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REVIEW ARTICLE

Clozapine-resistant Schizophrenia: Strategies for the Busy Clinician

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ABSTRACT

Introduction: Schizophrenia is a debilitating psychiatric illness where relapse and nonrecovery are common. Clozapine has been heralded as a management option for treatment-resistant schizophrenia (TRS). The aim of the current review is to provide a clinical overview of strategies that may be used in the management of patients that fail to show an adequate response to clozapine. The term clozapine-resistant schizophrenia and its implications are discussed along with a description of various pharmacological and nonpharmacological strategies for the management of clozapine-resistant cases or partial responders to clozapine. The evidence is discussed and the strategies are presented.

There is a need for emerging strategies to augment clozapine therapy in the absence of response or in case of partial response in patients.

Keywords: Augmentation, Clozapine, Clozapine-resistant schizophrenia, Schizophrenia, Treatment-resistant schizophrenia.

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INTRODUCTION

Schizophrenia is a debilitating psychiatric illness with a wide variety of symptoms. The symptoms of schizophrenia include positive, negative, cognitive, and affective domains.[1] Due to the complex symptom profile and multiple theories of etiopathogenesis, complete remission of symptoms is rare in schizophrenia with treatment resistance being one of the most important challenges.[2] Despite the absence of uniform diagnostic criteria, failure of response to a 2- to 8-week trial of at least two antipsychotics in adequate doses from different groups out of which at least one is a second-generation antipsychotic is the most common working definition of "treatment resistance".[3] The prevalence of "true" TRS would vary depending upon the criteria used for such a diagnosis; however, consensus states that nearly 20 to 30% of all patients show inadequate response and have persistent symptoms despite adequate trial of antipsychotic therapy.[4] Clozapine, a serotonin–dopamine antagonist and a prototypical second-generation antipsychotic, is considered the first line as well as the "gold standard" for treatment of schizophrenia in the above cases.[5,6] Despite undisputable superiority over other antipsychotics, 40 to 70% of patients with TRS on clozapine continue to have incomplete remission [less than 20–30% reduction is baseline brief psychiatric rating scale (BPRS) or Positive and Negative Syndrome Scale score] and are referred to as "ultraresistant".[7,8]

Clozapine is considered the first-line drug for TRS. Optimization of clozapine monotherapy with adequate doses to achieve therapeutic levels in the body is usually the first step in cases of poor response to clozapine. There is a consensus in literature that a plasma level of about 350 to 450 ng/mL has to be attained at least for 8 weeks before the patient is considered to be nonrespondent to clozapine.[9-11] Before labeling a patient as truly treatment resistant, multiple other factors need to be ruled out, which are causing poor response to treatment. These include misdiagnosis, nonadherence, inadequate doses, inadequate duration of treatment, suboptimal plasma drug levels (drug to drug–drug interaction or enzyme metabolism), comorbid medical disorders, comorbid substance use, side effects of antipsychotics masking their benefits, organic causes, and ongoing psychosocial stressors. Nonresponse to antipsychotics in the above cases is termed as "Pseudoresistance".[12] Rectifying the causes of "pseudoresistance" forms the first step of addressing clozapine resistance. Along the general principles of psychopharmacology, poor response or incomplete remission following any drug can be addressed in two ways, either by substitution or by combination/augmentation of the primary drug. In case of clozapine nonresponders, an inherent criterion of poor response to previous antipsychotics in the past is fulfiled and, hence, a combination or augmentation of clozapine is the subsequent step.

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STRATEGIES USED IN CLOZAPINE-RESISTANT SCHIZOPHRENIA

There are no fixed guidelines available for combination/augmentation of clozapine with various available psychopharmacological agents or biological treatments. In this review, we try to provide an account of existing evidence for the use of a particular agent or treatment modality and driving principles for augmentation of clozapine with various treatment modalities.

Combination with Second Antipsychotic Drug

Combination is defined as simultaneous administration of two drugs from the same pharmacological group. Combining clozapine with another antipsychotic rests on the premise of weak blockade of D2 receptors by clozapine. Clozapine has a complex receptor-binding profile with major action at the serotonin 2A receptor and dopamine receptors; however, it has lesser affinity for D2 dopamine receptors compared with other antipsychotics. From a pharmacological point of view, combining antipsychotic agents with low antidopaminergic properties, such as clozapine with antipsychotics that have strong affinity to dopamine receptors, such as amisulpride, haloperidol, or risperidone, seems prudent. Commonly used antipsychotics belong to the second generation due to less preponderance for extrapyramidal side effects out of which risperidone is the most studied single combination with clozapine. Josiassen et al[13] have shown that patients with suboptimal response to clozapine when given a combination of risperidone had improvement in overall symptoms and positive and negative symptoms of schizophrenia measured on the BPRS scale.[14] A meta-analysis of five studies showed no benefit of risperidone–clozapine combination over clozapine placebo combination.[8] On the contrary, there are also studies reporting increased side effects from the combination. Risperidone–clozapine combination has greater preponderance for impaired metabolic profile, raised serum prolactin, and loss of cognitive advantages compared with clozapine monotherapy.[15,16]

Along with few reports of improved negative symptom profile, combination of clozapine with aripiprazole, a partial dopamine antagonist, has shown an improved side-effect profile with minimal evidence for improvement in the general psychopathology or positive symptom domains of schizophrenia over clozapine monotherapy. Keeping in line the pharmacological properties of aripiprazole, its combination with clozapine reduces raised serum prolactin, improves impaired lipid profile, decreased body mass index and central obesity, and sometimes causes akathisia or worsening of anxiety symptoms.[17-20]

Clozapine with amisulpride is one of the most commonly used combinations in clinical practice. In a study, combination of amisulpride with clozapine demonstrated better response with no significant difference in side-effect profile when compared with the clozapine and quetiapine combination.[21] Combination of clozapine with amisulpride has not only shown to ameliorate positive and negative symptoms, but also allowed reduction of dose of clozapine and reduced side effects of clozapine like sialorrhea.[22,23] Combination of clozapine with ziprasidone was superior compared with the quetiapine–clozapine combination. Also, in a randomized controlled clinical trial (RCT), ziprasidone combination was at least as effective as the combination with risperidone, if not superior.[24-26]

Augmentation with Other Mood Stabilizers

Augmentation refers to the concomitant use of drugs from different classes. Based on the glutamate hyperfunction hypothesis of schizophrenia, drugs with glutamate antagonism at N-methyl-D-aspartate receptors have been tried to achieve symptom remission. Among mood stabilizers, lamotrigine augmentation of clozapine seems to be the most practiced clinically. A study shows benefits of clozapine–lamotrigine combination in reducing overall psychopathology, positive as well as negative symptoms.[27,28] Lamotrigine augmentation of clozapine results in early onset of improvement of global psychopathology scores, which are sustained in the long term.[29]

However, a meta-analysis reports no significant improvement in symptoms of TRS after excluding an outlier study from five other double-blind RCTs.[30] These findings have been duplicated by other researchers.[31]

Addition of topiramate also has contrasting evidence in various studies. While some studies show a definite benefit from the addition of topiramate, the effect is either only on the general psychopathology scale with no benefit in the positive and negative symptom domain, or absent in the long term.[32,33] Moreover, the meta-analysis by Sommer et al[30] reports dissolution of this beneficial effect after the exclusion of an outlier study. At present, the only definitive evidence for topiramate augmentation is to counter the weight gain due to clozapine.[34,35]

Use of valproate or divalproate with clozapine is usually done for seizure prophylaxis in patients receiving high doses of clozapine, but evidence for use as an augmenting agent is scarce. Studies have shown improvement in BPRS scores as well as reduction in anxiety and aggression with the combination.[36] However, there is an increased risk of weight gain with the combination. There is lack of significant evidence for use of lithium as an augmenting agent in schizophrenia,[37] but some evidence of use in schizoaffective disorder where it has

demonstrated improvements in negative and cognitive symptoms, but paradoxical worsening of the same parameters in schizophrenia.[38]

Augmentation with Antidepressants

There is little evidence or pharmacological basis for augmentation of clozapine with antidepressants. The combination is usually used in clinical practice for treating severe negative symptoms, concurrent depressive symptoms, or simply to manage the side effects of clozapine, e.g., sialorrhea or obsessive compulsive symptoms. Amitriptyline and other tricyclic antidepressants are used to control sialorrhea or nocturnal enuresis due to clozapine.[39]

Augmenting with most selective serotonin reuptake inhibitors (SSRIs) is not advisable, as SSRIs may increase blood concentration of clozapine beyond therapeutic range by inhibiting enzyme metabolism, seen maximally with fluvoxamine. Most studies demonstrating benefit from combination of clozapine with an SSRI might be due to raised plasma concentration of clozapine. Studies have attributed a better metabolic side-effect profile when clozapine is combined with fluvoxamine, possibly due to reduced norclozapine levels.[40] Addition of mirtazapine is associated with improvement in negative and cognitive symptoms with no significant effect on clozapine metabolism or side-effect profile.[41-43]

Augmentation with Other Drugs

Benzodiazepines are usually used to manage aggression in acute situations, but no evidence for long-term benefit for the use of the same is found for psychotic symptoms of schizophrenia.[44] Donepezil is used based on the observation that it improves psychotic symptoms in dementia, whereas memantine has antiglutamatergic properties without strong evidence of efficacy.[45] Agents like raloxifine, aspirin, gingko, and omega-three fatty acids have weak evidence for use as augmenting agents. Transdermal estradiol has shown to have better efficacy when compared with placebo in women of childbearing age, already on antipsychotic therapy.[46] Among glutamatergic drugs like glycine, sarcosine, D-cycloserine, D-serine and CX516, only CX516 showed some efficacy in a small sample size study when compared with placebo.[47]

Use of Nonpharmacological Biological Treatments

Among biological modalities, electroconvulsive therapy (ECT) is the oldest and most studied for augmentation with clozapine. The ECT was primarily developed for treatment of schizophrenia, but its use declined with the discovery of potent antipsychotics. The ECT combined with clozapine has been shown to be more effective than either modality alone in cases of TRS.[48,49] Evidence suggests safety and short-term efficacy of this combination.[50,51] A single-blind study demonstrated efficacy of ECT patients with poor response to clozapine along with no increased risk of seizures or additional cognitive impairment.[52] However, there is little evidence for maintenance of benefit over the long term.[53,54]

Repetitive transcranial magnetic stimulation (rTMS) use in treating schizophrenia is based on the observation of increased activity of the left temporoparietal cortex in auditory hallucination. Low-frequency stimulation of the region is postulated in treating the symptoms. Researchers have demonstrated no immediate advantage over placebo, but long-term benefit of rTMS in treatment of positive symptoms in patients with inadequate response to clozapine.[55] A meta-analysis on treatment with rTMS of patients with medication-resistant auditory hallucination induced a moderate reduction of auditory hallucinations in comparison with sham treatment.[56] However, in cases of TRS, patients receiving rTMS had an improvement in general psychopathology, but not in auditory hallucinations compared with sham treatment.[57] Also, a meta-analysis of seven studies has shown benefits of rTMS over sham in treating negative symptoms of schizophrenia.[58]

Transcranial direct current stimulation (tDCS) induces prolonged hyperpolarization in the area of cerebral cortex underlying the cathode and prolonged depolarization in the area of cortex underlying the anode, which is similar to effects of low- and high-frequency rTMS stimulation of cortex, leading to cortical inhibition and excitation respectively.[59-61] In a randomized sham-controlled study, significant advantage of tDCS over sham was seen in reducing the severity of auditory hallucinations and negative symptoms; however, none of the patients reported complete remission in hallucinations.[62]

Psychosocial Treatments

Psychosocial modalities like family therapy to reduce expressed emotions, occupational therapy, social skills training, cognitive behavioral therapy, and cognitive remediation have proven benefits in patients with schizophrenia even in those with poor antipsychotic response. However, there is lack of data on their use as augmenting agent with clozapine in resistant cases.[63-66]

DISCUSSION

Clozapine remains the choice of treatment in cases of TRS; however, cases showing poor response to clozapine therapy need careful evaluation for ruling out pseudoresistance. The evidence for augmentation or combination

of clozapine with other psychopharmacological agents is at present weak; similarly, use of biological modalities for augmentation needs further studies for strengthening evidence. One of the constraints of existing evidence is absence of long-term follow-up/assessment. Most evidence at present demonstrates benefits in the short term with no data for long-term efficacy or relapse prevention of illness. Also, the majority of studies address improvement in positive symptom domain of schizophrenia with undermining of negative, cognitive symptoms and overall quality-of-life in patients.[67]

Another setback is absence of uniform definition of treatment resistance and heterogeneity among research methodologies. Most studies demonstrating benefits fail to monitor plasma clozapine levels making it difficult to exclude pharmacodynamic interactions as a cause of improvement. Miyamoto et al[68] compiled evidence for management of TRS.

The categories of evidence and recommendation grades are adopted from studies reported by other researchers.[4,64] Table 1 shows the strategies of management

[a]Category of evidence where

- A = full evidence from controlled studies based on two or more double-blind, parallel-group, RCTs showing superiority to placebo and one or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered noninferiority trial (only required if such a standard treatment exists). In the case of existing negative studies (studies showing nonsuperiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and noninferiority to an established comparator treatment. Studies must fulfill established methodological standards. The decision is based on the primary efficacy measure.
- B = limited positive evidence from controlled studies based on: One or more RCTs showing superiority to placebo or a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a noninferiority trial and no good-quality negative studies exist.
- C = evidence from uncontrolled studies or case reports/expert opinion.
- D = inconsistent results (positive RCTs are outweighed by an approximately equal number of negative studies).
- E = negative evidence (the majority of RCTs show nonsuperiority to placebo).
- F =lack of evidence.

[b]Recommendation grade where[69]

- 1 = based on category A evidence and good risk benefit ratio
- 2 = based on category A evidence and moderate risk benefit ratio
- 3 = based on category B evidence
- 4 = based on category C evidence
- 5 = based on category D evidence.

Table 1: Strategies for the management of clozapine resistance/partial responders

Strategy	*Category of evidence*[a]	*Recommendation*[b]
Clozapine	B	3
Clozapine + Antipsychotic drug	B	3
Clozapine + Lamotrigine	B	3
Clozapine + Topiramate	D	5
Clozapine + Tetrabenazine	E	–
Clozapine + CX516	D	5
Clozapine + D-serine	E	–
Clozapine + Glycine	E	–
Clozapine + Sarcosine	E	–
Clozapine + Citalopram	B	3
Clozapine + Fluoxetine	E	–
Clozapine + Mirtazapine	E	–
Estradiol	B	3
Clozapine + ECT	B	3
rTMS	D	5
tDCS	B	3

CONCLUSION

Most augmenting agents show promise, but lack conclusive evidence at present. However, given the debilitating nature of the illness and widespread consequences on patients as well as caregivers, even moderate response to a particular augmenting agent may be clinically important for individual patients. While augmenting, side-effect profile of augmenting agent needs to be kept in mind, and in case of intolerability or inefficacy, clozapine monotherapy should be reinstituted. Finally, the progressive nature of schizophrenia needs to be kept in mind while setting goals for functional recovery as unrealistic expectations may do more harm than good.

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