Life After Clozapine:

Managing Treatment-Resistant Schizophrenia When Clozapine Is No Longer an Option

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Treatment-resistant schizophrenia (TRS) is a major clinical challenge that occurs in approximately 40% of patients with schizophrenia.[1] TRS can develop early in the treatment or later in individuals who initially responded to antipsychotic therapy.[2] Up to a quarter of patients with first-episode psychosis will develop TRS in the early stages of treatment.[2] TRS is linked to poorer clinical outcomes, marked functional impairment, and higher hospitalization rates.[3] Moreover, compared with individuals with non-TRS, those with TRS have greater medical comorbidity, higher healthcare costs, and reduced quality of life.[4]

The Value of Clozapine

Clozapine is the most effective treatment for positive symptoms and is the gold standard for TRS.[5] A large meta-analysis of cohort studies with over 109,000 patients found that clozapine resulted in greater symptom improvement compared to other second-generation antipsychotics (SGAs), fewer treatment discontinuations, and lower hospitalization risk.[6] Compared with other antipsychotics, clozapine shows efficacy in reducing aggressive and violent behaviors and lowers relapse risk in patients with substance use disorder.[7,8] Clozapine has also shown to reduce suicide risk in randomized controlled and epidemiological studies.[9] Additionally, a systematic review and meta-analysis of long-term studies indicated that clozapine was associated with significantly lower all-cause mortality compared to other antipsychotics.[10]

Meta-analytically, around 40% of patients with TRS respond to clozapine,[11] but response rates can be as high as 80% if clozapine is initiated within the first 2–3 years after establishing treatment resistance.[12]

Challenges With Clozapine

Clozapine is associated with adverse effects common to antipsychotics, but some of them are more frequent and/or severe than with other antipsychotics, including sedation, constipation, weight gain, and metabolic abnormalities.[13,14] Additionally, clozapine is also associated with somewhat unique side effects, which complicate its use. These tolerability issues include often transient and manageable side effects (eg, tachycardia, sialorrhea) as well as serious and potentially life-threatening side effects (eg, ileus, pneumonia, myocarditis, severe neutropenia).[13,14] In this context, despite unique efficacy for TRS, approximately 30%–40% of patients discontinue clozapine, mainly due to nonadherence (35%), side effects (28%), and, less so, inefficacy or professional or patient preference.[15,16]

Clozapine Discontinuation

Clozapine discontinuation should be avoided or revisited for non–life-threatening adverse effects.[13,14] In case of life-threatening adverse events, such as severe neutropenia, ileus, myocarditis, and neuroleptic malignant syndrome (NMS), however, clozapine discontinuation has to be accomplished abruptly,[14] which can result not only in cholinergic rebound but also in acute worsening of psychotic symptoms.[17] Cholinergic rebound symptoms can be observed in up to 50% of cases and may include vomiting, diarrhea, headache, diaphoresis, dystonia, and dyskinesia, and in more severe cases agitation, delirium, and hallucinations. Anticholinergic treatment with benztropine is commonly recommended. However, the optimal drug, dose, and duration remain unknown.[18] In clinical practice, benztropine is typically initiated at 1–2 mg twice daily and can be titrated up to 4–6 mg/d in divided doses in patients previously treated with moderate to high doses of clozapine, depending on the severity of symptoms.[19]

Various studies have reported rapid relapse following clozapine discontinuation.

Seppala et al[20] found a rapid deterioration in mental state following withdrawal in almost half of the patients on long-term clozapine treatment, while another study reported that the risk of relapse in patients withdrawn from clozapine was 5 times higher than that for traditional antipsychotics such as haloperidol or flupenthixol.[21]

Rechallenge after severe neutropenia has been reported to be successful in only 20% of patients,[22] making rechallenge in the face of this severe adverse event generally inadvisable. However, clozapine rechallenge may be considered in selected cases, after a careful benefit-risk evaluation including current indication and past clear clinical benefit, plus evaluation of possible secondary causes (viral infection, drug-induced neutropenia).[23] When rechallenge is pursued, very slow retitration and intensive hematological monitoring are recommended.[23] The use of colony-stimulating factors, such as filgrastim, has supported a successful rechallenge in approximately 75% of cases of severe neutropenia according to recent data.[24,25]

Clozapine-associated myocarditis is an uncommon but also potentially fatal adverse event that may be more likely when titrating clozapine too fast. Recently published reviews suggest that rechallenge may be carried out with an approximately 70% success rate, where benefit is clear, using very slow titration, inpatient initiation when feasible, and intensive cardiac monitoring.[26,27] Regarding other inflammatory complications, such as drug reaction with eosinophilia and systemic symptoms (DRESS) or nephritis, when rechallenge is undertaken after complete clinical and laboratory recovery and using very slow titration, successful rechallenge has been achieved.[22] Rechallenge after clozapine-associated NMS, which is a rare but potentially fatal event, can be considered with very slow retitration in selected cases after full recovery and with careful risk mitigation.[25] On the contrary, rechallenge after ileus is generally discouraged due to its high mortality risk.[13,28]

Treatment Options After Clozapine Discontinuation

Although most patients receiving clozapine have TRS, a subset may have been misclassified because of nonadherence or pharmacokinetic reasons leading to suboptimal antipsychotic blood levels.[29] Therefore, the adequacy of previous antipsychotic trials should be carefully reviewed, and the use of long-acting injectable formulations or other strategies to ensure adequate exposure should be considered before initiating other pharmacological interventions.[30]

There are no randomized clinical trials (RCTs) on treatment options in patients who discontinued clozapine. Hence, there is a lack of evidence and guidelines on treatment options after clozapine discontinuation.

In a study evaluating treatment persistence as an indirect measure for efficacy and tolerability, oral SGAs were associated with better persistence than alternative antipsychotic treatment options in patients discontinuing clozapine, with clozapine reinitiation actually being the most effective option, followed by olanzapine and risperidone as monotherapy.[31] A recent Finnish registry study showed that reinitiation of clozapine and switching to oral olanzapine was associated with a lower risk of psychiatric rehospitalization, treatment failure, and all-cause mortality compared with switching to other antipsychotics in patients discontinuing clozapine.[32] These data, albeit naturalistic, indicate that when clozapine is discontinued, clozapine rechallenge should likely be carefully considered first, after a full review of the circumstances leading to the clozapine discontinuation and in a shared decision approach.

As an alternative option, a 2023 systematic review evaluated the efficacy and tolerability of high doses (>20 mg) of olanzapine in patients with TRS.[33] Compared with standard treatment, high-dose olanzapine was noninferior in 4 RCTs, 3 of which used clozapine as a comparator, encouraging for the use of high-dose olanzapine where clozapine use is problematic.[33]

Thus, reinitiating clozapine appears to be the first choice in patients with TRS discontinuing clozapine. When clozapine rechallenge is not an option, olanzapine seems to be the second best choice. This strategy is also supported by a 2024 network meta-analysis of efficacy, acceptability, and tolerability of antipsychotics in TRS[34] in which clozapine and olanzapine were more efficacious than risperidone, haloperidol, fluphenazine, sertindole, chlorpromazine, and quetiapine. The difference between clozapine and olanzapine in this meta-analysis was trivial and uncertain. The only aspect in which clozapine was clearly better than olanzapine was in discontinuation due to inefficacy. However, RCTs may underrepresent patients with true or severe TRS, which may reduce the efficacy signal for clozapine versus first-line antipsychotics.

It should always be taken into consideration that most pharmacological strategies proposed after clozapine discontinuation lack convincing evidence of efficacy in TRS. Therefore, careful consideration of clozapine rechallenge should remain a priority whenever clinically feasible.

ECT has shown short-term efficacy for symptom reduction in patients with TRS, including those receiving antipsychotics other than clozapine.[35] However, available trials are limited by short follow-up periods, and there is insufficient evidence to support sustained medium- or long-term benefit when clozapine is not part of the treatment strategy.[17,35] Conversely, evidence for repetitive transcranial magnetic stimulation in TRS remains limited and heterogeneous, with small effect sizes and substantial methodological variability across studies.[36]

A meta-analysis comparing studies of antipsychotic monotherapy versus polypharmacy found evidence of a significant reduction in symptoms when a second antipsychotic was added.[37] However, these findings derived from open-label and low-quality studies. Double-blind and high-quality studies showed no significant benefit from augmentation with a second antipsychotic.[4,37] The same is true for multiple other antipsychotic augmentation strategies that were either not superior to placebo or based on low-quality studies.[4,38] Even more, most trials included in these meta-analyses did not specifically target individuals with established clozapine-resistant illness or those unable to undergo clozapine rechallenge. Therefore, the generalizability of these findings to patients with confirmed TRS after clozapine discontinuation is limited.

In another, recent meta-analysis studying non-clozapine interventions for TRS,[39] augmentation of antipsychotics with glycine modulatory site agonists improved positive symptoms. However, sample sizes were small. Other interventions, including transcranial magnetic stimulation and adjunctive antidepressants, did not reach the threshold of evidence to be routinely recommended as a viable alternative to clozapine.

Another possible intervention with efficacy for symptom reduction in TRS is psychotherapy. In a meta-analysis on psychological and psychosocial interventions for TRS, including 52 RCTs and 5,034 participants, cognitive-behavioral therapy was effective for reducing overall symptoms in patients with TRS.[40] When clozapine is no longer an option and alternative pharmacological strategies are of limited efficacy, approaches including structured psychological and psychosocial interventions should be delivered alongside identifying life goals and functional and social barriers and maximizing family support.

Conclusions

Clozapine remains the gold standard for patients with TRS. However, after life-threatening adverse events, like severe neutropenia, ileus, or myocarditis, clozapine rechallenge may be too risky. In this case, evidence-based options remain very limited. Evidence suggests that olanzapine may be a suitable alternative, followed by risperidone. However, given the complexities involved in treating TRS, it is crucial to conduct a comprehensive evaluation of the patient before adjusting treatments. This includes confirming that the diagnosis of TRS is accurate and ruling out pseudoresistance due to nonadherence, comorbid substance misuse, or misdiagnosis. A personalized approach is essential for ensuring optimal patient outcomes in this context. Further research is needed to provide clearer guidelines, and novel pharmacologic and biological treatments are needed to provide viable alternatives for clozapine in the management of TRS.

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