Why Not Clozapine?

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Abstract

Clozapine is the only antipsychotic medication approved for treatment-resistant schizophrenia. The superiority of this second-line antipsychotic for reducing positive psychotic symptoms compared to other antipsychotics in treatment-resistant schizophrenia is well established. Clozapine is also effective for reducing suicide risk and physical aggression, reducing hospitalizations and overall treatment costs, improving quality of life and is associated with a longer treatment duration compared to most other antipsychotic agents. Despite these positive attributes, the prescription of clozapine in the U.S. is infrequent and disproportionately low relative to the estimated prevalence of treatment-resistant schizophrenia. In fact, use of clozapine in the U.S. accounts for approximately 5% of all antipsychotic prescriptions and is much less widely used than in other countries. Many possible explanations likely contribute to clozapine's underuse in the U.S. including the potential for serious side effects. However, new advances in genetic testing that may help predict risk for agranulocytosis may soon make clozapine a more viable treatment option. Efforts to understand the apparent under prescribing of clozapine and to provide education and interventions to optimize its use in appropriate patients should be undertaken.

Key Words: Clozapine, Schizophrenia, Agranulocytosis, Genetic, Underuse

Approximately 1.5 million people in the United States suffer from schizophrenia, and between 20-30% of these patients are unresponsive to first-line antipsychotic therapy. Clozapine is the only antipsychotic medication approved for treatment-resistant schizophrenia. The superiority of this second-line antipsychotic compared to conventional antipsychotics in treatment-resistant schizophrenia is well established (1). Additionally, recent findings from the CATIE II effectiveness trial demonstrate the superiority of clozapine over other second-generation antipsychotics (SGAs) (2) in a population of patients who prospectively failed an optimized antipsychotic trial. According to current treatment guidelines for schizophrenia, a trial of clozapine is warranted following inadequate response to optimized trials of two different antipsychotic medications (3-5).

In addition to clozapine's superior efficacy for positive symptoms, it is superior to other antipsychotics for reducing suicide risk (6) as well as physical aggression and violence (7,8). Clozapine has also been shown to reduce hospitalizations and overall treatment costs (9,10), improve quality of life (11), and is associated with a longer treatment duration compared to most other antipsychotic agents (conventional and SGA) (12,13). Clozapine treatment has also been associated with fewer substance abuse relapses compared to other antipsychotics (14). Thus, clozapine offers benefits over other available treatments for a host of symptom domains.

Despite these positive attributes, the prescription of clozapine in the U.S. is infrequent and disproportionately low relative to the estimated prevalence of treatment-resistant schizophrenia (15-19). In fact, use of clozapine in the U.S. has been steadily declining since the introduction of the other SGA medications, with use of clozapine accounting for 11% of all prescriptions for SGAs in 1999, 9% in 2000, and 5% in 2002 (20). In addition, antipsychotic polypharmacy in the Veteran's Administration setting is more frequently prescribed than clozapine monotherapy demonstrating that clinicians are less likely to use clozapine as compared to combination agents, a practice with little empirical evidence (21). Despite its generic availability and more fervent use in other countries (e.g., 36-38% of outpatients in Australia, 16% of outpatients in China) (22,23), use of clozapine accounts for less than 5% of all antipsychotic prescriptions in the U.S. (16,20). Moreover, for various reasons, racial disparities in the use of clozapine have been consistently observed, with African-Americans less likely to receive this medication than Caucasians (24-26).

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Guidelines for Clozapine Use

When to Consider	■ Clozapine should be introduced at the earliest opportunity if evidence of treatment resistant schizophrenia is present. Treatment refractory schizophrenia is considered when there is a failure of full remission of positive symptoms, or the lack of satisfactory clinical improvement despite sequential use of recommended doses of two or more antipsychotic medications for 6-8 weeks. Treatment refractory illness may be obvious early in treatment (within 6 months) or emerge later following a series of episodes (43). ■ Clozapine should be considered for people with schizophrenia who are suicidal (6). ■ Clozapine should be considered for people with schizophrenia with aggressive behaviors (7,8). ■ Clozapine should be considered for people with schizophrenia who have tardive dyskinesia or tardive dystonia (3).
Contraindications	■ The patient has a history of a drug-induced blood dyscrasia. ■ The patient has an uncontrolled seizure disorder. ■ The patient has a white blood cell count (WBC) of <3500/mm^3. ■ The patient has an absolute neutrophil count (ANC) of <2000/mm^3. ■ The patient has a history of a myeloproliferative disorder. ■ The patient is pregnant. ■ The patient is under the age of sixteen. ■ The patient has a paralytic ileus.
Discussion with Patient and Family	■ Prior to initiation, the potential benefits and risks of clozapine should be explained to the patient and his/her family. ■ The requirements for hematologic monitoring should be discussed. It is recommended that a person sign informed consent once all risks and benefits are understood. ■ The patient should be encouraged to participate in regular exercise and to make efforts to avoid significant weight gain.
Prior to Initiation	■ The clinician should call one of the national registries to obtain a rechallenge number and to confirm clinician and pharmacy registration. A DEA number is required if registering for the first time. ■ Obtain a baseline WBC with ANC from the patient. Prior to prescribing, the WBC and ANC need to be within normal limits (i.e., WBC ≥3500/mm^3, ANC ≥2000/mm^3). Submit the WBC and ANC to the registered pharmacy.
Dosing	■ Initiate clozapine at 12.5-25 mg/day (BID) on the first day. Increase by a maximum of 25 mg increments daily to reach a target dose of 300 mg by day 14. Consider slower titration with 25 mg/day increments every third day reaching 300 mg/day in 24 days if patient experiences initial postural hypotension (5). Optional subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg/day (44). ■ Patient should be titrated to therapeutic dose within 1 month. If partial or no response in 1 month, obtain serum level and adjust dose accordingly (target dose 600 mg/day). The clozapine serum level should be > 350 ng/ml to maximize efficacy and should be drawn prior to the morning dose (12 hours since last dose) once receiving the same dose for at least 5 days (5). ■ Maintenance treatment is generally administered twice daily with 1/3 of the dose in the morning and 2/3 in the evening. The total daily dose should not exceed 900 mg/day (5).
Hematologic Monitoring	■ During the first 6 months, blood work must be performed weekly and WBC and ANC must be provided to the pharmacy prior to dispensing. After 6 and 12 months, blood work is performed every two weeks and monthly, respectively.
Laboratory and Side Effect Monitoring	■ Supine and standing blood pressures and pulses should be obtained and documented at least every two weeks until the dosage is stabilized for at least two consecutive weeks. Blood pressure should be checked at baseline, 12 weeks, and at least annually. ■ It is recommended to obtain serum creatinine, BUN, alkaline phosphatase, AST (SGOT), and ALT (SGPT) six months and twelve months after clozapine initiation and then annually. ■ Weight and metabolic side effects should be closely monitored: o Weight (BMI) should be checked (at minimum) at baseline, four, eight, and twelve weeks after clozapine initiation (45). o Fasting plasma glucose should be checked (at minimum) at baseline, 12 weeks, and annually. Check more frequently in patients with risk factors for diabetes (45). Some experts recommend every 3-6 months (46). o Fasting lipid profile should be checked (at minimum) at baseline, after 12 weeks, and annually (45). Some experts recommend every 3-6 months (46).
Reinitiation if Clozapine is Stopped	■ If the administration of clozapine is interrupted for a period of 48 hours or more, then clozapine therapy should be restarted at a dose of 12.5 mg once or twice a day and then retitrated to the desired dose.

To date, there have been few empirical investigations of the reasons for the infrequent use of clozapine in the U.S. (27), although possible explanations include its hematologic monitoring requirements and the potential for serious side effects including agranulocytosis, myocarditis, other inflammatory reactions, seizures, sedation, obesity, diabetes mellitus and other metabolic abnormalities (17,28). Other possible explanations include lack of knowledge about clozapine's benefits or negative attitudes towards the medication by physicians, patients and families. More aggressive marketing of other second-generation antipsychotics by pharmaceutical companies may also be contributory.

While serious side effects undoubtedly limit the use of clozapine, the fact still remains that many more patients may benefit from this medication than do now currently in the U.S. (29). With such infrequent use, the next generation of prescribers and clinicians may have little training in prescribing and managing clozapine, leading to even more infrequent use in the future. New advances, however, may soon make clozapine a more viable treatment option, especially regarding hematologic monitoring and the risk for agranulocytosis. Reports of concordant twins both developing agranulocytosis following clozapine treatment suggest that genetic factors may play an important role (30), and genetic variants within the Human Leucocyte Antigen (HLA) system have been linked to agranulocytosis in small studies (31-33). A private biotechnology firm conducted a case-control study of clozapine-induced agranulocytosis and reported that variants of five genes, HLA-DQB1, HLA-C, granulocyte-macrophage colony stimulating factor receptor B (CSF2RB), dopamine receptor 1 (DRD1), and neurotensin receptor type 1 (NTSR1), were associated with risk for agranulocytosis associated with clozapine (34). This evidence led to the development and launch in January 2007 of PGxPredict:CLOZAPINE™, the first pharmacogenetic test claiming to predict high (2.5 relative risk [RR]) or low (0.5 RR) risk of agranulocytosis based on analysis of a simple blood sample and the genotyping of two single nucleotide polymorphisms of a specific HLA gene (HLADQB1).

These are promising results and another study, independent of industry sponsorship, is currently underway to replicate these findings as well as perform a more comprehensive examination of other candidate genes in a larger population. Thus, a new era of pharmacogenetic testing is beginning to emerge, which may greatly facilitate our ability to use clozapine through increased ability to identify prospective patients at greater risk for developing agranulocytosis.

Nevertheless, the underutilization of clozapine in the U.S. is due to many factors and not limited solely to the fear of agranulocytosis and associated cumbersome monitoring requirements. It is estimated that the incidence of this blood dyscrasia is approximately 0.8% and occurs mostly in the first months of treatment (35-37). There need to be more attempts to understand this underuse and to provide education and interventions to optimize treatment with clozapine in the U.S. Clozapine has many serious side effects; however, it is a medication that can improve the lives of people who suffer from schizophrenia and many feel there would be an overall improvement in the care of people with psychosis if this drug had broader use (2,29,38). We do recognize that the use of clozapine may not be appropriate for all patients and all situations (39), but feel it deserves a trial in many more patients than for which it is currently being used.

For more than a decade, the newer second-generation antipsychotics have dominated the antipsychotic market and were believed by most in the field to be far superior to conventional antipsychotics. And, while SGAs do have arguable advantages, we are more aware of the limitations of SGAs and the lack of robust differences in effectiveness compared to conventional agents (40,41). Is it time to more fervently embrace the "gold standard" of the second-generation antipsychotic class (42), and come full circle back to clozapine for patients who do not respond adequately to other treatments (3-5)? This time, however, we should more diligently address and attempt to limit weight gain and other cardiovascular and metabolic complications that can limit the overall effectiveness of this very efficacious treatment.

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