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Treatment of Schizophrenia: Past, Present and Future

Mesut Cetin[1]

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Schizophrenia, which throughout history and to this day has been met in all socioeconomic layers at a rate of around 1%, is one of the most important mental disorders, leading to severe impairments in mental, social, professional, and economic realms due to a severe loss of abilities[1,2].

Treatment attempts were begun in the middle of the last century, originally with the "First Generation Antipsychotics (FGAs)", the first of which, chlorpromazine, was discovered in 1952, and in 1996, the first second-generation antipsychotic (SGA), risperidone, was introduced on the market. Both FGAs and SGAs were focusing on psychopathology and positive symptoms. While the positive symptoms were successfully treated; patients with schizophrenia were discharged from large mental asylums and thus saved from living in isolation from society for many years. During the age of the use of FGAs; physicians were still more inclined towards an attitude of omnipotence with less regard for patient's understanding, assuming that all problems would eventually be solved pharmaceutically, which later gave rise to problems such as polypharmacy with insufficient evidence base[3] and inappropriate applications and/or over dosages of antipsychotics[4].

While FGAs as D2 receptor antagonists act on all dopamine pathways in the brain, causing extrapyramidal symptoms (EPS) and thereby leading to stigmatization, the SGAs act as work as antagonists not only on the D2 receptor but also on 5HT2A, which caused very few or no EPS at all, and the patients were not stigmatized, which allow for them to be discharged in a short period of time and to live within society[5].

But SGAs consist of a very varied group of drugs. Thus, they affect different receptors, their half lives are different, and their metabolism through the CYP 450 enzyme systems differ as well[6,7].

While SGAs like olanzapine, clozapine, or quetiapine initially giving great hopes to patients suffering from the EPS of FGAs, the NIMH-funded CATIE study that was conducted in 57 centers in the USA, involving 1493 patients, demonstrated that SGAs like clozapine and olanzapine led to significant weight gain and caused metabolic side effects[8].

Consequently, in a number of therapeutic guidelines; olanzapine and quetiapine were separated from other SGAs, advising physicians not to use them as the first choice in first-episode schizophrenia, as had been the case previously, because of the understanding of their metabolic side effects[9].

In brief, in a sense we have today jumped out of the frying pan into the fire: abandoning FGAs because of EPS, we have been caught up in SGAs' metabolic side effects which are more serious than EPS, and now we have to find a solution for these, because one of the most important results of the CATIE study was the realization that we have to take SGA metabolic side effects into account. It is crucial for physicians to be very knowledgeable about the desired effects and undesired side effects of antipsychotics in order to prevent negative effects by individualization of treatment, even before initiating antipsychotic treatment. It is

helpful for the clinician to share information about side effects and preventive measures with the patient and their relatives right at the beginning of the therapy in order to be able to prevent metabolic problems that may develop during the course of treatment. It is essential to assess the patient's risk profile and adapt the drugs to be selected for treatment according to this profile. There are other antipsychotic drugs that, in addition to metabolic side effects, can also induce cardiovascular effects, and it is necessary to avoid using QT interval-prolonging drugs such as pimozide or ziprasidone together with other agents that can interact with these drugs and increase their blood levels. In patients with EPS and tardive dyskinesia (TD); before any more significant side effects occur, pimozide, haloperidol, depot FGAs or SGAs such as risperidone, paliperidone and their long-acting injection (LAI) formulations should not be prescribed.

In order to prevent weight gain, hypertension and hypercholesterolemia, diet and exercise can be recommended. Patients and relatives should know these side effects and help patients to increase their mobility and maintain a healthy diet over time; in addition, it is most important that either the patient or his relatives or the physician ensure a regular weight control.

Some schizophrenia patients are more inclined to follow the recommendations from their physicians or other healthcare providers. A number of patients have been seen participating in walking programs prepared by the nurses and other sport events suitable for their state of health. Uncontrolled food services and a lack of attention to patients' nutrition can cause significant damage. It is harmful to use food as a reward for patients in behavioral therapy. Especially patients with mental retardation or pervasive developmental disorders should be removed from behavioral programs based on food rewards and rather be directed towards programs where rewards consist of activities and plays the patient likes, such as swimming and other sport activities.

In patients who are already overweight, not only should antipsychotics with a lower metabolic risk be selected, but patients using antipsychotics should also be examined in specific intervals, every few months, with metabolic tests, controlling their blood sugar and sugar metabolism and the triglyceride and cholesterol levels, as the risk for developing various physiological diseases and early death is already significantly increased in patients with schizophrenia compared to the general population[10]. In patients with schizophrenia; especially those using certain antipsychotics such as clozapine, olanzapine, or quetiapine, obesity and insulin resistance as well as high triglyceride levels and hypertension are often found as core elements and identifiers of metabolic syndrome (MS). Another factor contributing to early death in patients with schizophrenia is smoking, found to be twice higher[11,12]. In patients with schizophrenia using clozapine and olanzapine, the prevalence of type 2 diabetes mellitus (DM II) is five times higher than in the general population[13,14]. In patients with schizophrenia, risk for coronary heart diseases[15] and stroke[16] is higher than in the general population. In addition to metabolic and cardiovascular diseases, infections such as pneumonia and tuberculosis or COPD as a consequence of heavy smoking are four times increased compared to the general adult population. These, as well as ventricular arrhythmias, sudden death, and other cardiovascular death risks, strokes and MS etc. can at least partly be reduced by preventive measures during initial antipsychotic selection and subsequently by exercise, obesity control, smoking cessation, and other preventive measures[17-19]. Also cancer-related death is more common in schizophrenia patients compared to the general population, by 39% in males and 24% in females[20]. Hyperprolactinemia, a side effect common to FGAs and some SGAs such as amisulpride or risperidone, might be associated with breast cancer, osteoporosis, and hypogonadism[21].

According to a systematic review, the lifelong risk of suicide for schizophrenia patients is around 5-10%[22]. Among the risk factors for suicide, we find

low level of education, male gender, young age, previous suicide attempts, depressive symptoms and poor compliance with the use of antipsychotic drugs, leading to hallucinations, delusions, lack of insight and, especially in the last few years, substance abuse with an increasingly common use of new-generation synthetic cannabinoids in society. Given the severity and irreversibility of suicide, for patients with a record of attempted suicide or with a perceived risk, irrespective of side effects, the most effective antipsychotic to be used, the only one approved by the FDA for its antisuicidal effect, is clozapine[23].

At the onset of schizophrenia, another problematic social dysfunction comes to the fore. Therefore, in an effective therapy for the first episode of schizophrenia, it is not only important to reduce the positive symptoms, but at the same time, social withdrawal should be prevented. That is why therapy and follow-up of first-episode schizophrenia patients for up to five years is very important[24].

While traditionally schizophrenia treatment was given in the hospital, focusing on symptoms, nowadays the approach has been broadened to encompass psychosocial approaches and include family and society comprehensively. It is therefore necessary to plan and deliver treatment from the beginning including the patient and the environment, aiming at the patient's integration into society[25].

Despite all of these psychosocial approaches to schizophrenia treatment in the last decade, the basis of therapy remains to be pharmacotherapy with antipsychotic medications. The most striking evidence is a study by Leucht et al. published in 2013, a broad meta-analysis assessing the data of 43,049 participants to compare the effectiveness and tolerability of 15 antipsychotic drugs. They found that all 15 antipsychotic drugs were significantly more effective than placebos[26]. It is also well known that patients not taking antipsychotics are exposed to delusions and hallucinations that would make them difficult to reach through psychotherapeutic approaches.

It is therefore imperative to make sure that patients would use antipsychotic drugs. However, long-term follow-up studies such as the CATIE Trial demonstrate that there is another big problem with adherence to treatment. Patients discontinuing their medication are also more frequently suffering relapses or need to be re-hospitalized. In patient groups with poor adherence, it has been tried to provide depot drugs or long-acting antipsychotics. While Leucht et al. in their first studies[27] found a significant reduction in relapses with depot or long-acting injectable (LAI) antipsychotic drugs, other researchers could not confirm these results. Thus, Rosenheck et al.[28] found long-acting injectable risperidone in patients with schizophrenia or schizoaffective disorder who were at high risk of hospitalization or had been hospitalized superior to the oral therapy chosen by the psychiatrist. Kane et al.[29], too, found that olanzapine long-acting injection was efficacious in the maintenance treatment for schizophrenia for up to 24 weeks, with a safety profile similar to that of oral olanzapine, except for injection-related adverse events. Macfadden et al.[30] found that results failed to demonstrate superiority with injectable risperidone long-acting therapy versus oral aripiprazole in a prospective study comparing the long-term effectiveness of injectable risperidone long-acting therapy and oral aripiprazole in patients with schizophrenia. In the same sense; Kishimoto et al.[31], in their comprehensive new meta-analysis including 21 randomized clinical trials, could not find a significant difference between long-acting injectables and oral antipsychotics in the prevention of relapses in schizophrenia. Also, Leucht et al.[32] performed a systematic review comparing placebo and antipsychotic drugs in the prevention of schizophrenia relapses and found in their meta-analyses that in patients with schizophrenia, taking oral and depot antipsychotics was superior placebo. However, the sudden or gradual discontinuation of the antipsychotics did not effect the relapse risk.

But as a general consensus therapy in patients with poor adherence, depot or long-acting

injectable antipsychotics tend to be seen as an appropriate choice.

Among the current unmet needs in the treatment of schizophrenia, there are negative symptoms, drug side effects, mood symptoms, comorbid disorders, alcohol and substance dependency, stigma, psycho-social and pharmacoeconomic needs, integrated, evidence-based interventions to improve the quality of life, care outside the institution, and unmet psychosocial needs.

To address these unmet needs in the treatment of schizophrenia, studies are being conducted outside the dopaminergic system, with drugs acting on glutamate, GABA, glycine, D-serine, and nitric oxide etc.[33]. This kind of studies sometimes produces disappointments, as was the case with bitopertin[34].

But scientific evidence shows that without exhausting our hope, we can increasingly individualize our therapies, which is to say, set up individual plans and applications for each patient; by trying to assess the patient's family, work environment and society as a whole, we can integrate them more closely and can work as a team, beyond the healthcare team, using patient and family, social institutions and in cooperation with non-governmental organizations (NGOs) with psychosocial approaches for a better understanding between physicians and patients as well as their families, improving empathy, and thus achieve better results[35].

[1]M.D., Professor of Psychiatry, Editor -in- Chief, Klinik Psikofarmakoloji Bulteni-Bulletin of Clinical Pychopharmacology, Istanbul-Turkey

Correspondence Address: Prof. Dr. Mesut Cetin, Turkish Association for Psychopharmacology (TAP) Office, Caddebostan Mahallesi, Bagdat Caddesi, Birgen Is Merkezi 226/7, Ciftehavuzlar, 34728 Kadikoy, Istanbul-Turkey

Phone: +90-216-464-2888

Email address: editor@psikofarmakoloji.org

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