

Clozapine underutilization in treatment-resistant schizophrenia

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How to cite: Stanton RJ II, Paxos C, Geldenhuys WJ, Boss JL, Munetz M, Darvesh AS. Clozapine underutilization in treatment-resistant schizophrenia. Ment Health Clin [Internet]. 2015;5(2):63-7. DOI: 10.9740/mhc.2015.03.063.

Abstract

It has been shown that up to one third of patients with schizophrenia do not respond to antipsychotic therapy. Thus, treatment-resistant schizophrenia (TRS) remains a major mental health care challenge.

Clozapine has been shown to provide superior therapeutic benefits and is approved as first-line therapy for TRS. These benefits include improvement in both positive and negative symptoms, and reduction of suicidal behavior in patients with schizophrenia. Clozapine, however, remains significantly underused for TRS. A major reason for clozapine's underuse is its substantial adverse effect profile, mainly the risk of life-threatening agranulocytosis which necessitates regular hematologic monitoring. Another factor contributing to reduced clozapine prescribing is the increased use of other second-generation antipsychotics. In TRS patients, there is often a considerable delay in clozapine use, which is prescribed only after other unsuccessful second-generation antipsychotic trials. To combat this trend, there is a push for increased awareness to optimize clozapine prescribing. An important aspect in improving the use of clozapine therapy is physician and patient education. Furthermore, pharmacist involvement can improve clozapine prescription trends in TRS.

Keywords: treatment-resistant, schizophrenia, clozapine, prescriptive practices

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Introduction

Schizophrenia has a lifetime prevalence of approximately 0.7% to 1% of the world's population.¹ Both first-generation antipsychotics as well as second-generation antipsychotics (SGAs) are the mainstay of schizophrenia treatment.² However, up to one third of patients given a diagnosis of schizophrenia do not respond to antipsychotic pharmacotherapy, a finding that is consistent in the literature.^{3,4} Management of treatment-resistant schizophrenia (TRS) remains a significant mental health care challenge because TRS patients often require extensive periods of hospitalization, have social dysfunction, and have a low quality of life.⁵ Clozapine, the first SGA, has consistently demonstrated efficacy in the management of TRS.⁶ However, clozapine therapy is associated with several serious adverse effects, such as agranulocytosis, weight gain, diabetes, and myocarditis.⁷ It has been



shown that clozapine is highly underused for TRS therapy.⁸ In a retrospective chart review conducted at Akron General Medical Center, only 2 of 37 patients with TRS were prescribed clozapine, prompting this review. This article reviews the current barriers that contribute to clozapine underuse in the management of TRS.

Treatment-Resistant Schizophrenia

In the past, frequent hospitalization was considered to be the primary indicator of TRS. However, current and persistent positive symptoms along with at least moderate severity of illness have become essential for a diagnosis of TRS.^{4,9} Chronic and frequent hospitalization may occur because of various factors besides being refractory to antipsychotic therapy, such as poor drug adherence and history of violent behavior.¹⁰ Thus, standardized criteria have been developed to establish a diagnosis of TRS.

Kane and colleagues^{11,12} initially defined TRS in the Multicenter Clozapine Trial as lack of improvement in patient symptoms after at least three periods of treatment in the preceding 5 years with conventional antipsychotics (from at least two chemical classes) at dosages equivalent to at least 1000 mg/d of chlorpromazine for 6 weeks each without significant symptom relief, persistent symptoms, Brief Psychiatric Rating Scale total score ≥ 45 , and Clinical Global Impressions score ≥ 4 with item scores of ≥ 4 on 2 of 4 positive symptom items. Conley and Kelly⁴ have presented a modified version of the Kane criteria for TRS to better reflect optimal dosing and clinical practice patterns. They proposed the criteria to determine TRS as at least two periods of antipsychotic treatment for a period of 4 to 6 weeks at dosages equivalent to 400 to 600 mg/d of chlorpromazine, persistence of symptoms, Brief Psychiatric Rating Scale total score >45 , and Clinical Global Impressions score >4 on at least 2 of 4 positive symptom items during a 5-year period.⁴

Up to one third of all patients with a diagnosis of schizophrenia have been shown to be resistant to antipsychotic pharmacotherapy.^{3,4,23} Persistence of positive symptoms has been classically associated with a diagnosis of TRS; however, there is awareness that persistence of negative symptoms and impairments in cognitive function also require adequate management.⁴ Consequences of TRS are numerous, including poor interpersonal and occupational functioning, cognitive dysfunction, decreased quality of life, and caregiver burden.¹⁴ Management of TRS has been associated with a disproportionately high percentage of the total expenses used for treating schizophrenia.¹⁵

Clozapine

Clozapine was developed by Sandoz in 1961 and was introduced in European and North American markets in the 1970s. It was later withdrawn after reports of clozapine-induced agranulocytosis led to death in some patients.¹⁶ Kane, Meltzer, and colleagues,^{11,12} in their landmark study in 1988, demonstrated the superiority of clozapine over the first-generation antipsychotics in the improvement of both positive and negative symptoms in TRS patients. Clozapine was approved for use by the US Food and Drug Administration in 1989 specifically for TRS with required hematologic monitoring to detect agranulocytosis. Clozapine remains the only antipsychotic that has consistently shown therapeutic benefit in well-defined TRS and has definite superiority over other agents in the TRS patient population.¹⁷

Aside from demonstrating significant improvement in both positive and negative symptoms, clozapine therapy has been shown to provide several other benefits. These include improvements in cognitive impairment, reversal of first-generation antipsychotic-induced tardive dyskinesia, reduction of physical aggression and violence, reduction of hospitalization, and improvement in quality of life.^{8,14,18,19} Clozapine also reduces the risk of recurrent suicidal behavior and is Food and Drug Administration approved for use in patients with schizophrenia and schizoaffective disorder at risk for suicidal behavior. Unfortunately, there is serious concern that clozapine is being underused in patients at high risk for suicide.²⁰

Clozapine possesses moderate dopaminergic antagonism accompanied by significant serotonergic antagonist properties, and shows binding at adrenergic, cholinergic, and histaminergic receptors.^{2,19,21} Clozapine therapy can produce serious adverse effects, with the most notorious being the risk for life-threatening agranulocytosis, which necessitates regular hematologic monitoring. Clozapine currently carries 5 Food and Drug Administration boxed warnings and is known to produce seizures, sedation, myocarditis, diabetes, weight gain, metabolic syndrome, constipation, hepatitis, sialorrhea, and fever.^{7,22}

Clozapine and TRS

Currently, clozapine is the only Food and Drug Administration–approved drug for TRS as well as the only drug to consistently demonstrate its therapeutic superiority in the management of TRS.^{14,23–25} Treatment guidelines recommend the use of clozapine after two failed trials of antipsychotic monotherapy.^{26–28} Despite its positive attributes, clozapine is considerably underused in the management of TRS.²⁹ Kelly and colleagues⁸ reviewed several studies demonstrating that clozapine prescribing is not only infrequent for treatment of TRS, but is in fact on a

steady decline in the United States following the introduction of other SGAs. Antipsychotic polypharmacy, as well as augmentation of antipsychotic therapy with agents such as antidepressants, benzodiazepines, and mood stabilizers, has been commonly used in TRS.^{4-6,25,30} Studies have shown that there is considerable delay in prescribing clozapine for TRS treatment because of patients receiving other SGAs or antipsychotic polypharmacy prior to receiving clozapine therapy.^{29,31,32}

Clozapine's serious adverse effects remain an important factor leading to clinician hesitation in prescribing clozapine for the treatment of TRS.⁸ Clinician perceptions regarding clozapine's adverse effects and familiarity in the management of those adverse effects remain key factors in low clozapine prescribing rates.³³ It has also been suggested that clinicians in the United States tend to overemphasize the adverse effects of clozapine, which leads to discouragement of a patient's acceptance of clozapine therapy.^{34,35} It has been estimated that only 25% of TRS patients in the United States are currently prescribed clozapine therapy.³⁵ Clozapine's risk for agranulocytosis, as well as its accompanying requirement of regular hematologic monitoring along with access to laboratory facilities, remains an impediment to improving clozapine prescribing practices.⁸ In addition to difficulties coordinating prescriber, pharmacy, and weekly laboratory services throughout therapy, the additional pill burden of adding medications for metabolic disturbances, constipation, and sialorrhea can be substantial. Although clozapine was widely prescribed in the 1990s, its market share fell considerably with the arrival of newer SGAs that promised similar therapeutic efficacy without the associated life-threatening risk of agranulocytosis. The generic availability of clozapine, as well as the lack of commercial promotion, due to a lack of patent protection also remains an important factor in clozapine underuse.³⁶⁻⁴⁰ Aggressive marketing of other SGAs by pharmaceutical companies and the unfamiliarity of newer prescribers with managing clozapine therapy may further contribute to low clozapine prescribing.⁸ Finally, benign ethnic neutropenia, lower white blood cell counts in African Americans, may also contribute to the underuse and discontinuation of clozapine therapy in this patient population.⁴¹

Prescription trends for clozapine use have been studied across various geographic locations. Studies indicate that clozapine has been consistently underused in the United States, United Kingdom, Canada, Australia, and New Zealand. However, recent reports suggest that clozapine use has shown some improvement in Australia and New Zealand, primarily because of government subsidies as well as improved training of clinicians.^{35,39,42-46} Prescribing rates in New Zealand were estimated at nearly 33% for patients with schizophrenia or schizoaffective disorder, whereas rates have been estimated in Canada and the

United States at only 16% and 5%, respectively.^{8,43,46} Clozapine use showed a distinctly different prescribing pattern in China in years past. Clozapine use was markedly higher in China compared with Western countries, with clozapine not only used for TRS but also in first-episode schizophrenia. A combination of economic factors, as well as health care and insurance policies, were responsible for this trend. Currently, however, clozapine use has gradually decreased in many regions of China.^{47,48}

Future Directions and Conclusions

It is clearly evident that despite the fact that clozapine is the gold standard for TRS, it remains consistently underused. In recent years, there has been a growing awareness and a concerted effort to improve use of clozapine.^{35,38} Because clozapine's adverse effect profile remains one of its biggest stumbling blocks to optimal use, there exists a need to improve its management.⁷ One strategy to prevent and manage clozapine's adverse effects is to optimize dosing. Conley and Kelly⁴ have recommended a slow dose escalation and monitoring of drug plasma levels as a means to improve clozapine use. Another strategy may involve the expansion of clozapine clinics to assist in monitoring and preventing the development of metabolic disturbances, managing other adverse effects, coordinating hematologic monitoring, and promoting medication adherence.⁴⁹ Both strategies present ideal opportunities for pharmacists given their unique training and skills. Pharmacist involvement in these settings may possibly result in cost savings and increased patient satisfaction.⁵⁰ The biochemical and pharmacologic mechanisms responsible for clozapine's adverse effect profile have yet to be fully elucidated; therefore, an increased effort to investigate these processes is warranted. A review of the current guidelines for hematologic monitoring in clozapine patients is also recommended.³⁸

Prescriber and patient education is vitally important for the successful use of clozapine in the treatment of TRS and patients at a high risk for suicide. Experience in managing clozapine therapy should be an integral part of psychiatric training. Furthermore, expansion of clozapine clinics, which include pharmacists, may improve clozapine prescribing.^{49,50} Benefits of clozapine therapy in TRS outweigh its risks of adverse effects in most patients; therefore, clinicians should be encouraged to use clozapine as a first-choice therapeutic option for TRS rather than a drug of last resort.³⁷

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