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Editorial

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Sights for Sore Eyes and Disappointments in Psychopharmacology

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Pleasing serendipities that brings a little smile to our lips, such as the discovery of hydrostatics by Archimedes because of floating in a bath or the discovery of gravity by Sir Isaac Newton when an apple fell on his head when he was sleeping beneath a tree, have occurred several times in the history of science.

Similar serendipities have happened in medicine in the discovery of new drugs. That is why the late 19th and the early 20th centuries were known as "the age of serendipitous observations". Serendipity played an important role in the discovery of drugs such as penicillin, aspirin, sulfonamides and some other antibiotics. Beyond any doubt, the isolation of penicillin from the mould penicillium notatum by Alexander Fleming in 1928 is the best known one of such discoveries. The finding that the side effects of some drugs work as the treatment for another illness happened also due to serendipity. Among those, the most widely known cases are the discovery of sulfonamides as oral antidiabetic drugs, in the course of their use as antibacterial agents for the treatment of typhoid fever and the discovery of minoxidil's stimulant effect on hair growth while it was being investigated for its antihypertensive effects, resulting in its approval for use in the treatment of androgenic alopecia. As is the case for physical medicine, we can provide examples for serendipitous discovery of new drugs in psychopharmacology, such as the discovery of MAOIs based on the observation of antidepressant activity of iproniazid, originally intended to be used for the treatment of tuberculosis, and chlorpromazine that was discovered to have antipsychotic effects when it was originally developed for use as an anesthetic[1].

Despite the existence of several serendipitous drug discoveries in both general medicine and psychopharmacology, there have been plenty of frustrations too. We can come up with numerous examples of these frustrations such as nomifensine, a potent antidepressant, that was reported to cause severe immune hemolytic anemia a couple of years after its launch or nefazodone, another potent antidepressant with no sexual side effects and REM sleep disturbance, that was withdrawn from the market because of its severe hepatotoxicity or thioridazine, an antipsychotic with a successful history of more than 50 years that was stopped due to its serious prolongation of QTc interval or tianeptine that had the same end after its use in Europe and Turkey for almost a decade, because of hepatotoxicity and risk of abuse.

It is well known that antipsychotics in current use are successful in treating the positive symptoms of schizophrenia; however, there has been no agent developed that is effective on negative symptoms. It has been remarkably frustrating and disappointing to witness the withdrawal of a new drug because of adverse effects and/or lack of efficacy whereas the launch of a new drug brings great enthusiasm. Withdrawal or failure in launching of a new drug entity is not only a disappointment for patients and their families, who have been waiting hopefully, but also for healthcare providers like us. The most recent example of this is bitopertin* study. We were informed by Prof Daniel Umbricht, who had made remarkable contributions to the 4th and the 5th International Congresses on Psychopharmacology held by Turkish Association for

Psychopharmacology as the translational medicinal leader at F. Hoffman – La Roche company and a valuable scientist whom we have got the opportunity to know personally, that bitopertin study was dropped because of lack of efficacy on negative symptoms of schizophrenia in comparison to placebo by the end of phase III clinical trials, despite the investment of billions of US dollars and initially promising results as the adjunct treatment of negative symptoms of schizophrenia, a demanding goal that has never been achieved before. Knowing about this has meant both a frustration of us on behalf of Dr Umbricht and the sustained hopelessness of a group of patients suffering from the negative symptoms of schizophrenia. Drop out of bitopertin project was another extinction of flickers of hope for millions of patients, who had no response to antipsychotics including clozapine, either alone or in combination since many years. As the investigator in the Turkish arm of the study, I have felt desperate for the negative impact of schizophrenia on tens of those recruited patients as well as their families, who were expecting a cure. It was another disappointment recorded in the history of medicine, like many other billion-dollar phase II or III projects stopped before launch[2,3].

As uttered during the round-table meeting participated by R&D executives of Turkish and global pharmaceutical companies, held in the course of the 5th International Congress on Psychopharmacology in Antalya on 30 October – 03 November 2014, there are prosperous studies though the number of pipeline compounds are the fewest of all times. Especially the results of those studies on resistant schizophrenia patients are interesting. As known, 1/3 of schizophrenia patients are treatment-resistant (TR) and 1/3 of TR population is resistant even to clozapine.

In other words, clozapine is effective in about half to 2/3 of treatment resistant patients. An antihypertensive/vasodilator agent, namely sodium nitroprusside** that has been in use for TR schizophrenia and its negative symptoms, should be mentioned. Among those studies, a placebo controlled clinical trial by Hallak et al. has reported that has for the first time demonstrated a safe, rapid (within hours), and long-lasting (several weeks) improvement of positive, negative, anxiety, and depressive symptoms in patients with schizophrenia after a single intravenous injection of sodium nitroprusside at a randomized, placebo-controlled trial[11].This paper has provided a breathing space for clinicians, who have been feeling desperate in the field of schizophrenia. Though the small size of sampling of this study was a notable limitation, it would be a new potential and may expand horizons of the pharmacotherapy on schizophrenia. If confirmed by new studies, the findings of this scientific work could provide a novel initiative about the relationship between the observed NMDA receptor hypofunction and the negative and cognitive symptoms of schizophrenia[12].

In conclusion, although there are still numerous unmet needs and pending problems in the treatment of schizophrenia, it is hopeful to have ongoing phase II and phase III clinical trials (mostly phase II) on new drug entities exerting activity through the glutamatergic system or NO to have been proceeding quickly and accumulating data in a positive direction, to our knowledge[12]. We anticipate that the outcome of the ongoing studies in the field would please the patients, their families and healthcare providers.

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* *It is well known that the traditional models of schizophrenia have emphasized dopaminergic dysfunction. Over the last 20 years, however, limitations of the dopamine model have become increasingly apparent, necessitating development of alternative models. Rapidly accumulating evidence suggests that the glutamatergic system plays an important role in the neuropathology of schizophrenia. Recently it has been shown that accumulating evidence suggests that the N-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptors, plays an important role in the neurobiology and treatment of this disease. Latest investigations are focused mainly on the glutamatergic system, an excitatory amino acid neurotransmitter system in the brain. Studies*

performed in animal tests and early clinical investigations brought a new insight in the pharmacotherapy of schizophrenia. The preclinical evidence has shown that it might be possible to develop glutamate-based antidepressants by not only modulating ionotropic (NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) and metabotropic glutamate (mGlu) receptors, but also by altering synaptic concentrations of glutamate via specialized transporters[4,5]. Researches on bitopertin are the one example of these efforts and proposed as a new class of treatment for schizophrenic patients. Bitopertin (RG1678) is a drug under development intended to be used in combination with antipsychotics for the treatment of persistent negative symptoms or positive symptoms of schizophrenia. It is a selective glycine transporter type 1 (GlyT1) inhibitor that increases levels of the glycine in synaptic cleft by inhibiting its reuptake. Glycine acts as an obligatory co-agonist along with glutamate at NMDA receptors. Dysfunction of NMDA receptors may play a role in the pathogenesis of schizophrenia and modulation of glutamatergic signalling via increased concentrations of glycine in the synaptic cleft may help potentiate NMDA receptor function and improve the symptoms of schizophrenia. It has a high binding density in the pons, the superior and inferior colliculi, and various thalamic nuclei. Moderate binding site density has been shown in the caudate nucleus, the dentate gyrus, the putamen, and the CA 1–3 regions of the hippocampus and low binding in cortical regions. Bitopertin is administered orally at 10 mg or 20 mg once daily for 56 weeks. In a Phase II study patients on Bitopertin experienced a significant improvement in the Negative Symptom Factor Score from baseline within 8 weeks and then it moved to Phase III trials. Unfortunately, recently it has been announced that as a new promising drug specially for negative symptoms was not in Phase III any longer since it has not been found effective enough[6-10].

** *Sodium nitroprusside is an antihypertensive drug that has vasodilatation-effects. It owes its principal activity to being a NO donor, so that it raises NO synthesis. When administered to schizophrenic patients via infusion, NO production escalates, so the tissue levels increase directly, without mediation by NMDA receptors in brain. It is a prominent finding that a single dose administration of nitroprusside in schizophrenia patients provides amelioration in symptoms that lasts up to 2 weeks. It is highly likely that a single dose sodium nitroprusside infusion given to treatment resistant schizophrenia patients yielded a rapid and weeks long improvement just like ketamine, an NMDA receptor antagonist, provided in treatment resistant depression. The effects of nitroprusside on schizophrenia symptoms could be explained by an increase in cerebral perfusion due to vasodilatation. Studies have proven that the blood stream in frontal and temporal cortex, which are concluded to be related to the negative symptoms of schizophrenia, decay in schizophrenia patients when compared to healthy controls[11]. This finding provides additional evidence for NMDA receptor hypofunction in schizophrenia. The above-mentioned results are consistent as far as the positive therapeutic effects of NMDA are concerned. The effect of nitroprusside should be repeatedly observed in additional clinical trials with sufficient sample size of schizophrenic patients, for confirmation.*

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