Editorial

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Risk Evaluation and Mitigation Strategy for Clozapine

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INTRODUCTION

Clozapine efficacy as an "atypical" antipsychotic agent has been recognized since the early 1960s[1]. However, the release of alarming reports of agranulocytosis in Finnish patients created panic among prescribers; a total of 17 cases were confirmed among 100 patients treated with clozapine, 8 of those cases resulted in fatalities. Clozapine was immediately withdrawn from the market by Sandoz in 1976[1]. Clozapine demonstrated superiority to chlorpromazine in treatment-resistant schizophrenia patients in many outcomes including treatment response, with improvements in positive and negative symptoms of schizophrenia. This led health agencies to grant clozapine access to the US markets in 1990[2].

Clozapine is an atypical antipsychotic medication that has been found to be more efficacious than other antipsychotics in numerous studies. It is the unique antipsychotic medication that has been shown to be superior to other medications in patients with treatment-resistant schizophrenia[3]. Moreover, in a recent meta-analysis authors suggest that in individuals with serious mental illness, clozapine users had a diminished risk of mortality due to both natural and unnatural causes[4]. Another advantage to other antipsychotics, clozapine has a unique antisuicidal effect approved by the FDA[5].

Despite evidence-based treatment guidelines, abundant delays observed in clozapine initiation. Antipsychotic polypharmacy and higher doses are also commonly practiced before initiation of clozapine. There is evidence that clozapine is an underused antipsychotic agent and clinicians' fears related to clozapine must be re-evaluated[6].

Effectiveness

In 2003, a meta-analysis of Davis et al. compared clozapine with five other antipsychotics (amisulpride, risperidone, olanzapine, zotepine, and aripiprazole) and found that the effect size for clozapine was substantially stronger than the closest competitor (amisulpride) and twice that, or greater, of the other four drugs[7]. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (phase II), those used clozapine found to continue treatment for significantly greater time compared with patients treated with other antipsychotics (2.7 to 3.3 months)[8]. In the randomized Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) trial, clozapine was associated with greater improvement in total score of Positive and Negative Symptom Scale (PANSS) compared with risperidone, olanzapine, quetiapine, and amisulpride[9].

The CATIE trial suggested that clozapine was more effective than quetiapine in management of depressive symptoms in patients with diagnosis of schizophrenia. Findings suggesedt that clozapine demonstrated superior antidepressant effects to quetiapine and comparable effects to olanzapine and risperidone in chronic schizophrenia1[0].

A recent meta-analysis of blinded studies comparing second-generation antipsychotics

head-to-head, included 78 studies with 167 relevant arms and 13,558 participants. Leucht et al concluded that clozapine proved superior to zotepine and, in doses >400 mg/day, to risperidone. These differences were due to improvement in positive symptoms rather than negative symptoms[11].

Because of the debate about whether second-generation antipsychotic drugs are better than first-generation antipsychotic drugs, Leucht et al ran a meta-analysis of randomized controlled trials to compare the effects of these two types of drugs in patients with schizophrenia. They compared nine second-generation antipsychotic drugs with first-generation drugs for overall efficacy (main outcome), positive, negative and depressive symptoms, relapse, quality of life, extrapyramidal side-effects, weight gain, and sedation. The results suggested that only four of the second generation drugs were better than first-generation antipsychotic drugs for overall efficacy, with small to medium effect sizes (amisulpride -0.31, clozapine -0.52, olanzapine -0.28, and risperidone -0.13). The other second-generation drugs were not more effective than the first-generation drugs, even for negative symptoms[12].

Clozapine has also been shown to reduce the incidence of suicide, aggression, risk of relapse of substance, and rate of re-hospitalization[13]. In contrast, the evidence suggests that patients receiving clozapine are happier and more satisfied with the medication when compared to other antipsychotics[14]. Other researchers who have evaluated patients' perceptions about clozapine also insist that for majority of patients think that advantages of clozapine would outweigh its disadvantages[15]. Despite the evidence related to the effectiveness of clozapine, prescription rates of clozapine reported to be too low and delayed. This also shows that clinicians have developed a kind of phobia: clozaphobia. This phobia was named and published along with justifications for this qualification as an editorial in one of our previous issues. You can find detailed information in that editorial[16].

Agranulocytosis and Other Side Effects

Clinicians indicated concerns about side effects such as agranulocytosis, myocarditis, weight gain, drowsiness or sedation, salivation, tachycardia, dizziness, and constipation. Undoubtedly the most significant barrier holding clinicians back from the use of clozapine is the restrictions around blood monitoring. Clozapine was first introduced in the 1970s in Europe but was withdrawn after the drug was shown to be associated with agranulocytosis—an acute condition involving severe leukopenia. When the FDA approved clozapine, it mandated stringent blood monitoring including regular white blood cell and absolute neutrophil counts (ANC).

Clozapine is known to have low extrapyramidal side effects including tardive dyskinesia and low tendency to elevate prolactin. However, it has a number of uncommon but life-threatening side effects such as agranulocytosis, myocarditis, and cardiomyopathy. Overestimation of side effects, clinicians' perception of them and lack of knowledge on how to manage them has been hypothesized as underlying reasons for clinicians' hesitations in using clozapine[16,17]. However, with adequate resources and monitoring, a significant number of them can be identified early on and appropriate measures can be taken to minimize their negative impact[18].

Agranulocytosis is defined as an ANC of less than 500/ml. Before a patient can start taking clozapine, ANC must be greater than or equal to 2,000/ml and the white blood cell count must be greater than or equal to 3,500/ml; the drug must be discontinued when the ANC is less than 1,000/ml or the white blood cell count is less than 2,000/ml.

There is a further wrinkle, complicating access to the drug for a segment of the population: Africans and African-Americans typically have a lower WBC, a phenomenon that has been termed "benign ethnic neutropenia" (BEN)[19].

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 to six months. The risk for leukopenia can occur at any

point during treatment. On the other hand, agranulocytosis occurs primarily in the first 18 weeks with 87.5% of cases developing the blood dyscrasias during this time frame with the meantime to the occurrence of 68 days[20]. In the US clozapine records comprising the first five years of use, 382 out of 99,502 patients (0.38%) developed agranulocytosis and 12 (0.01%) of them 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 disorders[21]. At the same time, in some patients side effects of clozapine treatment, such as weight gain can occur. However, while the risk of weight gain is similar to olanzapine, glucose dysregulation that can manifest itself as insulin resistance, type II diabetes mellitus, diabetic ketoacidosis, and rise in lipids. These metabolic side effects can be mostly managed by exercise, lifestyle change, diets, and similar measures[7].

Studies indicate that clozapine may not confer additional cardiovascular risk or even be protective against cardiovascular-related mortality compared to other antipsychotics[22].

Reasons for Clozapine Underutilization

Most experts feel the use of clozapine is far below the estimated need[23-25]. Data from Australia demonstrate that only 8.4% of individuals with refractory schizophrenia are prescribed clozapine[26]. According to a study, significant proportions of psychiatrists (64%) prefer to combine two other antipsychotics rather than use clozapine alone[27,28].

It is likely that clozapine's underutilization is related in part to needing frequent monitoring for agranulocytosis. A recent survey of clinical staff reported that patients concerns about tolerability and patients' refusal to adhere to blood test monitoring are the common barriers to clozapine prescriptions[21].

Today, only 2.3% of antipsychotic prescriptions are for clozapine in Turkey[16]. Some presume the underuse of clozapine is due to the monitoring required for use of the drug. Some cite that besides the adverse effects and required monitoring, there is a lack of training of providers on the appropriate use of clozapine or perhaps a lack of understanding of its benefits. Still others feel that perhaps marketing of other second-generation antipsychotics has led to the decline in the use of clozapine.

In a recent study, reasons for delayed use of clozapine in UK by psychiatrists are listed as: reluctance to have blood test, side effects, metabolic problems, lack of experience, patient/ family reluctance to use clozapine, clinicians concerns about poor compliance, need to admit/ bed shortage, tendency to try other antipsychotics first, delayed diagnosis/ not sure about diagnosis, and negative views of others[16].

Given the high costs of medication discontinuation, re-hospitalization and inadequate treatments for schizophrenia, the underutilization of clozapine is noteworthy. The results of surveys suggest that clinicians are aware of the delayed use and underutilization of clozapine[3,20]. The cost does not seem to be a barrier now as clozapine has become generic with a significant cost reduction.

FDA has recently announced the new the requirements for monitoring, prescribing and receiving clozapine under the title of "Risk Evaluation and Mitigation Strategy" (REMS).

Risk Evaluation and Mitigation Strategy (REMS)

Most common factors related to hesitation to initiate clozapine were the history of poor medication compliance and need for monitoring. To decrease the administrative burden associated with clozapine registration and monitoring, FDA developed a centralized registry system, namely Clozapine REMS Program. By help of REMS strategy, FDA aimed to ensure that the benefits of the clozapine outweigh the risk of severe neutropenia[29].

Severe neutropenia occurs in a small percentage of patients taking clozapine. Severe neutropenia is

defined as ANC less than 500/ml. Severe neutropenia associated with clozapine is not dose-dependent[30]. If clozapine is used concurrently with medication(s) known to cause neutropenia, the clinician must consider monitoring patient more closely than the treatment guidelines recommended.

The changes that came along with REMS are as follows[31]:

- Neutropenia will be monitored by the ANC only, rather than in conjunction with white blood cell count.

- The ANC thresholds for treatment with clozapine are being lowered, which will allow more patients to continue treatment

- Benign Ethnic Neutropenia (BEN) patients, who previously were not eligible for clozapine treatment, are now eligible to receive the drug.

- Prescribers will have more flexibility to make individualized treatment decisions if they determine that the risk of psychiatric illness is greater than the risk of recurrent severe neutropenia, especially in patients for whom clozapine may be antipsychotic of last resort.

Previous guidelines were requiring WBCs to be >3500/ml before clozapine is initiated, and the drug must be discontinued if WBCs fall below 3000/ml or if the absolute neutrophil count (ANC) goes below 1500/ml (red alert zone)[2]. Now REMS require, before initiating treatment with clozapine a baseline ANC must be at least 1500/μL for the general population and must be at least 1000/μL for patients with documented Benign Ethnic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring.

Weekly ANC monitoring is required for all patients during the first six months of treatment. If the ANC remains in the normal range (ANC greater than or equal to 1500/ml for the general population, ANC greater than or equal to 1000/ml for patients with BEN) for the first six months of therapy, monitoring frequency can be reduced to every two weeks.

If the patient's ANC continues to remain in the normal range for the second six months of treatment, ANC monitoring may be reduced to once in every four weeks.

Before starting treatment with clozapine, the baseline ANC must be at least 1500/ml for the general population and at least 1000/ml for patients diagnosed with BEN.

A patient in the general population can continue clozapine treatment even with an ANC less than 1000/ml. However, prescribers should follow the treatment recommendations carefully and determine if the benefits of continuing clozapine treatment outweigh the risks. If monitoring ANC and symptoms of infection are not done appropriately, patients with ANCs less than 1000/ml are at risk of developing complications of severe neutropenia.

For patients with BEN, REMS recommends interrupting clozapine treatment only when the ANC is less than 500/ml. No interruption in treatment is recommended for ANC 500-999/ml, although a hematology consultation is recommended.

For some patients who experience, or have experienced, moderate clozapine-related neutropenia (ANC less than 1000/ml) or severe clozapine-related neutropenia (ANC less than 500/ml), the risk ofserious psychiatric illness from discontinuing clozapine may be greater than the risk of rechallenge. This may be relevant for schizophrenia patients with a severe form of illness who have no treatment options other than clozapine. In making the decision to rechallenge a patient, REMS recommended considering a hematology consult, the patient's medical and psychiatric history, the severity and characteristics of the neutropenic episode, and a discussion with the patient and his or her caregiver about the benefits and risks of clozapine rechallenge.

Suggestions

Clozapine, has been repeatedly shown to be superior to other antipsychotics for treatment-resistant schizophrenia; however it is underutilized by clinicians. Given the high costs of medication discontinuation, re-hospitalization and inadequate treatments for schizophrenia, the underutilization

of clozapine in the Turkey is noteworthy. The superior effectiveness of clozapine relative to other antipsychotics merits increased efforts to encourage greater use in appropriate patients and to more efficiently monitor for side effects. Many patients with treatment-resistant schizophrenia who could benefit from clozapine are not getting it. We can beat our fear and clozapine can be more available.

We think that FDA's Clozapine Risk Evaluation and Mitigation Strategy (REMS) program of Clozapine is a very important step towards defeating the clozaphobia of clinicians and encouraging them to prescribe when indicated.

Clinicians must identify those patients most at risk— and prescribe to others. Residency programs must train their residents in how to use it; otherwise junior psychiatrists will not enter the field fully aware of the effectiveness of clozapine. Important areas of concern such as managing side effects and deficiency in evidence-based use of clozapine were identified. These can be targeted in training and professional development programs.

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