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Treatment-Resistant Schizophrenia: A Brief Overview of Treatment Options

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Although antipsychotic medications have been the mainstay of treatment for schizophrenia, approximately one-third of individuals with schizophrenia show a limited response to antipsychotic treatment,¹ which has led to the term *treatment-resistant schizophrenia* (TRS).² The static failure to respond to treatment suggests that schizophrenia is a heterogeneous condition with different etiologies.² In addition, symptoms of schizophrenia are also varied rather than uniform. Moreover, there is no pathognomonic symptom, but rather different combinations of positive, negative, and cognitive symptoms, supporting its diverse nature.

Clozapine and TRS

Since the pivotal study by Kane et al,³ clozapine has been established as the gold standard to treat TRS. Guidelines⁴ and a Cochrane review⁵ for TRS have generally confirmed this. However, a recent study has challenged this conventional wisdom. A meta-analysis⁶ assessing the efficacy of antipsychotics for TRS failed to establish clozapine as the most efficacious antipsychotic, with few statistically significant differences among various antipsychotics. The authors of the meta-analysis provide several limitations, including an average clozapine dosage that could be considered low (392 mg/d) and the lack of a uniform criterion to diagnose TRS. To address the issue of diagnostic ambiguity, a working group created a consensus guideline on the minimum and optimum diagnosis and terminology for TRS.⁷ The working group concluded that without uniform criteria, comparing studies on TRS is akin to comparing apples to oranges. Some consensus recommendations from the group are that treatment failure should include ≥ 6 weeks of treatment with each antipsychotic, equivalent to ≥ 600 mg of chlorpromazine per day, and ≥ 2 past adequate treatment episodes with different antipsychotic drugs (not necessarily from different classes). Symptom severity needs to be monitored using a standardized rating scale (eg, Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale). Systematic monitoring of medication adherence should also be assessed using at least 2 sources (eg, pill counts, depot medication, plasma levels, medication administration records) to rule out “pseudo-resistance,” possibly the greatest source of unrecognized error in studies on TRS.⁷ Reasons for nonadherence include anosognosia, side effect burden, pill schedules, and cognitive difficulties, as well as combinations of these and other factors.⁸

Despite clozapine's challenging safety profile,⁹ one study¹⁰ demonstrated a 2-fold higher all-cause mortality rate among individuals with TRS *not* treated with clozapine compared to clozapine-treated individuals. These results were primarily driven by periods with no antipsychotic treatment, with nonsignificantly higher mortality during treatment with other antipsychotics. The reduced mortality in clozapine-treated TRS patients reinforces the unique therapeutic advantages of clozapine. Given the lack of clear guidance on what to do after clozapine failure, the importance of optimizing clozapine treatment cannot be overstated. Monitoring steady-state trough serum levels can be helpful, and most evidence indicates that the threshold for therapeutic response is in the range of 350–420 ng/mL; however, it may be as high as 500 ng/mL, and although there is no defined upper limit, there may be a ceiling effect in the range of 600–838 ng/mL.¹¹

Glutamate Hypothesis of Schizophrenia

An explanation for clozapine's superior efficacy may rest with the glutamate hypothesis of schizophrenia. In individuals with schizophrenia, there is an increase in striatal presynaptic dopamine synthesis capacity. However, recent studies have suggested that non-dopaminergic neurotransmitters could be responsible for TRS.¹² In individuals with TRS, striatal dopamine synthesis levels were not statistically different from control levels but were significantly lower than the levels from antipsychotic responders. This suggests that patients may be treatment resistant because they lack the classic elevation in dopamine that would respond to dopamine-blocking agents—our current treatment mainstay. Although individuals with TRS did not have the expected elevation in dopamine, they did demonstrate increased levels of glutamate in the anterior cingulate cortex.¹²

A key glutamate receptor is the *N*-methyl-D-aspartate (NMDA) complex, containing binding sites for glutamate and glycine, both of which must be present in order for activation to occur.¹³ Persons with schizophrenia are hypothesized to have NMDA receptor hypofunction, with the net result being pathologically increased dopamine release downstream in the mesolimbic pathway. Clozapine is unique from other antipsychotics in that it may function as an NMDA receptor modulator by increasing glycine levels and thus alleviating NMDA receptor hypofunction and consequently reducing excess dopamine signaling in the mesolimbic pathway.¹³

Treatment Alternatives for TRS

Despite recent controversy, clozapine for TRS remains the most established treatment option. However, if an individual is unable to tolerate or is refusing clozapine, high-dose monotherapy with an alternative antipsychotic can be considered. High-dose olanzapine, at a dosage of 30–40 mg/d, can be utilized in selected situations.¹⁴ Although the maximum approved dosage for olanzapine is 20 mg/d, in treatment-resistant or severely ill patients with schizophrenia, there is evidence to suggest that higher dosing than the approved labeling can provide additional efficacy.¹⁴

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Augmentation Options for TRS

As many as 40%–70% of TRS patients will fail to sufficiently respond to clozapine, demonstrating the need for both optimization of clozapine treatment, as discussed previously, and augmentation strategies. A recent meta-analysis¹⁵ evaluated 42 common augmentation strategies to antipsychotic monotherapy in schizophrenia. Based on the heterogeneity of studies, variable quality in the methodology and overall study quality, and publication and author biases, the meta-analysis found insufficient evidence to recommend any one augmentation strategy for a nonspecific patient with schizophrenia.¹⁵

A meta-analysis of randomized controlled studies of antiepileptic drug augmentation for clozapine-treated patients with TRS demonstrated that sodium valproate (800–1,125 mg/d) was effective for general psychopathology and the positive symptoms of schizophrenia.¹⁶ However, this study utilized 5 randomized controlled trials, all conducted in China, with high heterogeneity ($I^2 = 91\%$). Clozapine levels were tested in only 1 of the 5 trials, and the average Chinese person has a lower clozapine metabolic capacity compared to the average Westerner. Topiramate was also found to be effective for positive and negative symptoms, as well as general psychopathology, but is not recommended due to a higher discontinuation rate. With lamotrigine, after removal of 2 outliers, there was no significant difference between lamotrigine augmentation and clozapine monotherapy.¹⁶

Medications targeting glutamate have been utilized as augmentation strategies for the negative and cognitive symptoms of TRS. Minocycline and memantine modulate the NMDA glutamate receptor and perhaps moderate glutamate-mediated excitotoxicity. A memantine augmentation study for clozapine-refractory patients showed memantine to be effective for negative symptoms, with mixed findings on cognitive symptoms.¹⁷ A meta-analysis of minocycline augmentation in schizophrenia showed similar findings but will need to be duplicated in a TRS population.¹⁸ Glycine analogs such as D-serine and D-cycloserine, and glycine reuptake inhibitors like sarcosine and bitopertin, have been studied as augmentation strategies.^{1,13}

Electroconvulsive therapy (ECT) has been shown to have synergistic effects with clozapine.¹⁹ In a randomized study, ECT was used to augment therapy in individuals with TRS and an insufficient response to clozapine (average dosage 525 mg/d, plasma level 854 ng/mL). ECT-treated subjects showed a robust response when ECT was added to their treatment regimen. There were no differences in dropouts between the ECT group and those receiving clozapine monotherapy and no significant difference in neurocognitive or negative symptom response.

Cognitive behavioral therapy (CBT) has been shown to be efficacious as an augmentation strategy for the positive and general symptoms of TRS. A meta-analysis²⁰ of 12 randomized controlled trials showed that individuals with TRS receiving CBT showed significant improvement when compared to controls. The results were sustained at follow-up ranging from 3 months to 2 years.

Conclusion

For individuals with TRS, clozapine should be considered. Some evidence supports high-dose olanzapine for TRS. Due to the varied symptom presentation of TRS, individual symptoms should be specifically addressed rather than utilizing a “one size fits all” approach. ECT has promising data in 1 study, and CBT shows efficacy for positive symptoms. Glutamatergic augmentation strategies following clozapine failure are promising but inconclusive, reinforcing the importance of optimizing clozapine.

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