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The effect of the clinical pharmacist in minimizing drug-related problems and related costs in the intensive care unit in Turkey: A non-randomized controlled study

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Abstract

What is known and objective: Drug-related problems (DRPs) are common in hospitalized patients in intensive care unit (ICU). The aim of the study is to reduce DRPs and associated costs with clinical pharmacist's (CP) recommendations.

Methods: The study is a prospective, non-randomized controlled study conducted in the ICU for a total of 6 months (1 January 2021–30 June 2021) in 2-month control, 2-month study, and 2-month control periods. Patients who were hospitalized for more than 24 h and used more than one medication were included in the study. The PCNE V9.1 Classification system was used in the classification of DRPs. During the intervention period, CP recommendations for DRPs were proposed to the healthcare team.

Results and discussion: A total of 146 patients were included in the study. A total of 1061 DRPs from all periods were detected. The most common causes of DRPs were potential drug–drug interactions (31.76%), high dose (12.44%), and dose timing instruction errors (9.24%). For 347 DRPs identified during the study period, 259 interventions (74.63%) were recommended, and 238 (91.89%) were accepted by physicians. Interventions were mostly made as interrupting/discontinuing the drug (28.02%), changing the dose (25.27%), changing the instructions for use (20.32%), and starting a new drug (15.93%). Cost savings were achieved with CP recommendations applied.

What is new and conclusion: The CP's recommendations were highly accepted by the healthcare team. With the CP's participation in routine patient rounds in the healthcare team of the ICU, drug-related costs would also decrease.

KEYWORDS
clinical pharmacist, cost saving, drug-related problems, intensive care unit, PCNE

1 | WHAT IS KNOWN AND OBJECTIVE

Because intensive care units (ICUs) are complex for patients and medications, the risk of prescribing errors and related adverse drug events (ADE) is high.[1–3] An adverse drug event, on the other hand, may be associated with the need for extra treatment, extended hospital stay, morbidity and mortality, and causes extra healthcare costs.[2,4] A drug-related problem (DRP) is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes."[5] Most DRPs are predictable or potentially preventable, and their frequency can be reduced by optimizing pharmacotherapy.[4] Interventions by

clinical pharmacists (CPs) have significantly reduced DRPs. Clinical pharmacy services in the ICU can contribute to the shortened length of hospital stays, reduced overall costs, and even lower mortality.[2,6]

CPs contributions include attending daily rounds, performing medication review and making recommendations for DRPs in the ICU. Recommendations by CPs to reduce DRPs are about dose, indication, dosage form, compliance with the route of administration, management of drug–drug interaction, duration of treatment, prevention of duplication, prevention of missed drug dose, therapeutic drug monitoring with appropriate methods, drug initiation-discontinuation the drug, side effect control.[2,7–9]

1.1 | Aim of the study

In this study, it was aimed to detect and classify DRPs in the ICU and to reduce these DRPs and related costs with the recommendations of the CP.

2 | METHODS

2.1 | Study design

The study is a prospective, open-label, non-randomized controlled study conducted between 1 January 2021 and 30 June 2021, in the ICU of a university hospital (700-bed) providing tertiary care located in Istanbul, Turkey.

The study consisted of three separate periods, each period covering 2-months, and lasted for a total of 6 months. In the first (P1) and third (P3) periods of the study, only observation was made without any intervention by the CP. In the second period of the study (P2), interventions were recommended by the CP to minimize DRPs in the ICU. The first observation period was planned to see the status of DRP during the period before CP interventions, that is, during the period of routine practice. In the second period, clinical pharmacy services were tried to be implemented in the ICU. In the third period, the effects of clinical pharmacy services on DRPs in ICUs were followed in terms of sustainability.

2.2 | Sample size

In order to calculate the sample size of the study, standard deviation 1, alpha 0.05 and 95% power values, based on the data that DRP was reduced from 5.2 to 4.2 (approximately 20%) per patient in the patient groups recommended by the CP in the literature.[10] It was determined that there should be at least 23 patients in each group (period), and considering the 15% dropout rate, it was decided to include a total of 78 patients, with at least 26 patients in each group (period).

2.3 | Participants

Patients over the age of 18 who were hospitalized in the ICU for more than 24 h and were using at least one medication were included in the study. The drug review was performed after the patient was hospitalized for 24 h. Patients who were hospitalized at the weekend and could not be followed up were excluded from the study.

2.4 | Assignment method

Patients were assigned without any randomization during the study periods. Care was taken to include all patients who met the inclusion criteria to avoid potential selection bias in the study.

2.5 | Interventions

The CP attended patient visits on weekdays and made recommendations for DRPs during the day. Interventions for DRPs were carried out face-to-face, in the form of attendance at routine patient rounds and recommendations to the patient's responsible physician. The CP's interventions were a verbal recommendation to prevent or resolve possible DRPs at any stage of the drug prescribing process. Accordingly, intervention recommendations such as adding or stopping medication, recommending an alternative treatment, changing the route of administration, preventing or managing side effects, performing therapeutic drug monitoring, optimizing drug administration technique, or adjusting dosage were provided through the CP's daily review of the patient's medications. Only "Major" and "Contraindicated" level interactions are included in the evaluation of potential drug–drug interactions (pDDIs). Contraindicated interactions refer to avoidance of drug combinations, while major level interactions refer to consideration of treatment modification. Drug monographs, Uptodate Drug Information, Micromedex Drug Information and other resources have been used for information on pDDIs, dosing and administration of drugs. The PCNE V9.1 Classification system was used in the classification of DRPs. The process and tools used to define DRPs are presented in the flowchart in Figure 1. Clinical pharmacist interventions (CPIs) in this study process were described according to the Template for Intervention Description and Replication (TIDieR).[11] In order to reduce DRPs in ICU, online and face-to-face education, and consultancy services were provided to the healthcare team on guideline-consistent treatment.

2.6 | Data collection

Data on clinical course, disease and drug history, current treatment, relevant laboratory results, need for extracorporeal support, need for mechanical ventilation, nutritional status, Charlson Comorbidity Index, and Glasgow Coma Scale scores were collected from the patient records.

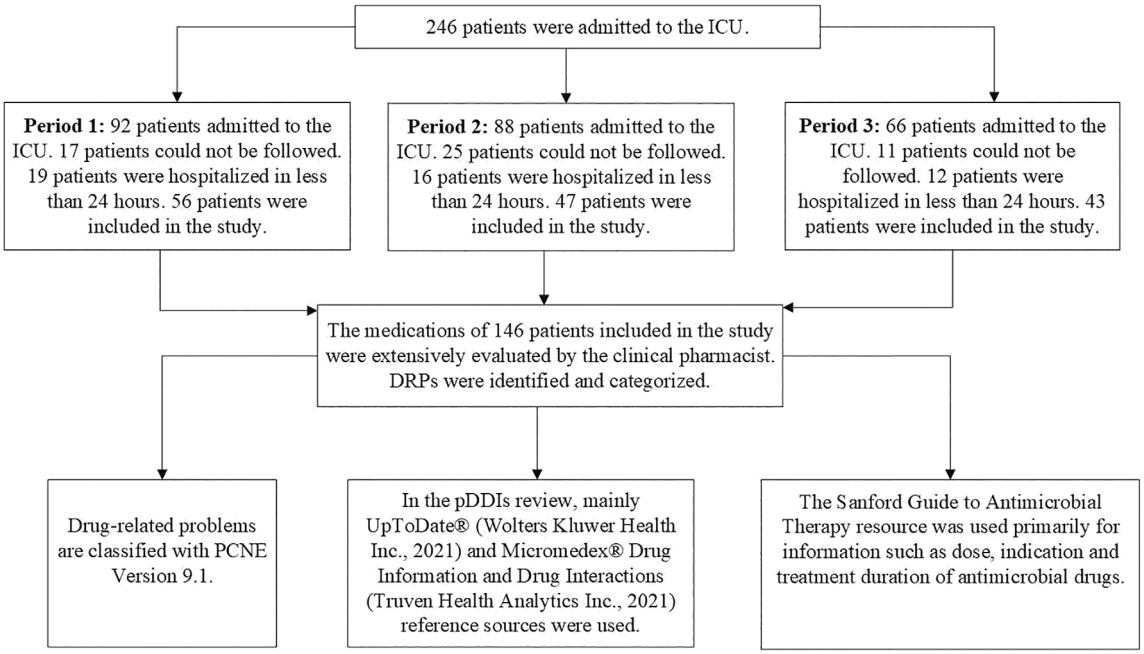

FIGURE 1 Flow diagram describing the process of identification of drug-related problems

2.7 | Primary outcome measures

The primary outcome is the reduction of DRPs after the CPI and the determination of the acceptance rate of CP recommendations.

2.8 | Secondary outcome measures

The secondary outcome was saving costs by reducing DRPs. In the second period of the study, cost savings as a result of the interventions accepted and fully implemented by physicians was calculated. In this context, the savings provided by all the recommendations regarding medication treatment were calculated. Only drug costs were taken into account in the cost savings analysis. Pharmaceutical services, nurse services or the cost of medical supplies used were not taken into account in the calculation. The cost difference between the regimen applied by the healthcare team and the regimen suggested by the CP (such as discontinuing the medication, reducing the dose, recommending a more cost-effective agent) was calculated. All costs were adjusted to US dollars and the March–April 2021 exchange rate was used for the conversion of Turkish Lira to US dollars.

2.9 | Data analysis

Statistical evaluation of the results was analysed using the SPSS 25.0 programme. Chi-square analysis was applied to compare categorical data. Whether the distribution was normal for continuous variables was analysed with the Kolmogorov Smirnov test, and it was seen that the data did not fit the criteria of normal distribution. Therefore, the differences between the two groups were compared with the Mann Whitney *U* test. Study periods were compared with the Kruskal Wallis *H* test. Whether the presence of different clinical conditions poses a risk for DRPs was determined by the odds ratio. There is no missing data in the patients included in the study. All data are given at a 95% confidence interval, with $p < 0.05$ as statistically significance.

3 | RESULTS AND DISCUSSION

A total of 246 patients were admitted to the ICU during the entire study period, and 100 patients were excluded due to hospitalization of less than 24 h and weekend admission-discharge (Figure 1). A total of 146 patients were followed up for evaluation and included in the study (P1: 56, P2: 47, P3: 43). The median age (interquartile range [IQR]) of patients was 62.5 (51–74) years and 55.4% were male. The majority of the patients (60.2%) were admitted to the ICU for non-surgical reasons. The rate of hospitalization due to surgery in P3 (58.1%) was significantly higher than in other periods ($p = 0.013$). The most common comorbidities in patients were hypertension (17.8%), diabetes mellitus (11.91%) and chronic kidney disease (8.1%). The mortality rate in all patients is 28.7%. In P3, this rate is 20.9%, which is significantly lower than in other periods ($p = 0.023$). At baseline, there was no significant difference between the periods in terms of other sociodemographic and clinical characteristics of the patients ($p > 0.05$; Tables 1 and 2).

A total of 1061 DRPs (7.26/patient) from all periods were detected. Inappropriate combination of drugs (C1.3) (31.7%), high dose (C3.2) (12.4%) and errors in dose timing instructions (C3.5) (9.2%) causes were encountered the most in all periods in the causes category. Excluding pDDI-derived DRPs, the number of DRPs per

TABLE 1 Sociodemographic characteristics of patients

	Period 1		Period 2		Period 3		All Periods		
	Patient (*n*)	Median (IQR)	Patient (*n*)	Median (IQR)	Patient (*n*)	Median (IQR)	Patient (*n*)	Median (IQR)	*p* Value
Age	56	62 (51.25–74)	47	65 (51–74)	43	59 (46–72)	146	62.5 (51–74)	0.537
Gender, *n* (%)									
Male	27	%48.2	30	%63.8	24	%55.8	81	%55.48	0.283
Female	29	%51.8	17	%36.2	19	%44.2	65	%44.52	
CCI	56	4 (2–6)	47	4 (2–5)	43	3 (1–5)	146	4 (2–5)	0.201
Number of Comorbidities	56	2 (1–4)	47	2 (1–4)	43	2 (1–4)	146	2 (1–4)	0.831
GCS score	43	15 (7–15)	26	14 (7–15)	25	15 (11–16)	94	15 (8.75–15)	0.401
Total Hospitalization Days	56	9 (4–28)	47	6 (3–17)	43	7 (3–15)	146	7 (3–17.25)	0.256

Abbreviations: CCI, Charlson Comorbidity Index; GCS, Glasgow Coma Scale; IQR, interquartile range.

TABLE 2 Clinical characteristics of patients for all periods

	Period 1		Period 2		Period 3		All periods		
	Patient (*n*)	Median (IQR)	Patient (*n*)	Median (IQR)	Patient (*n*)	Median (IQR)	Patient (*n*)	Median (IQR)	*p* Value
Number of medications in hospitalization	56	5 (3–8)	47	4 (1–6)	43	2 (2–7)	146	4 (2–7)	**0.004**
Number of medications in discharge	56	6 (4–9)	47	5 (3–7)	43	5 (4–8)	146	6 (4–8)	0.288
	Patient (*n*)	Percentage (%)	Patient (*n*)	Percentage (%)	Patient (*n*)	Percentage (%)	Patient (*n*)	Percentage (%)	
Nutritional status									0.080
Oral	18	32.1	17	36.2	16	37.21	51	34.93	
Nasogastric	18	32.1	9	19.1	5	11.63	32	21.91	
Intravenous	8	14.3	12	25.5	15	34.88	35	23.97	
PEG	6	10.7	4	8.5	2	4.65	12	8.21	
TPN	4	7.1	1	2.1	0	0.00	5	3.42	
Orogastric	2	3.6	4	8.5	5	11.63	11	7.53	
Mechanical ventilation status									0.293
Available	30	53.6	18	38.3	21	48.8	69	47.26	
None	26	46.4	29	61.7	22	51.2	77	52.73	
Renal status									
Normal	26	46.4	32	68.1	28	65.1	86	58.90	0.290
Decreased GFR	16	28.6	9	19.1	6	14.0	31	21.23	
CVVHD	9	16.1	3	6.4	6	14.0	18	12.32	
Haemodialysis	5	8.9	3	6.4	3	7.0	11	7.53	

Note: *p* values written in bold indicate statistical significance ($p < 0.05$).
Abbreviations: CVVHD, continuous venovenous haemodialysis; GFR, glomerular filtration rate; IQR, interquartile range; PEG, percutaneous endoscopic gastrostomy; TPN, total parenteral nutrition.

patient was 5. Information on the causes of DRPs for all periods is shown in Table 3. Statistically significant decreases were observed in inappropriate drug according to guidelines (C1.1), inappropriate outcome monitoring (C9.1) and other causes (C9.2) after the CP's intervention period when DRPs were compared between periods ($p = 0.046$; $p = 0.041$; $p < 0.001$, respectively). There was no statistically significant difference between periods in other DRP items ($p > 0.05$).

Intervention recommendations for the solution of DRPs were made only at the level of the prescriber and drug in the second period. A total of 259 (74.6%) recommendations were made for 347 DRPs identified in the second period. Of these recommendations, 238 (91.8%) were accepted by the healthcare team. Intervention recommendations are mostly interruption or discontinuation of treatment (28.0%), dose adjustment (25.2%), changing the instructions for use (20.3%) and starting a new drug (15.9%; Table 4).

TABLE 3 Classification of drug-related problems for all periods

Classification divisions	Period 1 *n* (%)	Period 2 *n* (%)	Period 3 *n* (%)	All Periods *n* (%)	*p* Value
The causes (including possible causes for potential problems)					
1. Drug selection	**170 (44.1)**	**178 (51.2)**	**195 (59.2)**	**543 (51.1)**	
C1.1 Inappropriate drug according to guidelines/formulary	6 (1.5)	13 (3.7)	2 (0.6)	21 (1.9)	**0.046**
C1.2 No indication for drug	20 (5.1)	37 (10.6)	24 (7.2)	81 (7.6)	0.112
C1.3 Inappropriate combination of drugs. or drugs and herbal medications. or drugs and dietary supplements	113 (29.3)	88 (25.3)	136 (41.3)	337 (31.7)	0.521
C1.4 Inappropriate duplication of therapeutic group or active ingredient	0	2 (0.5)	0	2 (0.1)	0.120
C1.5 No or incomplete drug treatment in spite of existing indication	26 (6.7)	34 (9.8)	33 (10.0)	93 (8.7)	0.438
C1.6 Too many different drugs/active ingredients prescribed for indication	5 (1.3)	4 (1.1)	0	9 (0.8)	0.136
2. Drug form	**41 (10.6)**	**36 (10.3)**	**19 (5.7)**	**96 (9.0)**	
C2.1 Inappropriate drug form/formulation (for this patient)	41 (10.6)	36 (10.3)	19 (5.7)	96 (9.0)	0.166
3. Dose selection	**109 (28.3)**	**94 (27.0)**	**93 (28.2)**	**296 (27.8)**	
C3.1 Drug dose too low	25 (6.4)	21 (6.0)	20 (6.0)	66 (6.2)	0.884
C3.2 Drug dose of a single active ingredient too high	52 (13.5)	34 (9.8)	46 (13.9)	132 (12.4)	0.559
C3.5 Dose timing instructions wrong. Unclear or missing	32 (8.3)	39 (11.2)	27 (8.2)	98 (9.2)	0.677
4. Treatment duration					
C4.2 Duration of treatment too long	18 (4.6)	24 (6.9)	17 (5.1)	59 (5.5)	0.501
6. Drug use process					
C6.5 Wrong drug administered by a health professional	0	2 (0.5)	0	2 (0.1)	0.120
9. Other	**47 (12.2)**	**13 (3.7)**	**8 (2.4)**	**68 (6.4)**	
C9.1 No or inappropriate outcome monitoring (incl. TDM)	22 (5.7)	10 (2.8)	6 (1.8)	38 (3.5)	**0.041**
C9.2 Other cause; specify	24 (6.2)	3 (0.8)	2 (0.6)	29 (2.7)	**<0.001**
C9.3 No obvious cause	1 (0.2)	0	0	1 (0.1)	0.448
Total DRP	385	347	329	1061	

Note: *p* values written in bold indicate statistical significance ($p < 0.05$).
Abbreviation: C, cause; DRP, drug related problem.

TABLE 4 Distribution of interventions for drug-related problems in the second period

The planned interventions	*n*
I0.1 No intervention	88
I1.1 Prescriber informed only	14
I1.3 Intervention proposed to prescriber	244
I3.1 Drug changed to …	2
I3.2 Dosage changed to …	46
I3.3 Formulation changed to …	17
I3.4 Instructions for use changed to …	37
I3.5 Drug paused or stopped	51
I3.6 Drug started	29
I1.4 Intervention discussed with prescriber	1
I4.1 Other intervention (specify)	2
Total DRP	347

Abbreviations: DRP, drug related problem; I, intervention.

Considering all periods, a total of 337 interactions and 171 different pDDI pairs were detected in 98 patients (67.1%). The contraindicated level interaction rate among interactions is 3.5%. Evidence levels for interactions are mostly (81.3%) "Weak." The most frequently detected major level interaction pairs in all periods, with their frequencies were remifentanil-tramadol (18), dexmedetomidine-tramadol (15) and propofol-tramadol (8). The most frequently detected contraindicated level interaction pairs, with their frequencies were linezolid-tramadol (3) and dexamethasone-desmopressin (2).

According to the results of the analysis on the relationship between the clinical characteristics of the patients and the number of DRPs, those who received mechanical ventilation (MV) support ($p < 0.001$), used antibiotics ($p = 0.003$), death ($p < 0.001$), hospitalized for non-surgical reasons ($p = 0.020$), orogastric fed ($p = 0.001$) and patients with decreased glomerular filtration rate (GFR) ($p < 0.001$) had a statistically higher number of DRPs. Considering the risk factors that increase the number of DRPs for all periods (OR; 95% CI, *p*), the use of antibiotics increased the risk of DRP by 5.101 (5.101; 1.089–23.905,

TABLE 5 Cost savings analysis of clinical pharmacist recommendations

Suggestion type	Number of interventions (percentage in total)	Cost savings in US Dollars (percentage of total)
Drug change	1 (1.1)	188.8 (10.2)
Dose change	23 (26.1)	983.1 (53.1)
Formulation change	16 (18.1)	328.4 (17.7)
Change of instruction for use	1 (1.1)	7.6 (0.4)
Interrupted or discontinued drug	47 (53.4)	340.9 (18.4)
Total	88 (100.0)	1849 (100.0)

0.014), and the use of MV support increased it 3.435 times (3.435; 1.735–6.800, <0.001). The risk of DRP is 9.286 times higher in patients with abnormal renal status (9.286; 4.326–19.932, <0.001).

Accordingly, as a result of the cost analysis of 88 DRPs in 32 patients (68%) in this period, a total of 1849 US Dollars was saved. Clinical pharmacist recommendations (for 88 DRPs) accepted and fully implemented by the healthcare team were analysed for cost savings. Of these, 47 (53.4%) were discontinued medication, 23 (26.1%) were dose reductions, and 16 (18.8%) were dosage forms modification. Most savings consisted of recommendations for dose changes (53.1%) and interrupted or discontinued the drug (18.4%; Table 5).

3.1 | Statement of key findings

The number of DRPs per patient did not show a statistically significant difference between the periods. pDDIs, high dose, timing and administration of dose, and inappropriate dosage form use were the most common causes of DRPs. DRPs showed statistically significant reductions in CPIs due to drug use not conforming to guidelines and formularies, and lack of monitoring of treatment outcome (including therapeutic drug monitoring). The CP's recommendations for DRPs were highly accepted. Cost savings were achieved as a result of the CP recommendations applied.

3.2 | Strengths and weaknesses

This study is important in terms of comparing DRPs before and after intervention in the ICU in Turkey, and as far as we know, it is one of the rare studies conducted in this area in Turkish patients. One of the strengths of this study is that it has a comprehensive perspective that classifies DRPs in ICU, offers recommendations for the management of DRPs, analyses cost savings of CPIs, and analyses other issues. The study's main limitations are that it was conducted during the pandemic period and that it was conducted in a single centre and with a relatively small number of patients. The study design limitations are the inability to reach a reconciliation on medications in hospitalized patients. This study was conducted in an academic tertiary hospital and our findings may not be generalizable to other hospitals and ICUs.

3.3 | Comparison with the literature

Many studies classifying DRPs in the ICU have defined different numbers of DRPs per patient. In other studies, DRPs numbers per patient; 0.13–2.46, which is considerably lower than the average in this study.[4,6,12–19] These differences in results may be due to various factors such as the technological resources used, characteristics specific to the ICU environment and patients, the method used for DRP detection, and the accepted definition of DRP. The lack of familiarity with CP recommendations in the ICU team where the study was conducted is also one of the factors affecting the DRP numbers.[16,17,20]

In this study, drug selection (51.2%) and dose selection (27.9%) were the most common causes of DRPs. Martin et al stated the most common causes of DRPs as C1.3 (27.7%), C3.2 (13.2%) and C1.1 (9.1%).[4] Li et al. reported the most common causes of DRP as C1.1 (18.2%) and C3.2 (13.4%). When all causes of DRPs were examined, the most common causes of DRPs were drug selection (41.3%) and dose selection (29%).[15] Chapuis et al stated that the most common cause of DRPs is high doses (30%).[9] The high rate of DRPs due to drug and dose selection reveals the necessity of a CP in a multidisciplinary team. The DRP rates due to the dose and drug selection stated in the literature are quite different from the rates in this study. It is consistent with pDDIs and high dose-related DRP rates reported in other studies. However, the problems caused by the inappropriate dosage form (C2.1) and timing of the dose instructions (C3.5) mentioned in this study were not mentioned much in other studies. Li et al reported the rate of C2.1 (1.5%) at a much lower rate than this study.[15] It was thought that this difference might be due to the medical team not being familiar with the drug dosage forms or the problems in obtaining the appropriate dosage form. DRPs depending on the drug administration instructions may result from the fact that the information about the route of administration, interval and infusion rate of the drug is not clearly stated.

DRPs detected due to pDDIs (C1.3) were the most frequently encountered problem (31.7%) in this study. DRP rates resulting from drug interactions reported in various studies were lower than in this study.[2,4,6,9,14,20,21] Advanced age, comorbidities, and the presence of polypharmacy have made pDDIs the most common problem.[22–24] Pharmacists' attendance at daily service rounds can play an important role in detecting and managing clinically significant pDDIs.[25]

A few studies have shown the rate of pharmacist interventions accepted in ICUs between 71% and 99%.[26–28] In their study conducted in two different intensive care units, Bosma et al found lower acceptance rates than the literature (61.8% and 67.3%).[2] The differences in these rates may be due to unfamiliarity with CPIs and different recommendation categories in the ICU where the study was conducted. The high acceptance of CPIs by physicians indicates that

the recommendations made are adequate and clinically relevant. The acceptance rate of the recommendations in this study is also comparable to the rates in the international literature. Factors related to the acceptance of recommendations include shared responsibility with physicians and nurses in drug treatment, participation in multidisciplinary rounds, ensuring safe drug use, and providing information to the multidisciplinary team.[27,29]

Medication review and pharmacist interventions are essential parts of clinical pharmacy activities. It is also considered necessary to prove the economic impact of these activities. In this study, it was seen that CPIs provide cost savings.

It was stated that 6-month CPIs and prescription reviews performed in a teaching hospital in France enabled prescription optimization and significantly reduced hospital stay days. Thus, health care cost savings were achieved. Pharmacist interventions mainly (38%) were on dose error.[30] Lucca et al, Zaidi et al and Bosma et al, similar to this study, stated that the most cost-saving intervention types were discontinuing the drug, changing the frequency of administration, and changing the drug dose.[2,13,14] The cost savings reported in the literature are mainly based on the CP's recommendations for dose changes and drug discontinuation. Direct comparisons could not be made since the differences in various aspects, such as the date of the studies, medication costs, patient groups, and hospital types, differ in the amount of saved costs. However, most studies highlight that the CP involved in the ICU team benefits from different aspects of interventions and services and cost savings.[13,14,30] In this study, although the acceptance rate of the recommendations for DRPs was high, the rates of complete implementation of the recommendations were not sufficient. The cost savings could have been even greater if the recommendations were fully implemented.

4 | WHAT IS NEW AND CONCLUSION

In conclusion, it was observed in our study that DRP was mainly caused by drug and dose selection. Patients with mechanical ventilation support, renal dysfunction and renal replacement therapy, antibiotic use, and hospitalized patients for non-surgical reasons have a greater risk for DRPs. The healthcare team highly accepted the CP's recommendations. Although statistically significant reductions could not be achieved in the number of DRPs between periods, proportional reductions could be achieved. It is anticipated that the CP's participation in routine patient rounds in the ICU with the healthcare team will significantly reduce DRPs and costs. Future research should evaluate the long-term effects of CPIs on patient outcomes in a randomized controlled trial.

CONFLICT OF INTEREST

The authors declare conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets generated and analysed during the current study were available from the corresponding author on reasonable request.

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