primary aim of the study was to analyse the prescribing patterns of the inactivated influenza vaccine in private healthcare settings in South Africa.
Methods: A retrospective drug utilisation study was conducted on a South African medical insurance administrator database for 2018. The database contained 4191138 records for medicine, medical devices and procedures dispensed by hospitals, medical practitioners and pharmacies. All products in ATC group J07BB01 (Influenza vaccine, inactivated) were extracted and analysed.
Results: A total of 1906 patients (57.82% males) were prescribed 1906 inactivated Influenza vaccines during 2018 at a total amount claimed of R148811.76. The average age of patients was 42.53 (SD=19.98) years (females: 41.58 (SD=21.63) years; males: 43.22 (SD=18.67) years). Two trade name vaccines were prescribed, both in pre-filled syringes of 0.5 ml. Five paediatric vaccines were prescribed in a 0.25 ml pre-filled syringe. The average cost per vaccine was R76.83 (SD=R6.32). Most vaccines were administered by registered nurses (72.17%), followed by pharmacies (18.53%), general medical practices (8.57%) and private hospitals (0.73%). Half of the vaccines (50.34%) were prescribed in April 2018, with nearly all vaccines (92.77%) claimed in three months of the year (March, April and May 2018). This coincides with the months just before the winter season in South Africa. Sixty percent (59.58%) of the vaccines were prescribed to patients in the economically active years of their life (between 30 and 59 years).
Conclusions: The patterns observed in this study are similar to those observed in a previous South African study conducted on the dispensing patterns of vaccines in community pharmacies in South Africa. Pharmacists, together with nurses, can play a more prominent role in promoting the influenza vaccine to members of the public, especially since these products are reimbursed by medical insurance schemes.

4447 | Individual and neighborhood factors associated with failure to vaccinate against influenza during pregnancy

Ousseny Zerbo[1], Thomas Ray[1], Lea Zhang[1], Kristin Goddard[1], Alyce Adams[2], Bruce Fireman[1], Saad Omer[3], Martin Kulldorff[4] and Nicola P. Klein[1]
[1]*Kaiser Permanente Northern California, Oakland, CA*; [2]*Kaiser Permanente Northern California, Oakland, CA*; [3]*Yale University, New Haven, CT, CT*; [4]*Harvard Medical School and Brigham and Women's Hospital, Boston, MA*

Background: The prevalence of influenza vaccination is low among pregnant women, a group considered to be at high risk of complication from influenza infection. Identifying whether unvaccinated pregnant women clusters geographically and factors associated with failure to vaccinate may lead to the development of strategies to improve vaccine uptake.
Objectives: The overall goal of this study was to determine whether unvaccinated pregnant women cluster geographically and to assess individual and neighborhood factors associated with failure to vaccinate against influenza.
Methods: The study setting was Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery organization that provides comprehensive care to approximately 4 million members. The cohort of women, pregnant in 2015 or 2016, with continuous membership 30 days before pregnancy onset until the end of pregnancy

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

was included. The outcome was influenza vaccination received anytime between pregnancy onset and pregnancy outcome. We used spatial scan statistics to identify geographical clusters of unvaccinated pregnant women and determined individual and neighborhood factors associated with failure to vaccinate using multivariate logistic regression.

Results: Among 77,607 pregnant women, more than half (53%) were unvaccinated. Spatial analysis identified 5 clusters with high prevalence of unvaccinated pregnant women. The proportion of unvaccinated ranged from 57% to 75% within clusters compared to 51% outside clusters. In covariate-adjusted analyses, residence in a cluster decreased the odds of vaccination by 1.42 (95% confidence interval (CI): 1.37 - 1.48). The odds of vaccination also decreased with black race (OR=1.40, 95% CI: 1.30 - 1.50), Hispanic ethnicity (OR=1.14, 95% CI: 1.04 - 1.26), subsidized insurance (OR = 1.11, 95% CI: 1.04 - 1.18), living in neighborhoods with high deprivation index (OR =1.15, CI: 1.07 - 1.23), neighborhoods with high proportion of adults with educational level less or equal high school (OR = 1.21, 95% CI: 1.06 - 1.37) and first prenatal visit not in the first trimester (OR = 1.16, 95% CI: 1.08 - 1.26). Furthermore, the odds of vaccination decreased by 12.01 (95% CI: 11.31 - 12.76) for women who had less than 5 prenatal visits.

Conclusions: More than half of insured pregnant women in the study were unvaccinated against influenza. Unvaccinated pregnant women clustered geographically and by key sociodemographic factors. Interventions to increase influenza vaccine coverage among pregnant women are needed, particularly in vulnerable populations.

4473 | Maternal Tdap vaccination trends in the United States, 2016-2018

Florence T. Wang, Li Zhou, Kelesitse Phiri and John D. Seeger
Optum, Boston, MA

Background: Pertussis is a highly contagious respiratory infection that can lead to hospitalization and death, especially among infants. In 2012, the Advisory Committee on Immunization Practices (ACIP) recommended the use of Tdap in the 27- to 36-week gestational age window of pregnancy so that maternal antibodies may be passed to infants, providing protection until the infants receive their first dose of DTaP vaccine at age 2 months. In 2017, ACIP updated its recommendation for Tdap to be administered early in the recommended window.

Objectives: To describe trends in US Tdap vaccination rates among commercially insured pregnant females from 2016-2018.

Methods: Pregnant enrollees age 12-45 years were identified from the Optum Dynamic Assessment of Pregnancies and Infants (DAPI), a database of pregnancy episodes derived from the Optum Research Database (ORD), from 2016 through 2018. The start of a pregnancy was defined as the estimated LMP, derived from an ICD-10 based algorithm, while Tdap vaccination was captured through the presence of CPT 90715. Tdap vaccine coverage by week of gestation is described, as are temporal trends in coverage.

Results: From January 2016 through December 2018, there were 363,051 pregnancies (314,531 women) identified within DAPI. The median age at LMP was 31 years and 68% of pregnancies resulted in livebirths. Among pregnancies that were still ongoing at 38 weeks (n=243,918), 161,473 (66%) received dTaP. Tdap coverage among pregnant females increased from 63% in 2016, to 66% in 2017, and 70% in 2018. Vaccine coverage was highest among those age 25-34 at 69%, as compared with 52% for those age 12-24 years, and 67% for those age 35-45 years. Of the women who were vaccinated with Tdap, 146,392 (91%) received their vaccination on schedule (between weeks 27 and 36 of gestation), and 77,665 (48%) received the vaccine between weeks 27-30 of gestation. The percent of vaccinated women receiving Tdap between weeks 27 and 36 of gestation increased from 90% in 2016 to 92% in 2018, and the percent of vaccinated women receiving Tdap between weeks 27 and 30 of gestation increased from 46% in 2016 to 47% in 2017, and 51% in 2018.

Conclusions: We observed increased trends in vaccine coverage among commercially insured women. Since maternal Tdap vaccination represents an effective intervention to prevent pertussis in infants, there appears to be an opportunity to improve infant health by promoting maternal vaccination in the US.

4652 | Flu vaccination in Portugal: Integration of community pharmacies as vaccination points of public NHS

José Guerreiro, Maria Cary, Heloísa Galante and António T. Rodrigues
Associação Nacional das Farmácias (ANF), Lisbon, Portugal

Background: The increase in flu vaccine coverage is a goal of the Health System, particularly in the elderly population. For these, flu vaccination is currently free of charge in the public National Health System (NHS), while in community pharmacies (CP) it requires medical prescription and is not fully reimbursed, and neither is the vaccine administration. Under an agreement with the Ministry of Health, a group of 38 CP in Loures, District of Lisbon, accepted to collaborate as vaccination points against influenza in people aged ≥65 years.

Objectives: To estimate the impact of the vaccination campaign in the number of registered inoculations, in the incremental vaccine coverage in patients aged ≥65 years and in the satisfaction of the population and its access to the service.

Methods: Between Oct. and Dec. 2018, 38 CP from Loures invited people aged ≥65 years to be vaccinated against influenza, without the need for a prescription and free of charges. A before-after analysis was used to compare aggregated data of vaccination coverage from Loures and Odivelas municipalities of the previous and the current flu season, to assess the impact of the pilot. A questionnaire was used in a sample of patients to collect data on sociodemographic characteristics and previous experience, satisfaction and access to the service. Descriptive analyses were performed.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Results: CP of Loures have dispensed 33.6% of the NHS stock vaccines. A 31.8% increase of the total vaccination coverage was estimated and, for patients aged ≥ 65 years, the increase was +6.9% with the contribution of the CP. A sample of 478 subjects were selected, 42.4% were male, with a mean age of 74 years old (sd=7) and 88.9% were vaccinated in the previous season (74.2 in the Healthcare center, 24.8% in the CP). Compared with the same service provided in the HC in the previous season, the satisfaction with the service provided in the CP was significantly higher and the average travel time was significantly lower (about 15 minutes less).

Conclusions: The pilot has shown that CP can successfully be integrated in the public NHS as vaccination points for influenza. Results suggests that the increase in vaccination points was associated with a substantial increase in vaccination coverage and particularly in patients ≥65 years. Thus, we recommend extending this service to CP in other parts of the country.

4674 | The safety of human papillomavirus vaccine among female adolescents in Korea: A cohort and self-controlled risk interval study

Dongwon Yoon, Ji-Ho Lee, Hyesung Lee and Ju-Young Shin
Sungkyunkwan University (SKKU), Suwon, Republic of Korea

Background: Though human papillomavirus (HPV) vaccine plays an important role in preventing cervical cancer, few studies have identified post-licensure safety of the HPV vaccine. Further, the safety profiles of bivalent HPV vaccines (HPV2) and quadrivalent HPV vaccines (HPV4) are uncertain.

Objectives: To evaluate the risk of serious adverse events after human papillomavirus vaccination among female adolescents.

Methods: We secured a vaccine safety large-linked database (LLDB) by linking the National Immunization Program database with the National Health Insurance Service database. The study included female adolescents 11-14 years of age who were enrolled in the LLDB from 2015 to 2017. The primary analysis used a cohort design that included vaccinated individuals. We selected the Tetanus-diphtheria-pertussis vaccine and Japanese encephalitis vaccine as a comparator vaccine, whose safety profile is well-developed, and which is commonly inoculated in the same age as the HPV vaccine. Incident autoimmune and neurologic events (29 different outcomes) were followed-up for up to 180 days after each vaccine dose. Rate ratios were estimated, comparing HPV vaccinated and Non-HPV vaccinated. The secondary analysis used a self-controlled risk interval (SCRI) design that included only HPV vaccinated and cases. The prespecified risk interval was Days 1-56 after vaccination; a 56-day-long control interval followed the risk interval. Subgroup analyses were conducted to both designs by HPV2 and HPV4.

Results: The current analyses included 382,336 HPV vaccinated and 59,412 Non-HPV vaccinated, among whom received a total of 431,396 HPV vaccine doses and 87,472 comparator vaccine doses, respectively. Among the 29 outcomes, no significant increase in risk was observed in the primary analysis. Whereas in the secondary analysis, the relative risk (RR) for 28 of 29 prespecified outcomes was not significantly increased, exposure to the HPV vaccine was slightly associated with hypothyroidism (RR 1.34, 95% confidence interval 1.08 to 1.66). In subgroup analysis, both HPV2 and HPV4 showed no association in risk in a cohort design, but HPV4 showed a higher risk of hypothyroidism than that of HPV2 in a SCRI design.

Conclusions: No evidence was found of associations between HPV vaccine and serious adverse events in the 180 days after vaccination. Although the secondary analysis suggested a potential risk of hypothyroidism, it should be considered in light of the established benefits of HPV vaccination.

4744 | Determinants of the HPV vaccination among girls attending Spanish primary care settings

Belén Castillo Cano, Mar Martín-Pérez, Dolores Montero-Corominas and Elisa Martín-Merino
Spanish Agency for Medicines and Medical Devices (AEMPS), Madrid, Spain

Background: The human papilomavirus (HPV) vaccination is scheduled for girls in the Spanish public health system but the coverage is lower than expected.

Objectives: To identify determinants of HPV vaccination among factors recorded in girls´ primary care profiles.

Methods: We used the information recorded in the Spanish Primary Care Database for Pharmacoepidemiological Research (BIFAP) to perform an observational cohort study. This cohort included all girls aged 9-18 years in 2007-2016 with ≥1 year of data (start date). Girls were followed from the start date until a recorded HPV vaccination was identified (vaccinated girls) or they reached 19 years of age, died, end of the study or lost contribution (non-vaccinated girls). Adjusted Odds Ratios (of HPV vaccination) according to age, year, social factors, BMI, smoking, morbidity or medication [anytime or 2 years (for vaccines) before start date] were estimated after stepwise backwards selection (p_exit=0.1, p_entry=0.05).

Results: In the study cohort, 388,669 girls were included of whom 154,174 were vaccinated against HPV. The odds of vaccination decreased with age and among girls with social (37% decreased) or adaptation (27%) problems, anemia (28%), iron deficiency (21%), smoking (43%), prescriptions of contraceptives (59%) and benzodiazepines (43%), treatment for abdominal symptoms (34%) or asthma (4%), hepatitis (42%) or MMR (77%) vaccinations. The odds increased among girls with autoimmune diseases (14% increased), celiac disease (13%), allergy (5%), growing deficiency (13%), HPV infection (14%), family history of thyroiditis (OR>2), record of tuberculosis test (26%), any adverse drug reactions (18%), prescriptions of corticosteroids (26%) or iron supplements (77%), and vaccination against diphtheria-tetanus or meningitis (OR>7), flu (8%)

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

or varicela (79%) and with higher BMI. Calendar year and region varied the vaccination odds.

Conclusions: As expected by vaccination schedule and SmPC, we confirmed that age, year, region and the diagnosis of (auto)immune disorders were associated with HPV vaccination. However, a unexpected reduced probability of HPV vaccination among girls with recorded social problems was observed. HPV vaccination was less frequent among adolescent girls receiving vaccines such as hepatitis or MMR, and more frequent among those adapting to newer recommendations, i.e. vaccination against varicela or meningitis, or non scheduled vaccines (flu). The identified factors could inform interventions for high-risk patients to improve vaccination coverage.

4772 | "If It Does Not Endanger Me or the Health of My Baby, I Will Take It Up ···" Vaccine safety is an important consideration for maternal immunization acceptability in Rural Uganda: A qualitative study

Dan Kajungu[1], Michael Muhoozi[1], James Stark[2] and Daniel Weibel[3]
[1]*Makerere University Centre for Health and Population Research (MUCHAP), Kampala, Uganda;* [2]*Putnam Associates, Boston, MA;* [3]*EDCTP, The Hague, Netherlands*

Background: Maternal immunization is a successful and most cost-effective public health strategy that protects pregnant women and their infants from vaccine-preventable diseases directly associated with reduced morbidity and mortality. Uganda is exploring the introduction of new vaccines that target pregnant women in addition to Tetanus Toxoid (TT) and in the process of replacing Tetanus Toxoid (TT) with Tetanus-Diphtheria (Td). However, research exploring knowledge, attitudes, beliefs, and acceptability is still missing.

Objectives: To explore the knowledge, attitudes, beliefs and vaccine acceptability among pregnant women in rural Uganda.

Methods: A qualitative descriptive study explored the willingness, knowledge, attitudes, beliefs and acceptability of maternal immunization. Focus group discussions were conducted in the community and at antenatal care clinics. Data were thematically analyzed.

Results: Ten focus group discussions (FGDs) were conducted among 90 pregnant women. Women were willing to take on any new vaccines, had good attitude towards maternal immunization and were familiar with its importance. The pregnant women partners' role in health decision making was an important factor to accept a new vaccine. Acceptance of a new vaccine could be affected by worries about negative adverse effects and events (AE). There are misconceptions regarding the introduction of vaccines like being tested on a small group of mothers and being seen as a treatment for common diseases like malaria and general body weakness. Women also highlighted cultural and religious misconceptions related to vaccination.

Conclusions: Maternal immunization knowledge, willingness, attitudes, and acceptability among pregnant women was positive. However, fear for AE related to new vaccines, religion and cultural beliefs, coupled with the thinking that vaccines are for curing diseases like malaria and general body weakness, might counteract maternal immunization acceptability.

4787 | Seasonal influenza vaccine effectiveness: Evidence from test-negative design studies

George Okoli, Florentin Racovitan, Christiaan Righolt and Salaheddin Mahmud
University of Manitoba, Winnipeg, MB, Canada

Background: Seasonal influenza vaccine effectiveness (SIVE) varies across seasons and regions. Understanding the reasons for these variations is essential for designing effective seasonal influenza vaccination programs.

Objectives: We summarized SIVE estimates from test-negative design (TND) studies according to study region and age group, and explored variations between regions and across age groups.

Methods: We systematically searched appropriate bibliographic databases from January-2011-July-2018 for full-text publications of final SIVE estimates against laboratory-confirmed (PCR/culture) influenza in primary-care settings from TND studies conducted after the 2009 influenza pandemic. Two reviewers independently screened retrieved citations and extracted data from included studies. Disagreements were resolved by consensus or by a third reviewer. Pooled SIVE was calculated using inverse variance, random-effects model for all-Influenza, influenza types/subtypes.

Results: 70 articles met our eligibility criteria. We found significantly higher pooled SIVE in the Southern compared with the Northern hemispheres: 15% difference for each of all-Influenza, H1N1, H3N2, and influenza-B, and 13% difference (however, non-significant) for untyped-influenza-A. SIVE estimates from the Southern hemisphere were statistically homogeneous (I-squared (I^2)=0%) compared with those from the Northern hemisphere (I^2=78.8% for all-influenza, 55.1% for H1N1, 61.7% for H3N2, 71% for untyped-influenza-A, and 68.1% for influenza-B). The Southern hemisphere had more seasons with antigenically similar vaccines compared with the Northern hemisphere (57% vs. 47% for all-influenza; 89% vs. 75% for H1N1; 67% vs. 44% for H3N2; 100% (one-study) vs. 50% for untyped-influenza-A; and 89% vs. 62% for influenza-B). Vaccination status in the Southern hemisphere was determined solely from medical records whereas there were self-reported vaccinations in the Northern hemisphere (13% for all-influenza and H3N2; 14% for H1N1; and 12% for influenza-B). SIVE against all-influenza decreased significantly with increasing age from 59% (50-66%; I^2=0%) in <5 years old to 31% (20-42%; I^2=0%) in ≥65 years old (data only available for the Northern hemisphere).

Conclusions: Evidence from TND studies suggests that vaccine antigenic similarity with circulating viruses, study participants' age, and method of vaccination status confirmation influence SIVE. These factors should be considered when conducting studies of SIVE in any population.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4871 | Obstetric perinatal and early childhood health outcomes following pertussis immunization during pregnancy in Ontario Canada

Deshayne B. Fell[1], Romina Fakhraei[2], Meghan Laverty[3], Natasha Crowcroft[4], Shelly Bolotin[5], Kumanan Wilson[3], Steven Hawken[6], Laura Gaudet[7], Gayatri Amirthalingam[8], Anne Biringer[9], Jocelynn Cook[2], Vinita Dubey[10], Scott Halperin[11], Frances Jamieson[5], Jeff Kwong[12], Manish Sadarangani[13] and Mark Walker[6]

[1]University of Ottawa and Children's Hospital of Eastern Ontario Research Institute and ICES, Ottawa, ON, Canada; [2]University of Ottawa and Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada; [3]University of Ottawa, Ottawa, ON, Canada; [4]University of Toronto, Toronto, ON, Canada; [5]Public Health Ontario and University of Toronto, Toronto, ON, Canada; [6]University of Ottawa and Ottawa Hospital Research Institute, Ottawa, ON, Canada; [7]Queen's University, Kingston, ON, Canada; [8]Public Health England, London, United Kingdom; [9]University of Toronto and Mount Sinai Hospital, Toronto, ON, Canada; [10]University of Toronto and Toronto Public Health, Toronto, ON, Canada; [11]Dalhousie University, Halifax, NS, Canada; [12]University of Toronto and Public Health Ontario and ICES, Toronto, ON, Canada; [13]University of British Columbia, Vancouver, BC, Canada

Background: In 2018, Canada's National Advisory Committee on Immunization (NACI) recommended immunization with Tetanus-diphtheria-acellular pertussis (Tdap) vaccine during every pregnancy for protection of young infants against severe pertussis infection.

Objectives: To assess obstetric, perinatal and early childhood health outcomes after maternal Tdap immunization in Canada's largest province.

Methods: We performed a population-based retrospective cohort study of all live births in Ontario from 2012-2017. This was prior to the NACI statement, but some care providers were already immunizing on the basis of recommendations in other countries. We used multiple linked health administrative databases containing vaccine and pregnancy information of mothers and information on offspring from birth to a maximum of 6 years. Mother-infant pairs exposed to prenatal Tdap were propensity-score matched at a 1 to 5 ratio with unexposed pairs; outcomes were compared using adjusted hazard ratios (aHR), risk ratios (aRR) or incidence rate ratios (aIRR), depending on type of outcome.

Results: From a source population of 625,643 live births, we compared 12,045 Tdap-exposed mother-infant pairs to 60,225 unexposed pairs. There were no increased risks (aHR or aRR [95% CI]) for chorioamnionitis (0.98 [0.82-1.17]) or post-partum hemorrhage (1.04 [0.92-1.17]), nor for preterm birth (0.95 [0.89-1.02]), small-for-gestational age birth (0.91 [0.85-0.97]) or severe neonatal morbidity (0.79 [0.73-0.86]). There were no significant increased risks between prenatal Tdap and childhood morbidity outcomes; however, we observed small inverse associations (aIRR [95% CI]) with upper (0.96 [0.93-0.99]) and lower respiratory infections (0.93 [0.89-0.98]), gastrointestinal infections (0.88 [0.82-0.94]) and health services utilization (0.95 [0.94-0.97]).

Conclusions: Tdap immunization during pregnancy was not associated with adverse health outcomes in mothers or their infants, supporting the safety of this new strategy in Canada.

4906 | Active follow-up of adverse events following immunization during the mass measles rubella and polio vaccine campaign in Rural Uganda

Dan Kajungu Kajungu[1], Michael Muhoozi[1] and Victoria Nambasa[2]

[1]Makerere University Centre for Health and Population Research (MUCHAP), Kampala, Uganda; [2]National Drug Authority, Kampala, Uganda

Background: Uganda implemented a mass vaccination campaign that saw 18.7 million children vaccinated with Measles-Rubella and Polio vaccine. Active pharmacovigilance complements the passive or spontaneous surveillance system which suffers from low reporting rates.

Objectives: To document adverse events following immunization (AEFIs) with measles-rubella and polio during mass vaccination in Ugandan children

Methods: Prospective active vaccine safety surveillance was implemented for all eligible children that were vaccinated at school and community within the Iganga Mayuge Health Demography Surveillance Site (IMHDSS). They were monitored for 30min after immunization at the point of immunization (either school or health facility for those immunized in the community). Follow-up was on day 1, 2-3days, 10days and 14days after vaccination in class or household. Trained teachers asked children during class to report anything they felt after immunization. Village Health Team members (VHTs) in the community, on the other hand, visited each vaccinated infant in the household to ask the caretaker about any AEFI. AEFIs were reported on a user-friendly form. Healthcare workers in low-level health centers and hospitals in this area were advised to record and report any AEFI reported directly to capture AEFIs that could have been missed by the teachers or VHTs. Causality assessment was done at the National Pharmacovigilance Centre.

Results: A total of 4206 children was immunized and followed-up during the MR and PCV campaign. The incidence of reported AEFI was 9.1% (382). The incidence of AEFIs was 21.5%, 19.4%, 21.0% and 38.1% for children aged <2 years, 3 to 5 years, 6 to 9 years and 10 years and above respectively. Local skin reactions accounted for 85% of all reported adverse events. Rashes, fever, and loss of appetite often occurred in combination; taken separately, rashes, loss of appetite, fever, and bruise-like spots were observed in 46%, 38% and 26%, 27% of all reported reactions respectively. Convulsions were rare at 0.1%. The median out-of-pocket expenditure on treating an AEFI was 2.7US$ (IQR of 4.5US$).

Conclusions: The majority of AEFIs observed were either mild or moderate in severity. The AEs were expected as in vaccine literature. Severity was lower compared to the reports in the press or media. To get quick vaccine safety data, active follow-up should be considered during mass immunization campaigns. This will improve AEFI

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

reporting rates, provide more evidence on vaccine safety profiles, and improve public confidence in immunization programs.

4985 | Risk of central demyelination and use of vaccines 2009-2017 in France

Lamiae Grimaldi[1,2] and Lucien Abenhaim[3,4]
[1]*Université Paris-Saclay, Paris, France;* [2]*Unité de Recherche Clinique APHP.Paris-Saclay, Paris, France;* [3]*London School of Hygiene & Tropical Medicine, London, United Kingdom;* [4]*RESAL, London, United Kingdom*

Background: Some vaccines have been suspected to be linked to the occurence of central demyelination
Objectives: To study the association between vaccines exposure and the occurrence of a first central demyelination.
Methods: All cases of central demyelination (CD) leading to hospitalisation (of all type) with an ICD-10 code H46, G040, G35, G368, G369, G373, G378 and G379 were identified in the French SNDS database for the years 2007-2017 inclusively. The database collects all hospitalisations and health services delivered, including drugs, for nearly all the French population (over 60 million inhabitants). Patients with no demyelination diagnosis in 2007 and 2008 were considered as "incident" cases. A case-crossover study of analysis of the exposure to vaccines of any type, was conducted contrasting the one-month time window before the first hospitalisation for CD in years period 2009-2017 to the one-month time-windows 1 month before and exactly 1 year before.
Results: 188 571 CD cases were indentified, among whom 71973 had their first diagnosis in 2009. The mean age of incident cases at first diagnosis was 36.8 y.o [sd:16.7] and 66.1% were females. Overall, 62.1% of them had at least one vaccination during the study period which was an association of several vaccines in 47.9% of cases, individual flu vaccine in 17.9%, individual pneumococcus vaccine in 8.7%, hepatitis Bvirus (HBV) vaccine in 4.3%, tetanus vaccine in 3% and meningococcus vaccine in 2.7%. All other individual vaccines were used by less than 1% of cases. Exposures to vaccines were fairly stable over the years, except for meningococcus vaccination. Exactly 1000 cases (1.4%) had received at least 1 vaccine in the 30 days preceding the first hospitalisation for CD while 1046 (1.5%) had received a vaccine in the preceding month (odds ratio (OR): 0.95 [95% confidence interval (CI):0.87-1.04]) and 1059 (1.5%) had received a vaccine in the 30 days one year before (OR : 0.93 [95%CI: 0.84 -1.02]). The odds ratios for flu vaccine contrasting year-to-year 30 day time windows was 1.03 [95% CI: 0.87-1.23], for pneumococcus 0.93 [95%CI: 0.68-1.29], for HBV 0.94 [95%CI: 0.62-1.41] and for the association of multiple vaccines 0.90 [95%CI: 0.78-1.03]. Similar results were observed when other time windows were contrasted. Exposure to other individual vaccines was extremely low in the one-month time windows.
Conclusions: No excess risk of hospitalisation for central demyelination was observed for vaccines with large use in the population studied. The use of certain vaccines in that population was too low to conclude, despite studying 60 million individuals over 11 years.

5069 | Defining benchmarks for tolerable risk thresholds in cancer screening: Impact of human papillomavirus vaccination on the future of cervical cancer screening

Joseph Tota[1,2,3], Sandra Isidean[3] and Eduardo Franco[3]
[1]*Merck & Co., Inc., West Point, PA;* [2]*US National Cancer Institute, Division of Cancer Epidemiology and Genetics, Rockville, MD;* [3]*McGill University, Department of Oncology, Montreal, QC, Canada*

Background: The performance of cervical cancer screening is expected to decline as a function of lower disease prevalence - a result of successful human papillomavirus (HPV) vaccination. Replacement of cytology with molecular HPV testing as the primary screening test and adoption of risk-based screening, with less intense screening of vaccinated individuals and initiated at older ages is expected to improve efficiency. However, policy officials may decide to further reduce or eliminate screening as the ratio of benefits to harms continues to decline.
Objectives: To help inform decisions regarding changes to cervical screening programs in the future, we evaluated current risk tolerance in cancer screening in the United States, i.e., where the decision is made not to intervene though effective screening methods exist.
Methods: We systematically applied classic criteria proposed by Wilson and Jungner to evaluate the suitability of a screening program for different cancer sites. US Surveillance, Epidemiology, and End Results (SEER) Program Registry information were used to compare incidence (2008-2012) and survival (1988-2011) associated with different cancers for which organized screening is recommended and not recommended. Given that cancer risk generally increases with age and it is unlikely that screening would be recommended for individuals with low remaining life expectancy (i.e., benefits of screening are unlikely to outweigh the harms at very old ages) the highest age range that we focused on was 70-74 years.
Results: The most common cancer at ages 70-74 years satisfying Wilson and Jungner's classic screening criteria was vulvar cancer (incidence = 9/100,000 females). In comparison, the incidence of cervical cancer among females 65 years of age (the upper recommended age limit for screening) was 13 cases per 100,000 females (low as a reflection of effective screening), whereas 10-year survival was 66% (similar to vulvar cancer).
Conclusions: Our approach of defining tolerable risk in cancer screening could help guide future decisions to modify cervical screening programs.

5149 | A systematic review of active vaccine surveillance studies: Focused on the vaccine safety datalink

Eunsun Lim, Na-Young Jeong and Nam-Kyong Choi
Ewha Womans University, Seoul, Republic of Korea

Background: Vaccine active surveillance system is important to detect potential advanced effects after the introduction of the vaccine. Many

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

countries operate the active monitoring surveillance system. We reviewed Vaccine Safety Datalink (VSD) that is collaborative project between Centers for Disease Control and Prevention and health management organizations.

Objectives: To review and categorize the published literature to describe the characteristics of the studies using VSD database and also to identify possible study in vaccine active surveillance system such as VSD.

Methods: We reviewed all publications from January 1994 to August 2019 of the lists on the VSD website, and searched Medline and EMBASE for using the keyword 'Vaccine Safety Datalink', 'VSD database'. Two reviewers independently reviewed the literature and if they specify that they were focused on the vaccine, adverse events (AEs) following vaccination, vaccine preventable disease (VPD), or VSD database and they were conducted using VSD database. We divided the categories into four categories; 'Description' was divided into incidence, coverage, and pattern and 'Analysis' was divided into safety, effectiveness and factor. 'Methodology' were classified study design and statistical methodology, and in case of 'VSD database' were classified into database construction, linkage, and validation.

Results: From 335 studies, total of 206 studies were included. According to the type of studies, the majority was analytical study (n=135, 65.53%), including vaccine safety (n=125, 60.68%). Forty-two (20.39%) studies were classified into descriptive study such as incidence of diseases (n=19, 9.22%) and vaccine coverage (n=21, 10.19%). Others were categorized as methodological study (n=23, 11.06%) and study on VSD database (n=24, 11.54%). The number of published literatures by year was increased gradually, the most in 2014 (n=24, 11.54%). Compared to other studies, the number of studies for vaccine safety has increased particularly since after 2009. In descriptive studies for incidence, incidence of AEs following immunization (n=15, 78.95%) was studied more than that of VPD (n=4, 21.05%). Vaccine safety studies were carried on that focused mainly on influenza (n=39, 31.20%), followed by MMR (n=21, 16.80%), DTP/DTaP (n=17, 13.60%).

Conclusions: This review showed that various studies, including vaccine safety research, can be conducted in vaccine active surveillance system such as VSD.

10991557, 2020, S3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5114 by Marmara University, Wiley Online Library on [17/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License