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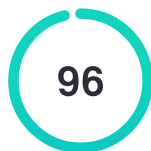
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Clozapine resistant schizophrenia: newer avenues of management

Management of clozapine resistance

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Abstract

About 40%-70% of the patients with treatment-resistant schizophrenia have a poor response to adequate treatment with clozapine. The impact of clozapine-resistant schizophrenia (CRS) is even greater¹ than that of treatment resistance in terms of severe and persistent symptoms, relapses and hospitalizations², poorer³ quality of life, and healthcare costs. Such serious consequences often compel clinicians to try different augmentation strategies to enhance the inadequate clozapine response

in CRS. Unfortunately, a large body of evidence has shown that antipsychotics, antidepressants, mood stabilizers,² electroconvulsive therapy, and cognitive-behavioural therapy are mostly⁴ ineffective in augmenting clozapine response. When beneficial effects of augmentation have been found, they are usually small and of doubtful⁶ clinical significance,⁷ or based on low-quality evidence. Therefore, newer treatment approaches that go beyond the evidence are needed. The options proposed include developing a clinical consensus about the augmentation strategies that are most likely to be effective and using them sequentially in patients with CRS. Secondly, newer approaches such as augmentation with long-acting antipsychotic injections or multi-component psychosocial interventions could be considered.⁸ Lastly, perhaps the most effective way to deal with CRS would be to optimize² clozapine treatment, which might prevent clozapine resistance from developing. Personalized² dosing, adequate treatment durations, management of side effects and non-adherence, collaboration with patients and caregivers, and addressing clinician barriers to clozapine use are the principal ways of ensuring

optimal clozapine treatment. At present, these three options could be the best way to manage CRS till research provides more firm directions about the effective⁹ options for augmenting clozapine response.

Key Words: Clozapine-resistance; Augmentation; Medications; ECT; Psychosocial treatments; schizophrenia

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Core Tip: About 40%-70% of the patients develop clozapine-resistant schizophrenia (CRS), which has serious health, economic, and social consequences. Research on CRS has provided little support for the efficacy of psychotropics, electroconvulsive therapy, and cognitive-behavioural therapy in augmenting clozapine non-response. Therefore, newer approaches are needed, including a clinical consensus about using the most effective of the currently available augmentation strategies. Augmentation with long-acting antipsychotic

injections or multi-component psychosocial interventions could also be tried¹⁰. Finally, the best option at present¹¹ may be to prevent clozapine resistance from developing by optimizing² clozapine treatment and collaborating with patients and caregivers to ensure its continuation.

INTRODUCTION

Although antipsychotic treatment is one of the principal options for the management of schizophrenia, about a third of the patients with schizophrenia do not respond well to first- or second-generation antipsychotics (FGAs or SGAs) [1, 2]. People with treatment-resistant schizophrenia (TRS) continue to have psychotic symptoms and functional impairment despite adequate antipsychotic use. TRS is associated with greater severity of symptoms, more frequent relapses, repeated hospitalizations², poorer socio-occupational functioning, and poorer¹² quality of life. Consequently, it imposes a substantial economic and social burden on patients, families, and healthcare services [1, 3]. Despite some contrary opinions, there is a widespread consensus that clozapine is the treatment of choice for patients with TRS

[4, 5]. However, even with optimal clozapine treatment, 40%-70% of the patients with TRS do not benefit from monotherapy with clozapine [6-9]. Patients with clozapine-resistant schizophrenia (CRS) are probably among the most severely ill of all patients with this disorder. A study comparing TRS and CRS found that the overall severity of the illness and positive and negative symptoms was significantly higher, while¹³ the quality of life (QOL) scores was significantly lower among patients with CRS [10]. Moreover, symptom severity among patients with CRS did not improve much over six months of follow-up. Other estimates have suggested that apart from the greater symptom severity, patients with CRS are likely to be more frequent users of healthcare services and more likely to have multiple and prolonged hospitalizations² [11].

Consequently, the cost of their care and the adverse impact of CRS on patients and their caregivers is also likely to be substantially greater than TRS [7, 12]. Such serious consequences of CRS often compel clinicians to try new and different strategies to treat these patients. The option most commonly adopted is to add another

psychotropic agent to clozapine to enhance its effects [9, 11]. However, the evidence to date indicates that augmentation with medications or other treatments yields little or no additional benefits for these patients [13]. The treatment of CRS thus continues to pose a formidable challenge for clinicians. Moreover, the size of this group of patients will increase as the use of clozapine for TRS increases. Therefore, newer ways of managing CRS have to be explored. Accordingly, this review attempts to briefly summarize² the research in this area, followed by discussing specific treatment options and strategies that appear promising.

AUGMENTATION STRATEGIES FOR CRS: FROM EVIDENCE TO PRACTICE

Relying on clinical consensus

This brief update of the existing literature shows that augmentation of clozapine response in CRS with medications, ECT, or CBT is largely¹⁴ ineffective. Any

favourable outcome for augmentation is usually based on low-quality or limited evidence, and the clinical significance of the small¹⁵ effects obtained in some meta-analyses is unclear. Moreover, the evidence offers no definite conclusions about the most effective augmentation strategies because of the inconsistent results and methodological uncertainties. Nevertheless, it has been suggested that the lack of evidence should not discourage clinicians from trying out these strategies in individual patients. This advice appears to be based on two assumptions. First, the lack of significant benefits applies only to entire groups of patients being evaluated in RCTs, whereas there¹⁶ may be considerable variability in individual responses of the patients comprising¹⁷ these groups [18, 25, 29, 40]. Thus, there is a possibility that some patients may benefit from augmentation, though at present, there is no way to identify these potential responders. Moreover, given the widespread adverse impact of CRS, even modest benefits are considered acceptable in clinical settings [7, 22, 46]. Therefore, the sequential use of different augmentation strategies is considered¹⁸ a realistic option in clinical practice.

To reduce the disparity between the evidence-based findings and clinical practice¹⁹, researchers have been increasingly relying on clinical consensus to guide the management of complex and burdensome conditions such as CRS. A recent effort on these lines arrived at the following recommendations for augmentation of clozapine non-response: personalizing² doses to reach plasma levels ≥ 350 ng/mL; a 3-month trial for patients with positive symptoms; shorter treatment trials for those with violence or self-harm (2 mo) and longer²⁰ periods (4 mo) for patients with negative or cognitive symptoms [13]. For persistent positive symptoms, adding aripiprazole, amisulpride, or ECT was suggested. Augmentation with antidepressants was recommended for negative symptoms while²¹ adding antidepressants, antipsychotics, mood stabilizers², or ECT to clozapine was proposed for CRS with increased risks of aggression or self-harm. Lastly, CBT or other psychosocial interventions were also felt to be useful²². It was apparent that these clinicians were going beyond the current evidence while making some of these recommendations. For example, though there is little support in the literature for

augmentation²³ of clozapine with a second antipsychotic, low-quality evidence or single RCTs have suggested that risperidone²⁴, aripiprazole, and amisulpride may be beneficial (Table-2). The group also relied on naturalistic studies showing that the clozapine-aripiprazole combination may have positive effects²⁵ [77]. Similarly²⁶, for recommendations about antidepressants, positive evidence for antidepressant augmentation in schizophrenia was cited [78, 79], though the evidence for similar effects of antidepressant augmentation in CRS is limited (Table-3). Augmentation with mood stabilizers² and ECT was recommended despite acknowledging that the evidence for these strategies is insufficient (Tables 3, 4). The recommendation for using CBT if other treatments failed was based on the recent CBT trial [75], which concluded that certain²⁷ individuals with CRS may²⁸ benefit from a practical trial²⁹³⁰ of CBT augmentation. Clozapine augmentation was preferred³¹ over a switch to a different antipsychotic because of the consistent evidence of adverse outcomes following cessation of clozapine [8, 11, 80-82]. Switching to high-dose olanzapine has been suggested as an alternative, but this option is not

supported by evidence [81, 83]. Finally, though most of the evidence indicates that these augmentation strategies are safe and well-tolerated [22, 25, 26, 29], the possibility of new side effects arising during combined treatment could not be discounted [9, 12, 18, 28, 32]. Therefore, cautious³² monitoring of all patients for the duration of the augmentation trial was also recommended.

Trying newer options for augmentation³³
Augmentation with long-acting antipsychotic injections
Apart from problems of resistance, non-adherence is a major³⁴ hindrance to effective treatment with clozapine. Although non-adherence with clozapine may be lower than other antipsychotics, rates of intentional non-adherence vary from 23%-55% during treatment [84-88]. In such situations initiating a long-acting antipsychotic injection (LAI) remains the only option [89]. Intramuscular clozapine appears to have some benefits in enhancing adherence, but it has not been used frequently³⁵ [90, 91]. Recent studies suggest that apart from reducing non-adherence, LAI augmentation of clozapine may also have

a role in enhancing clozapine response in CRS. As shown in table-6, this evidence is still preliminary and consists mostly³⁶ of series of patients and observational studies [92-102]. However, mirror-image studies that are³⁷ considered the current standard for evaluating LAI efficacy [103, 104] have also been conducted. Taken together, this body of evidence suggests that the combination of clozapine with LAIs leads to a reduction in all types of symptoms and behavioural problems such as aggression and suicidality, as well as improvements in social functioning. The lowered risk of relapses and reduction in the number and length of hospitalizations² has also been replicated consistently. Lastly, it appears that lower doses of both medications are required, while side effects are either less³⁸, or no more common³⁹ with the combination than with clozapine monotherapy.

Table-6 here

Indirect evidence for the effectiveness of clozapine-LAI combinations also comes from several Scandinavian nationwide cohort studies of antipsychotic treatment summarized² in table-7 [77, 82, 105-109]. These provide the strongest⁴⁰ support for the notion that clozapine and

LAIs are the two most effective treatments for patients with both⁴¹ first-episode and chronic schizophrenia.

Incidentally, some of these studies have also shown that the combination of clozapine and aripiprazole is more effective than clozapine monotherapy [77]. Therefore, the combination of clozapine and LAIs appears to be a promising option that needs to be examined further for its usefulness in the management of CRS.⁴²

Table-7 here

A re-evaluation of psychosocial augmentation strategies Although the evidence reviewed in table-5 suggests that augmentation with CBT does not yield consistent benefits in CRS, there are several reasons to re-examine the usefulness of psychosocial augmentation strategies. To begin with,⁴³ CBT augmentation appears to be effective for persistent positive symptoms in TRS [20, 68, 75, 76].

Moreover, the largest and most meticulously conducted CBT trial has shown a small but significant benefit for patients with CRS following the active intervention phase [66, 75, 76]. The same trial has suggested that CBT is one of the safest and acceptable augmentation options for patients with CRS. The evidence from this study and

other trials shows that CBT augmentation has added benefits such as improvements in socio-occupational functioning and QOL. ⁴⁴Moreover, symptomatic remission appears to be faster with CBT augmentation ⁴⁵and the ⁴⁶benefits obtained may persist longer [71, 72, 74]. CBT augmentation early in ⁴⁷the course of clozapine treatment may further enhance its ⁴⁸benefits [68-70, 74]. ^{49,50}Further, it has been proposed that rather than using only CBT, multi-component psychosocial interventions using different techniques might be more effective in enhancing clozapine response [33, 110, 11]. ⁵¹Though CBT is the most common psychosocial treatment used in patients with TRS, there is evidence to suggest that other types of ⁵²interventions might be equally effective [68, 112]. Psychoeducation and family interventions are also effective for schizophrenia [113], but they have not been tried ⁵³out as augmenting strategies in TRS or CRS [20, 68]. Lastly, psychosocial augmentation might be ⁵⁴useful in other ways, for ⁵⁵example in improving adherence to clozapine. An RCT that compared CBT with psychoeducation among patients with TRS on clozapine showed that both treatments ⁵⁶led to improvements in

patient empowerment, treatment alliance, and medication persistence [114]. Thus, while there may be no compelling evidence in favour of psychosocial augmentation strategies in CRS, there is scope for further evaluation of these potentially useful treatments.

DEFINING AND CONCEPTUALIZING CRS

The key elements of the current definitions of CRS are depicted in table-1. These include a diagnosis of schizophrenia, moderate baseline severity, and non-response and persistence of symptoms, and functional impairment despite adequate treatment with clozapine [12, 14-16]. Though these operationalized definitions of CRS represent an improvement, it is also apparent that the majority of clinical trials of patients with CRS have not utilized such definitions. Moreover, a major criticism of the current constructs of CRS is that they rely excessively on positive symptoms of schizophrenia [11, 17, 18]. Other domains such as negative, cognitive, or depressive symptoms, or QOL have not received sufficient attention. This gives rise to substantial heterogeneity in the CRS groups selected using such definitions, which

further hinders research. Although measures such as more precise delineation of target symptoms and differentiating between "minimum and optimal criteria" required for CRS have been proposed, [15, 16] the current definitions are still far from perfect [11, 15, 18, 19]. Finally, from a clinical perspective, there are many practical difficulties in determining adequate doses, estimating blood levels, judging adherence, and conducting prospective observation of patients⁶⁶ during treatment with clozapine [15, 16].

Table -1 here

AUGMENTATION STRATEGIES FOR CRS: A BRIEF REVIEW

Medication augmentation

In routine clinical practice, the commonest⁶⁷ strategy to deal with CRS is augmentation with another antipsychotic [9, 11, 20, 21]. Mood stabilizers² or antidepressant augmentation is used less frequently. Some treatment guidelines also endorse augmentation with antipsychotics [13]. Over the past 25 years, many trials of clozapine augmentation with medications and other treatments have been conducted. Additionally,

more than 50 reviews on the subject, including narrative and systematic reviews, individual meta-analyses, and reviews of different meta-analyses⁶⁸ have been published.

Antipsychotic augmentation

Some of the recent reviews of augmentation of clozapine with a second antipsychotic in CRS are included in table-2 [22-44].

Among all augmentation trials, the largest⁶⁹ number has involved antipsychotic augmentation of clozapine non-response. Risperidone, aripiprazole, and amisulpride are the most commonly evaluated augmenting agents.

Despite the size of the evidence, the majority of reviews have concluded that adding a second antipsychotic to clozapine does have any significant impact on clinical response, overall symptom-severity, or severity of positive symptoms [7, 8, 20, 45, 46]. Though some benefit has been noted when all trials are included, there appear to be no significant effects when only high-quality trials are considered [2, 18]. Even when benefits are evident in well-designed RCTs (randomized² controlled trials), the combined effect sizes are small to moderate, casting doubts on the clinical significance of these findings. The

effect of antipsychotic combinations with clozapine on negative and depressive symptoms has been examined less frequently. A similar inconsistency is apparent with⁷⁰ some meta-analyses showing modest benefits, while others report no effects on these symptoms.

Table-2 here

Antidepressant and mood stabilizer² augmentation

As depicted in table-3, the number of RCTs examining the augmentation of clozapine with antidepressants and mood stabilizers² is comparatively less. Moreover, the trials are more often of poorer⁷¹ quality. Consequently, there is little evidence of the benefits of antidepressant augmentation on the severity of symptoms [23, 24, 30, 37]. When some evidence of a positive effect has been found, it is usually based on single, high-quality RCTs [23, 24, 30, 37]. Similarly, though mood stabilizer² augmentation is reported to be beneficial in some meta-analyses [47, 48], others have either found no benefit [7, 24, 46, 49]⁷², or evidence of significant symptom reduction only in low-quality trials [2, 8, 23, 30, 50].

Table-3 here

Methodological lacunae

One of the principal reasons for the inability to find effective⁷³ medication augmentation options for CRS is the methodological shortcomings of current research. Even in the better quality RCTs, there is considerable heterogeneity in terms of the definitions used, the types and numbers of patients included, the duration of trials, and the outcomes examined. The methodological lacunae of the RCTs have in turn⁷⁴ affected the methodological quality of meta-analytic examinations of the evidence. For example, in a systematic review of 21 meta-analyses, only one was judged⁷⁷ to have "very little⁷⁸ risk of bias"; 7 had "low risk of bias", and the rest had "high risk of bias" [2]. Therefore, there is considerable uncertainty even about the findings of meta-analytic studies.

Augmentation with electroconvulsive therapy and recurrent transcranial magnetic stimulation

Some of the more recent reviews have concluded that electroconvulsive therapy (ECT) is an effective augmentation strategy, especially when medications fail to decrease persistent positive symptoms [2, 8, 20, 46, 51]. However, this conclusion appears to be based on a single meta-analysis of 18 RCTs [52], which showed that

the ECT-clozapine combination was better than clozapine alone in reducing positive symptoms. Then again, 17 ⁷⁹ of these RCTs were conducted in China and are not easily accessible [53]. As shown in table-4, there are only 2 ⁸⁰ small RCTs of ECT augmentation of clozapine response. The first showed ⁸¹ that the clozapine-ECT combination was more effective than clozapine alone in TRS, ⁸² [54], whereas the second did not find the combination ⁸³ to be ⁸⁴ more effective in CRS [55]. The rest of the evidence consists of non-randomized ² trials [56] and case studies. Thus, the higher response rates of the clozapine-ECT combination reported in systematic reviews [57-61] and other meta-analyses [62-64] are largely based ⁸⁵ on low-quality evidence, obtained mainly among patients with TRS, and limited to the short-term efficacy of ECT augmentation. Though the combination appears to be ⁸⁶ relatively safe, about 20% of the patients develop adverse effects, and there is some evidence of greater ⁸⁷ cognitive impairment [52, 57, 59, 62, 63]. Nevertheless, ⁸⁸ augmentation with ECT may result in a faster response, which is particularly useful ⁸⁹ among patients with high risks of aggression or self-harm [9, 11, 60, 65]. Therefore, though the evidence

is still inconclusive, the effects of ECT augmentation certainly merit further examination. On the other hand, augmentation⁹⁰ with recurrent transcranial magnetic stimulation appears to be⁹¹ largely ineffective in CRS despite promising results from recent trials [66, 67].

Table-4 here

Psychosocial augmentation strategies

Two systematic reviews of psychosocial interventions have concluded that cognitive-behavioural therapy (CBT) can be effective among patients with poor⁹² response to clozapine [33, 68]. As shown in table-5, the evidence-base for CBT till recently had consisted of a few trials with small numbers and inadequate study designs [69-71], or RCTs which had included some patients with CRS [72-74].⁹³ However, interest in the effects of CBT augmentation has been re-awakened with a large, well-designed RCT among patients with CRS [75]. This⁹⁴ was the largest⁹⁵ trial among all RCTs of clozapine augmentation. It employed standardized² definitions of CRS⁹⁶ and trained therapists who administered manual-based CBT to patients from routine clinical settings. After 9⁹⁷ mo of active treatment, the total PANSS scores, positive

symptoms, emotional distress, and excitement had reduced significantly in the CBT compared to the usual treatment group. However, at the end of 21 mo, there were no significant differences in the PANSS scores between the 2⁹⁸ groups, leading to the conclusion that CBT augmentation was not effective⁹⁹ in CRS. Nevertheless¹⁰⁰, other indices suggested that CBT might be useful for a¹⁰¹ proportion of patients and patients' ratings of recovery¹⁰² were greater¹⁰³ in the CBT group at 21 mo. Other noteworthy advantages of CBT were the high adherence rates, negligible adverse effects, high acceptability, and effect sizes comparable to medication augmentation. Therefore, others have interpreted these results differently to emphasize² the positive effects of CBT augmentation [2, 66, 76]. Moreover, it has been pointed out that the persistence of positive effects beyond the active treatment period is not the best indicator of the efficacy of CBT [76]. Thus, if the standards for medication trials were to be applied to this RCT, the conclusion would be that CBT was an effective augmentation strategy for CRS after 9¹⁰⁴ mo of treatment.

Table-5 here

PREVENTING RESISTANCE TO CLOZAPINE TREATMENT

The relative ineffectiveness of the different augmentation strategies suggests that a more fruitful option could be to try and prevent resistance to clozapine treatment from developing.

Predicting clozapine resistance

Predicting who among patients with TRS will not respond adequately to clozapine may be helpful because augmentation strategies could be instituted¹⁰⁵ early in such patients to mitigate the adverse effects of clozapine resistance. However, despite over 300 studies of prediction of clozapine response, consistent predictors of response have not been found. Some reviews have concluded that there are no reliable predictors of clozapine response because of the inconsistent results and methodological uncertainties of existing research [115, 116]. On the other hand, an older systematic review and a more recent meta-analysis have found that older age, greater severity of symptoms, especially¹⁰⁶ negative¹⁰⁷ symptom-severity, poorer functioning, and non-paranoid

subtypes could predict clozapine non-response [117, 118]. Low cerebrospinal homovanillic acid¹⁰⁸ to 5-hydroxyindoleacetic¹⁰⁹ acid ratios and normal¹¹⁰ structure and function of the prefrontal cortex have also emerged as reliable predictors of good response in some studies [117, 119]. However, because of the inconclusive nature of this evidence, currently, the only way to predict clozapine resistance is to carry out an adequate trial of clozapine treatment under optimal conditions [20, 115].

Optimizing² clozapine treatment

Ensuring adequate treatment with clozapine may thus be the best option to prevent clozapine resistance. The necessary steps for optimizing² clozapine treatment are listed in table-8. Personalized² dosing is a key¹¹¹ component because of the wide variations in dose-blood level ratios between individuals and because many patients respond at lower doses [120, 121].

Data on gender differences in clozapine treatment are scarce and¹¹² results are often inconsistent [122]. This particularly true for response to clozapine treatment. Though the response¹¹³ is usually poorer¹¹⁴ in women [116,

117, 122], research on clozapine's effectiveness has also found better outcomes among women, although¹¹⁵ these differences in their favour are often of doubtful clinical significance [115, 117, 123]. Others have found no differences in outcome between the two genders. [118] In contrast, differences in pharmacokinetics are reported more consistently [122, 124, 125]. Women have lower renal clearance than men because of differences in the¹¹⁶ activity of cytochrome P450 enzymes such as CYP1A2. Most studies have found higher plasma levels of clozapine in women, and some have also found higher levels of its metabolite norclozapine.¹¹⁷ Higher dose-blood level ratios have also been found in women. Therefore, women usually require lower doses of clozapine [124]. These pharmacokinetic differences also increase the risk of dose-dependent side effects in women, particularly metabolic side effects [122, 126]. Accordingly, most of the evidence on gender differences in side effects of clozapine relates to metabolic disturbances [122]. However, findings are not consistent and¹¹⁸ both genders appear to have increased risk of metabolic syndrome in different reports [122, 126-128]. Hypertension, elevated

triglycerides, lower high-density lipoprotein levels, and cardiac abnormalities appear to be more common in men [122]. Women are more likely to develop hyperglycemia and diabetes and increases in weight and BMI [122, 126]. There is very little evidence of gender differences in other side effects though certain studies have found haematological abnormalities and constipation to be commoner¹¹⁹ among women [122, 125, 128, 129].

Unlike the influence of gender, ethnicity does not appear to any impact on¹²⁰ treatment response obtained with clozapine [115, 130]. On the other hand, there are ethnic differences in pharmacokinetic profiles of clozapine [122]. More specifically, several studies among Asian patients have consistently indicated that they require about half the standard dose of clozapine due to their lowered clozapine metabolism [131 -135]. The dose¹²¹ of clozapine required¹²² for adequate response among Asians varies from 150mg/d among women to 300 mg/d for men who smoke. Therefore, Asian patients need lower doses at the start of treatment and slower upward titration to reach their optimum dose¹²³. Despite these

pharmacokinetic dissimilarities, ethnic differences seem to have minimal impact on the prevalence of adverse effects of clozapine [129]. Nevertheless¹²⁴, non-white ethnicity is a risk factor for metabolic syndrome, and certain¹²⁵ studies have found a higher prevalence of hypertension and weight gain in Asians [127, 136]. Others have found a higher risk of agranulocytosis in Asian patients [137]. This¹²⁶ again emphasizes² the fact¹²⁷ that the best way to individualize² clozapine doses is to base them on blood levels. Doing so has the added advantages of lessening side effects and allowing adherence to be monitored. However, facilities for blood levels are not always available. Standardized² dosing schedules could be used in such instances [132].

Many of the side effects encountered with clozapine are dose-dependent including¹²⁸ sedation, tachycardia, hypersalivation, enuresis, constipation, delirium, obsessive-compulsive symptoms, seizures, and orthostatic hypotension [81, 120, 138] Among all antipsychotics, the prevalence of metabolic dysfunction or metabolic syndrome is the highest for clozapine and olanzapine [81, 126, 127, 132, 139]. Whether metabolic

side effects are also dose-dependent is not clear [81, 138]. However, systematic reviews and meta-analyses have indicated a dose-outcome association between clozapine and metabolic side effects, particularly with¹²⁹ lipid levels and weight gain [140, 141]. Risk factors for metabolic syndrome include higher baseline weight or body mass index (BMI), gender, non-white and possibly Asian ethnicity, and several genetic and peptide markers [126, 127, 136, 139, 142]. Metabolic disturbances are also associated with a reduction in symptoms [126, 127].

Optimizing² clozapine doses is the principal way of managing most dose-dependent side effects. Using the lowest effective dose¹³⁰, slow increase in doses¹³¹, and dose adjustments to minimize² side effects is always recommended [81, 120, 123]. Discontinuation of concomitant medication that might not¹³² essential also reduces the side effect burden [120]. Only serious¹³³ and life-threatening adverse reactions such as agranulocytosis and some cardiopulmonary complications require abrupt discontinuation of clozapine [81, 120]. Some side effects such as neuroleptic malignant syndrome, thromboembolism, or

diabetic ketoacidosis may require¹³⁴ temporary discontinuation followed by re-initiation of clozapine [81]. In most other situations, the dose of clozapine should be reduced¹³⁵ very gradually to avoid worsening of clinical state or emergence of withdrawal symptoms [120]. When side effects persist despite optimizing² the dose of clozapine, the options include adding other medications, instituting non-pharmacological measures to manage side effects, or combining clozapine with another antipsychotic [120, 138]. In the case of¹³⁶ metabolic syndrome, adequate treatment of risk factors and metabolic derangements is essential [143]. Meta-analyses of interventions for metabolic side effects have shown that adjunctive metformin is the most effective strategy [144, 145]. Behavioural weight management strategies are also recommended though the evidence for their efficacy is uncertain [120, 138, 144]. Adding aripiprazole to clozapine to reduce both the clozapine dose and metabolic disturbances has also been suggested, but the evidence for this option is limited [120, 144]. Minimizing² the side effect burden is necessary because about 40% of the patients (range 21%-67%) stop taking clozapine in

the first few years of treatment [82, 84, 86, 87, 146]. In 20%-30% of them, discontinuation is because of intolerable side effects, though intentional non-adherence appears to be somewhat more common [84, 85, 87, 88, 147]. Managing non-adherence requires open and non-judgmental discussions about medication-taking with patients, monitoring of¹³⁷ adherence based on all available methods, including caregivers' reports, education to deal with misconceptions about treatment, and building trusting alliances with patients and families to ensure continued treatment. A collaboration with the patient and the family is an essential part of optimizing² clozapine treatment that is¹³⁸ often overlooked [65, 110, 111, 120]. Shared decision-making about treatment, education, stress-management, support, and involvement of caregivers are ways of ensuring truly collaborative alliances. Lastly, increasing evidence indicates substantial under-utilization² and delayed use of clozapine [148, 149]. Clinician's lack of awareness and experience with clozapine, their misplaced concerns about its use, and the discrepancy between clinicians' and patients' attitudes regarding clozapine are among

the main¹³⁹ causes of inappropriate use of clozapine [150, 151]. Therefore, dealing with these clinician-related barriers is also necessary to ensure the proper use of clozapine.

Table-8 here

CONCLUSION

Clozapine resistance is probably one of the most difficult¹⁴ conditions that clinicians treating patients with schizophrenia are likely to encounter. Unfortunately, the existing research evidence does not provide any firm guidelines about treatment options once clozapine fails. However, because of the seriousness of the condition and the widespread negative impact of CRS, clinicians need to look beyond the evidence and rely on consensus-based recommendations. At present, effective ways to deal with CRS are to optimize² clozapine treatment, choose among the best available options judiciously, explore newer ways of augmentation, and adopt a holistic approach to treatment that includes simple psychosocial measures in addition to pharmacological ones. Finally, cautious

optimism, commitment to treatment, patience, and persistence from clinicians, patients, and caregivers are almost always required for the effective use of clozapine.

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Figure Legends

none

1.	greater → more significant	Word choice	Engagement
2.	<i>hospitalizations; stabilizers; optimize; Personalized; optimizing; summarize; personalizing; summarized; CONCEPTUALIZING; operationalized; utilized; randomized; stabilizer; non-randomized; standardized; emphasize; Optimizing; emphasizes; individualize; Standardized; minimize; Minimizing; under-util...</i>	Text inconsistencies	Correctness
3.	poorer → more inferior	Word choice	Engagement
4.	mostly → primarily	Word choice	Engagement
5.	of	Wordy sentences	Clarity
6.	doubtful → uncertain	Word choice	Engagement
7.	significance,	Punctuation in compound/complex sentences	Correctness
8.	<i>newer approaches such as augmentation with long-acting antipsychotic injections or multi-component psychosocial interventions could be considered</i>	Passive voice misuse	Clarity
9.	effective → practical	Word choice	Engagement
10.	<i>Augmentation with long-acting antipsychotic injections or multi-component psychosocial interventions could also be tried</i>	Passive voice misuse	Clarity
11.	at present	Wordy sentences	Clarity
12.	poorer → more inferior	Word choice	Engagement
13.	, while → . At the same time,	Hard-to-read text	Clarity
14.	largely → mainly	Word choice	Engagement

15.	small → minor	Word choice	Engagement
16.	. In contrast, there	Hard-to-read text	Clarity
17.	the patients comprising	Wordy sentences	Clarity
18.	considered → regarded as	Word choice	Engagement
19.	<i>To reduce the disparity between the evidence-based findings and clinical practice</i>	Misplaced words or phrases	Correctness
20.	longer → more extended	Word choice	Engagement
21.	, while	Punctuation in compound/complex sentences	Correctness
22.	useful → helpful, valid	Word choice	Engagement
23.	the augmentation	Determiner use (a/an/the/this, etc.)	Correctness
24.	that risperidone	Wordy sentences	Clarity
25.	positively affect	Wordy sentences	Clarity
26.	Similarly → ¶ Similarly	Intricate text	Clarity
27.	certain → specific	Word choice	Engagement
28.	may → might	Faulty tense sequence	Correctness
29.	a practical → a pragmatic	Word choice	Engagement
30.	trial → test, problem	Word choice	Engagement
31.	<i>Clozapine augmentation was preferred</i>	Passive voice misuse	Clarity
32.	cautious → careful	Word choice	Engagement
33.	augmentation.	Closing punctuation	Correctness

34.	major → significant	Word choice	Engagement
35.	<i>Intramuscular clozapine appears to have some benefits in enhancing adherence, but it has not been used frequently [90, 91].</i>	Unclear sentences	Clarity
36.	mostly → mainly, primarily	Word choice	Engagement
37.	that are	Wordy sentences	Clarity
38.	less,	Punctuation in compound/complex sentences	Correctness
39.	more common → more familiar	Word choice	Engagement
40.	strongest → most vital, most robust, most substantial	Word choice	Engagement
41.	both	Wordy sentences	Clarity
42.	<i>Therefore, the combination of clozapine and LAIs appears to be a promising option that needs to be examined further for its usefulness in the management of CRS.</i>	Unclear sentences	Clarity
43.	<i>To begin with</i>	Misplaced words or phrases	Correctness
44.	Moreover → ¶ Moreover	Intricate text	Clarity
45.	, and	Punctuation in compound/complex sentences	Correctness
46.	benefite → services	Word choice	Engagement
47.	the course of	Wordy sentences	Clarity
48.	benefite → services	Word choice	Engagement
49.	Further → Additionally	Word choice	Engagement

50.	Further → ¶ Further	Intricate text	Clarity
51.	<i>Further, it has been proposed that rather than using only CBT, multi-component psychosocial interventions using different techniques might be more effective in enhancing clozapine response [33, 110, 11].</i>	Unclear sentences	Clarity
52.	<i>Though CBT is the most common psychosocial treatment used in patients with TRS, there is evidence to suggest that other types of interventions might be equally effective [68, 112].</i>	Unclear sentences	Clarity
53.	out as augmenting → to augment	Wordy sentences	Clarity
54.	useful → helpful, helpful to	Word choice	Engagement
55.	example,	Punctuation in compound/complex sentences	Correctness
56.	led to improvements in → improved	Wordy sentences	Clarity
57.	useful → helpful, valuable	Word choice	Engagement
58.	CRS	Unknown words	Correctness
59.	key → critical	Word choice	Engagement
60.	<i>These include a diagnosis of schizophrenia, moderate baseline severity, and non-response and persistence of symptoms, and functional impairment despite adequate treatment with clozapine [12, 14-16].</i>	Unclear sentences	Clarity
61.	the majority of → most	Wordy sentences	Clarity
62.	definitions → purposes, depictions, reports	Word choice	Engagement

63.	major → significant	Word choice	Engagement
64.	symptoms,	Punctuation in compound/complex sentences	Correctness
65.	<i>This</i>	Intricate text	Clarity
66.	patient observation	Wordy sentences	Clarity
67.	commonest → most typical, most standard, most familiar, most everyday	Word choice	Engagement
68.	meta-analyses,	Punctuation in compound/complex sentences	Correctness
69.	largest → most significant	Word choice	Engagement
70.	, with	Punctuation in compound/complex sentences	Correctness
71.	poorer → more inferior	Word choice	Engagement
72.],	Punctuation in compound/complex sentences	Correctness
73.	effective → adequate	Word choice	Engagement
74.	, in	Punctuation in compound/complex sentences	Correctness
75.	in turn	Wordy sentences	Clarity
76.	turn,	Punctuation in compound/complex sentences	Correctness
77.	<i>only one was judged</i>	Passive voice misuse	Clarity

78.	very little → minimal	Word choice	Engagement
79.	of these	Wordy sentences	Clarity
80.	2 → two	Improper formatting	Correctness
81.	showed → revealed	Word choice	Engagement
82.	TRS,	Punctuation in compound/complex sentences	Correctness
83.	combination → variety, mix, mixture, cross	Word choice	Engagement
84.	to be	Wordy sentences	Clarity
85.	largely based → primarily based, based mainly	Word choice	Engagement
86.	to be	Wordy sentences	Clarity
87.	greater → more significant	Word choice	Engagement
88.	Nevertheless → ¶ Nevertheless	Intricate text	Clarity
89.	particularly	Wordy sentences	Clarity
90.	augmentation → boost	Word choice	Engagement
91.	to be	Wordy sentences	Clarity
92.	poor → inadequate	Word choice	Engagement
93.	<i>As shown in table-5, the evidence-base for CBT till recently had consisted of a few trials with small numbers and inadequate study designs [69-71], or RCTs which had included some patients with CRS [72-74].</i>	Unclear sentences	Clarity
94.	<i>This</i>	Intricate text	Clarity

95.	largest → most significant, most prominent	Word choice	Engagement
96.	CRS definitions	Wordy sentences	Clarity
97.	9 → nine	Improper formatting	Correctness
98.	2 → two	Improper formatting	Correctness
99.	not effective → ineffective	Wordy sentences	Clarity
100.	Nevertheless → ¶ Nevertheless	Intricate text	Clarity
101.	useful for → helpful in, helpful for	Word choice	Engagement
102.	recovery ratings	Wordy sentences	Clarity
103.	greater → more significant	Word choice	Engagement
104.	9 → nine	Improper formatting	Correctness
105.	<i>augmentation strategies could be instituted</i>	Passive voice misuse	Clarity
106.	especially → predominantly, significantly	Word choice	Engagement
107.	negative → damaging, harmful	Word choice	Engagement
108.	homovanillic acid	Unknown words	Correctness
109.	hydroxy indole acetic	Misspelled words	Correctness
110.	normal → standard, typical	Word choice	Engagement
111.	key → crucial	Word choice	Engagement
112.	, and	Punctuation in compound/complex sentences	Correctness
113.	response → reaction	Word choice	Engagement

114.	poorer → more insufficient, more unsatisfactory	Word choice	Engagement
115.	, although → . However,	Hard-to-read text	Clarity
116.	the activity of	Wordy sentences	Clarity
117.	norclozapine → nor clozapine	Misspelled words	Correctness
118.	, and	Punctuation in compound/complex sentences	Correctness
119.	to be commoner	Wordy sentences	Clarity
120.	any impact on → impact	Wordy sentences	Clarity
121.	dose → amount, quantity	Word choice	Engagement
122.	required → necessary	Word choice	Engagement
123.	dose → amount	Word choice	Engagement
124.	Nevertheless → ¶ Nevertheless	Intricate text	Clarity
125.	certain → specific	Word choice	Engagement
126.	<i>This</i>	Intricate text	Clarity
127.	the fact	Wordy sentences	Clarity
128.	, including	Punctuation in compound/complex sentences	Correctness
129.	with	Wordy sentences	Clarity
130.	<i>Using the lowest effective dose</i>	Misplaced words or phrases	Correctness
131.	doses → quantities, amounts	Word choice	Engagement
132.	not be	Incomplete sentences	Correctness

133.	serious → severe	Word choice	Engagement
134.	require → direct	Word choice	Engagement
135.	<i>the dose of clozapine should be reduced</i>	Passive voice misuse	Clarity
136.	the ease of	Wordy sentences	Clarity
137.	of	Wordy sentences	Clarity
138.	that is	Wordy sentences	Clarity
139.	main → leading	Word choice	Engagement
140.	difficult → challenging	Word choice	Engagement
141.	ways → forms	Word choice	Engagement
142.	BN; UK; VA; U.K	Text inconsistencies	Correctness
143.	nor clozapine → nor clozapine	Misspelled words	Correctness
144.	a systematic	Determiner use (a/an/the/this, etc.)	Correctness
145.	<i>Conflict-of-interest statement: No potential conflicts of interest.</i>	Incomplete sentences	Correctness
146.	that was	Wordy sentences	Clarity
147.	in accordance with → by, following, per, under	Wordy sentences	Clarity
148.	, and	Punctuation in compound/complex sentences	Correctness
149.	Society ,	Improper formatting	Correctness
150.	Specialty → Speciality	Mixed dialects of English	Correctness
151.	Very good → Excellent, Perfect	Word choice	Engagement

