

Clozaphobia: Fear of Prescribers of Clozapine for Treatment of Schizophrenia



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Clozapine, the progenitor of atypical antipsychotic drugs, was first synthesized at Wander Laboratories in Bern, Switzerland in 1956, only a few years after the discovery of the first antipsychotic, chlorpromazine. However, it is interesting that in the beginning it was debated whether this drug, which did not cause catalepsy in animal models like other antipsychotics, could be a potential antipsychotic. Indeed, evidence suggests that clozapine does not cause extrapyramidal side effects, as also evidenced with the fact that it is well tolerated by patients with Lewy Body Dementia or L-DOPA-induced psychosis in Parkinson's disease.

Clozapine started to be used in Europe after 1971, but in 1975, because of deaths resulting from agranulocytosis, the pharmaceutical manufacturer withdrew clozapine from the market in all countries¹. After Kane et al.² in 1989 in the US demonstrated its efficacy in treatment-resistant schizophrenia patients, the FDA approved it for treatment-resistant schizophrenia. During the 14 years, clozapine had not been prescribed anywhere in the world. Despite the FDA approval, psychiatrists from 1989 to the present day have been reluctant to use clozapine. However, the criteria for treatment-resistance are encountered in at least 30% of schizophrenia patients^{2,4} and clozapine is the only antipsychotic that can be considered to be the "gold standard treatment" of schizophrenia. Despite that, according to Intercontinental Marketing Service (IMS) data for 2010, the market share of clozapine among antipsychotics in the US is only 4.4%⁵.

In Turkey, according to IMS data for the years 2013 and 2014, the usage rate of clozapine among

all antipsychotics is around 2.34%. Compared to Scandinavian and other European countries, and especially China with a rate of 10%, the use of clozapine in Turkey remains far below than in many other countries. The biggest reason is agranulocytosis risk of clozapine. Therefore, the "clozaphobia; phobia of *professionals for prescribing clozapine*," is justified, since 1975. Many clinicians have had reservations about its use, which continues to be the case around the world today. Actually the risk of developing granulocytopenia and agranulocytosis during clozapine therapy is between 0.7 and 1.0%, respectively and most of the cases are seen during the first six weeks or first six months. During the second six months of treatment, the rate is 7 per 10,000 patient years and after the first year 3.9 per 10,000 patient years. In the US clozapine records comprising the first five years of use, of 99,502 patients, 382 (0.38%) developed agranulocytosis and 12 (0.01%) died.

Despite the risk of agranulocytosis, metabolic side effects and cardiovascular problems such as myocarditis, because of its clear effectiveness advantage, clozapine should still be considered cautiously for 30-40% of patients with schizophrenia or schizoaffective disorders⁹⁻¹². At the same time, in a number of patients side effects of clozapine treatment, such as weight gain can occur. However, while the risk of weight gain is similar due to clozapine and olanzapine, a result of glucose dysregulation which can manifest itself as insulin resistance, type II diabetes mellitus, diabetic ketoacidosis and rise in lipids⁹⁻¹², these metabolic side effects can be mostly managed by exercise, lifestyle change, diets, and similar measures¹³.

Metformin treatment has been shown to be useful to reduce a wide range of metabolic side effects caused by clozapine¹⁴. A comprehensive study has assessed the genetic determinants for the risk of developing metabolic syndrome¹⁵. Patients with cases of diabetes mellitus in family members should be identified at the beginning of treatment in order to take active preventive measures against the risk because of their susceptibility. Clozapine is associated with a low risk of potentially fatal myocarditis or cardiomyopathy. Clozapine is not related to torsade de pointes, QTc elongation, or sudden death^{16,17}.

Results of epidemiological studies conducted in the US⁶ and Finland^{7,8} demonstrated that none of the potentially life-threatening risks are sufficient to reject the advantages of clozapine use in "real life." In the US, where clozapine has been used for twenty years, there is no evidence whatsoever for a rise in mortality due to the drug.

As explained above, the main cause of "clozapinophobia" is the possible development of granulocytopenia and agranulocytosis as an adverse effect. Through a weekly blood count during the first 18 weeks of clozapine treatment, the monitoring of white blood cells or neutrophils provides a chance for early detection of granulocytopenia, before the development of agranulocytosis, and to discontinue the clozapine treatment. As a result, full agranulocytosis is very rarely seen. If agranulocytosis develops, a treatment with *granulocyte colony-stimulation factor* before the onset of infections will in many cases be effective in restoring the normal level of white blood cells. Treatment with antibiotics is also generally effective in these cases, so that the mortality related to agranulocytosis is in the region of 1 per 10,000⁵. If we consider that patients suffering from treatment-resistant schizophrenia have a 10% mortality rate through suicide, the death risk related to clozapine adverse effects appears to be very small in comparison.

Not only has clozapine been proven the only effective drug for treating treatment-resistant schizophrenia, but at the same time it is still the only antipsychotic with a proven anti-suicidal

effect. While the rate of mortality through suicide of around 10% related to schizophrenia is a reality, there has been an increasing debate among psychiatrists worldwide why they would not accept a risk of 0.01% due to clozapine use. In addition to cases of high suicide risk, clozapine has been shown to be effective also in a sub-group of patients with residual medium-severe positive symptoms who are not responding well to therapy¹³. It has been found that suicide plays a big role in the early death of schizophrenia patients¹⁴. Generally, some 30-50% of schizophrenia patients attempt suicide, some 5% die of actual suicide, and the lifetime suicide risk of schizophrenia patients is five times higher than that of the general population^{15,16}. The anti-suicidal effect of clozapine in treatment-resistant schizophrenia and schizoaffective disorder patients through a reduction of suicidal behavior has been demonstrated^{19,20}.

In an epidemiological study of 67,000 cases of patients treated with clozapine in the US between 1989 and 1996, mortality for all causes dropped compared to the period between 1975 and 1988^{6,18-20}. Even if there was an advantage in the patients' being seen more frequently during clozapine treatment, in a multi-center randomized international two-year follow-up study (*the International Suicide Prevention Trial*, InterSePT) comparing the risk of suicidal behavior in patients with a high risk of suicide, the group treated with clozapine made significantly fewer suicide attempts than were found in the olanzapine group ($p=0.03$)²¹.

Another important epidemiological study has confirmed that clozapine, as it reduces the death rate due to suicide, indirectly also significantly reduces the death rate for all reasons compared to all other antipsychotic drugs. In a comparison using prescription data, based on the national prescription register, the death rates of 66,881 patients with a diagnosis of schizophrenia between 1996 and 2006, showed that the lowest general mortality risk was found among patients treated with clozapine⁷.

Regarding the prevention of relapses, between 1995 and 2001 for the first time a nationwide

cohort study was performed with 2,230 consecutive adults hospitalized in Finland, comparing clozapine, perphenazine depot, olanzapine and oral haloperidol; the study found that clozapine had the lowest discontinuation rate of antipsychotics for any reason and the lowest relapse rate⁸. Meltzer et al. reported, in a one-year study in the US with 57 patients suffering from treatment-resistant schizophrenia, a reduction in the relapse rate by 89.6% after treatment with clozapine²⁶. In a Korean cohort study²⁷, clozapine showed a similar benefit over five years.

The probability of developing tardive dyskinesia among patients using clozapine is lower than that with first generation antipsychotics²⁸. In the US during the 1980s, tardive dyskinesia developed in approximately 5% of schizophrenic patients not using clozapine but using typical antipsychotics⁴. Therefore, clozapine needs to be used in patients with treatment-resistant schizophrenia, tardive dyskinesia, and the patients with a high risk of suicide⁷. With clozapine, very rare cases of tardive dyskinesia and neuroleptic malignant syndrome (NMS) have been reported. In a study with 101 patients having taken clozapine on average for 12±6 years, a 3.96% prevalence of tardive orolingual dyskinesia was shown²⁹. Furthermore according to some studies, clozapine can prevent tardive dyskinesia^{30,31}. In a comparison of all antipsychotic drugs except quetiapine, clozapine was the one tolerated best by Parkinson patients treated for L-DOPA-induced psychosis³².

Clozapine has great advantages for positive and negative symptoms, general psychopathology, cognition and suicide; it causes fewer extrapyramidal side effects (EPS) and improves tardive dyskinesia³³. Clozapine shows positive effects in some cognitive areas such as verbal fluency, declarative memory, attention, and cognitive function³⁴⁻³⁷.

Even in treatment-resistant patients, clozapine can lead to a functional improvement in 30-50% of the cases, improving cognition and psychopathology and the quality of life³⁸⁻⁴². In order for clozapine to achieve an effect of

cognitive improvement, it may be necessary to use the drug for up to six months³⁴.

A study by the European Schizophrenia Outpatients Health Outcomes (EU-SOHO), including 9,340 patients, observed the results of receiving ambulatory antipsychotic treatment for schizophrenia over three years and compared the relevant effects of olanzapine and clozapine on health and quality of life found superior clinical effectiveness by clozapine. It also showed relevant pharmacoeconomical advantage, due to lower price and reducing hospitalization and days off from work⁴³⁻⁴⁵.

Clozapine is recommended by the Texas Medicine Algorithm Project for the treatment of treatment-resistant schizophrenia⁴⁶. The web-based International Psychopharmacology Algorithm (IPAP, www.IPAP.org) and the Schizophrenia Patient Outcomes Research Team (PORT)⁴⁷ propose clozapine as the treatment of choice for patients with schizophrenia or schizoaffective disorders if two attempts at treatment with other atypical antipsychotics at high doses over a sufficient period have failed.

In the treatment with clozapine, the first dose titration is important; after a start at a small dose around 12.5 mg/day, within a few weeks the target dose of 400-600 mg/day should be reached. In first 6 months, a weekly full blood count should be performed to screen for granulocytopenia and agranulocytosis; also other side effects such as sedation, hypersalivation, tachycardia, weight gain, myoclonia and seizures need to be monitored and countermeasures taken in a timely manner. Through psychoeducation and collaboration with the patient and family, they can be counseled that these side effects can be successfully managed.

In the early stages of treatment, especially in smokers and schizophrenic patients, it may be necessary to measure the clozapine blood level periodically; ≥350 ng / ml is a sufficient plasma level, while a higher dosage increases the risk level far more than is useful, and because it may disturb the patient's quality of life, the rate of discontinuation due to intolerance increases. It is

also very important that the transition between drugs is not random. Thus, if the patient, while being started on clozapine, still uses another antipsychotic, the first drug needs to be phased out once clozapine has reached a sufficient dose. As it is usually the last therapeutic option, clozapine monotherapy trial should continue up to six months. In resistant cases, sometimes a combination with a second antipsychotic such as aripiprazole or amisulpride can be effective^{48,49}. However, adding other atypical, such as risperidone, to clozapine was not found sufficiently effective^{50,51}. Given that patients with schizophrenia have a higher proportion of smokers than the general population, the interaction between clozapine and cigarettes is as important as the drug interactions. As smoking induces CYP P450 1A, the clozapine level in the blood can be reduced by up to one half, while smoking cessation can increase clozapine plasma levels significantly⁵². As for drug interactions, fluvoxamine inhibits CYP P450 1A and thereby increases the clozapine blood level by 50%, and some selective serotonin reuptake inhibitors such as paroxetine and fluoxetine also increase the clozapine blood level. In those cases, the clozapine dose should be reduced and if necessary the clozapine blood levels should be monitored. Sertraline, citalopram and escitalopram also interact with clozapine metabolism⁵³. The dosage of valproic acid needs to be reduced, because clozapine can increase its plasma levels⁵⁴. In order to increase the benefit for patients taking clozapine for the treatment of psychosis, negative symptoms and cognitive deficits, psychosocial therapy is required. Family and group therapy, cognitive behavioral therapy, supportive therapy, or occupational therapy allow for a lower dosage of clozapine, hence a reduction of side effects and better compliance, increasing the success rate of clozapine therapy.

In conclusion, despite the risks of agranulocytosis, metabolic side effects, and cardiovascular adverse events such as myocarditis, clozapine should be considered in 30-40% of schizophrenic or schizoaffective patients, who are

resistant to treatment with all typical and atypical antipsychotics except clozapine. The effectiveness of clozapine in this group of treatment-resistant patients is a good reason for its more frequent use in therapy. After all, because of the superior effectiveness in treatment-resistant patients and decreases in suicide and relapse rates²¹, and improvements of cognitive processes and working memory as well as social processes^{34,55}, and overall increased quality of life, we believe that a more widespread use of clozapine in psychiatric practice is reasonable. In addition, regarding extrapyramidal side effects and especially tardive dyskinesia, it has been shown that the risk is far lower than with all other antipsychotics. From a pharmacoeconomic perspective, given the relatively low cost of the drug, clozapine can also help by giving respite to social security institutions that are in serious economic straits.

On the other hand, potential serious side effects in some patients, such as agranulocytosis, insulin resistance and weight gain triggering type II diabetes mellitus⁹, hypersalivation, pulmonary embolism, tachycardia, myocarditis, cardiomyopathy, and sudden death^{16,17,57} and an increased risk of seizures need to be taken into consideration, but these should not impact a healthy and accurate decision-making process in the choice of antipsychotics and not reach the level of “*clozapinobia*”. Clozapine remains an effective, but underutilized therapeutic option for treatment resistant schizophrenia and every psychiatrist must appropriately review functional status of their patients to see, whether clozapine is indicated for better outcomes or not.

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