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Clozapine resistant schizophrenia: Newer avenues of management

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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 greater than that of treatment resistance in terms of severe and persistent symptoms, relapses and hospitalizations, poorer 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, electroconvulsive therapy, and cognitive-behavioural therapy are mostly ineffective in augmenting clozapine response. When beneficial effects of augmentation have been found, they are usually small and of doubtful clinical significance 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. Lastly, perhaps the most effective way to deal with CRS would be to optimize clozapine treatment, which might prevent clozapine resistance from developing. Personalized 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 until research provides more firm directions about the effective options for augmenting clozapine response.

Key Words: Clozapine-resistance; Augmentation; Medications; Electroconvulsive therapy; Psychosocial treatments; Schizophrenia

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Core Tip: About 40%-70% of patients develop clozapine-resistant schizophrenia, which has serious health, economic, and social consequences. Research on clozapine-resistant schizophrenia 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 tried. Finally, the best option at present may be to prevent clozapine resistance from developing by optimizing clozapine treatment and collaborating with patients and caregivers to ensure its continuation.

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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[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 hospitalizations, poorer socio-occupational functioning, and poorer quality of life(QOL). 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 were significantly higher, while the QOL score was significantly lower among patients with CRS[10]. Moreover, symptom severity among patients with CRS did not improve much over 6 mo 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 hospitalizations[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 summarize the research in this area, followed by a discussion of certain treatment options and strategies that appear promising.

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

Table 1 Key components of the current definitions of clozapine-resistant schizophrenia[12,14-16]

Diagnosis	Diagnosis of schizophrenia using standardized criteria and after ruling out psychosis due to substance use or medical conditions
Adequate clozapine treatment	
Dose	200-500 mg/d
Blood levels	≥ 350 ng/mL
Treatment duration	2-3 mo ¹
Treatment adherence	≥ 80% of prescribed doses for the duration of treatment
Response to clozapine	
Baseline symptom severity and functional impairment	Moderately severe illness either globally or in positive and negative symptom domains assessed using standardized scales (CGI, BPRS, PANSS, SAPS, SANS). Moderate levels of functional impairment assessed using standardized scales (GAF, SOFAS)
Non-response	< 20% reduction in symptoms and minimal response in levels of functional impairment during an adequate trial of clozapine treatment
Persistence	Moderately severe illness and functional impairment should persist following an adequate trial of clozapine treatment

¹It has been proposed that duration of clozapine trials should be 2 mo for patients with aggression or self-harm, 3 mo for those with positive symptoms, and 4 mo for those with negative and cognitive symptoms[13].

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression scale; GAF: Global Assessment of Functioning scale; PANSS: Positive and Negative Syndrome Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SOFAS: Social and Occupational Functioning Scale.

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 patients during treatment with clozapine[15,16].

AUGMENTATION STRATEGIES FOR CRS: A BRIEF REVIEW

Medication augmentation

In routine clinical practice, the commonest strategy to deal with CRS is augmentation with another antipsychotic[9,11,20,21]. Mood stabilizer 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-analyses 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 largest 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 not 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 randomized controlled trials (RCTs), 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

Table 2 Reviews of antipsychotic augmentation strategies in clozapine-resistant schizophrenia¹

Ref.	Type of review	Details	Effect on positive or psychotic symptoms	Effect on negative or depressive symptoms
Wagner <i>et al</i> [2], 2019	Systematic review	14 meta-analyses of FGA and SGA augmentation of clozapine.	Some evidence of benefits based on low-quality studies (SIGN grade B).	
Roerig <i>et al</i> [8], 2019	Systematic review	4 meta-analyses and 1 naturalistic study of FGA and SGA augmentation of clozapine.	No benefits of antipsychotics when high-quality RCTs were considered.	
Bartoli <i>et al</i> [22], 2019	Meta-analysis	12 RCTs of SGA augmentation of clozapine-risperidone (<i>n</i> = 5) and aripiprazole (<i>n</i> = 3).	No difference between SGA augmentation and placebo in improving positive symptoms.	A small benefit of SGA augmentation for negative and depressive symptoms.
Siskind <i>et al</i> [23], 2018	Meta-analysis	19 RCTs of FGA and SGA augmentation of clozapine-aripiprazole (<i>n</i> = 7), risperidone (<i>n</i> = 3), and amisulpiride (<i>n</i> = 2).	Evidence for benefit with aripiprazole, but effects were lost when low-quality studies were excluded.	
Correll <i>et al</i> [24], 2017	Meta-analysis	Meta-analysis of 29 previous meta-analyses of antipsychotic combinations-5 clozapine combinations examined.	Clozapine combinations no different from clozapine monotherapy for positive symptoms.	Clozapine combinations no different from clozapine monotherapy for negative symptoms.
Galling <i>et al</i> [25], 2017	Meta-analysis	20 RCTs of FGA and SGA augmentation of clozapine-risperidone (<i>n</i> = 6) and aripiprazole (<i>n</i> = 6).	No evidence for additional benefits of augmentation in double-blind, high-quality RCTs.	Improvement in negative symptoms with aripiprazole augmentation. No effect of augmentation on depressive symptoms.
Ortiz-Orendain <i>et al</i> [26], 2017	Meta-analysis	31 RCTs and quasi-RCTs of augmentation with SGAs (<i>n</i> = 26) and FGAs (<i>n</i> = 5) including clozapine augmentation.	Low-quality evidence that augmentation improves global clinical response. No specific effects on positive symptoms.	No effect of augmentation on negative symptoms.
Barber <i>et al</i> [27], 2017	Meta-analysis	5 RCTs of clozapine augmentation with SGAs or haloperidol.	Low-quality evidence that augmentation may improve global clinical response. Effects on positive symptoms not clear.	Effects on negative symptoms not clear.
Jiménez-Cornejo <i>et al</i> [28], 2016	Meta-analysis	17 prior meta-analyses and reviews of FGA and SGA augmentation (62 studies) of clozapine.	Little evidence that augmentation improves clinical response (> 20% reduction in PANSS/BPRS scores).	
Taylor <i>et al</i> [29], 2012	Meta-analysis	14 RCTs of FGA and SGA augmentation of clozapine.	A small benefit in overall symptom reduction with augmentation.	
Sommer <i>et al</i> [30], 2012	Meta-analysis	10 RCTs of FGA and SGA augmentation of clozapine.	One RCT showed that sulpiride augmentation led to overall symptom reduction. No specific effects on positive symptoms.	No specific effects on negative symptoms.
Porcelli <i>et al</i> [31], 2012	Systematic review and meta-analysis	Systematic review of 25 studies of SGA augmentation of clozapine - risperidone (11 trials) and aripiprazole (6 trials). Meta-analysis of 5 RCTs of risperidone augmentation of clozapine.	Low quality evidence indicated benefits for aripiprazole and amisulpiride augmentation. No benefit of risperidone augmentation.	Some benefit of aripiprazole in reducing negative symptoms from 1 RCT.

¹Several other systematic reviews[9,12,14,32,33] and meta-analyses[17,34-37] have been unable to find significant benefits, while others have reported modest benefits for antipsychotic augmentation of clozapine[38-44].

BPRS: Brief Psychiatric Rating Scale; FGA: First-generation antipsychotic; RCT: Randomized controlled trial; PANSS: Positive and Negative Syndrome Scale; SGA: Second-generation antipsychotic; SIGN: Scottish Intercollegiate Guidelines Network.

been examined less frequently. A similar inconsistency is apparent with some meta-analyses showing modest benefits, while others report no effects on these symptoms.

Antidepressant and mood stabilizer augmentation: As depicted in Table 3, the number of RCTs examining the augmentation of clozapine with antidepressants and mood stabilizers is comparatively less. Moreover, the trials are more often of poorer 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 stabilizer augmentation is reported to be beneficial in some meta-analyses[47,48], others have either found no benefit[7,24,46,49] or evidence of significant symptom reduction only in low-quality trials[2,8,23,30,50].

Table 3 Meta-analyses of antidepressant and mood stabilizer augmentation in clozapine-resistant schizophrenia

Ref.	Type of review	Details	Results
Antidepressants			
Siskind <i>et al</i> [23], 2018	Meta-analysis	10 RCTs of fluoxetine, paroxetine, duloxetine, and mirtazapine augmentation	Some evidence for fluoxetine augmentation in reducing in overall symptom severity based on 1 high-quality RCT.
Correll <i>et al</i> [24], 2017	Meta-analysis	Analysis based on the earlier meta-analysis of Veerman <i>et al</i> [37]	No benefit of antidepressant augmentation on reduction in overall, positive, and negative symptom severity.
Veerman <i>et al</i> [37], 2014	Meta-analysis	4 RCTs of mirtazapine, duloxetine, and fluoxetine augmentation	No benefit of antidepressant augmentation on reduction in overall, positive, and negative symptom severity.
Sommer <i>et al</i> [30], 2012	Meta-analysis	4 RCTs of mirtazapine, citalopram, and fluoxetine augmentation	Some evidence for citalopram augmentation in reducing overall and negative symptom severity based on 1 RCT.
Mood stabilizers			
Siskind <i>et al</i> [23], 2018	Meta-analysis	5 RCTs of valproate ($n = 2$), lamotrigine ($n = 2$), lithium ($n = 1$), and topiramate($n = 1$) augmentation	Low-quality evidence for valproate and lithium augmentation in reducing total symptom severity. Reduction of positive and negative symptom severity by topiramate augmentation based on 1 RCT.
Correll <i>et al</i> [24], 2017	Meta-analysis	Analysis based on the earlier meta-analysis of Veerman <i>et al</i> [37]	No benefit of lamotrigine and topiramate augmentation on reduction in overall, positive, and negative symptom severity.
Zheng <i>et al</i> [50], 2017	Meta-analysis	22 RCTs of valproate ($n = 9$), lamotrigine ($n = 8$), and topiramate ($n = 4$) augmentation	Significant benefits for valproate and topiramate in reducing total and positive symptom severity but based on low-quality studies. No effects on clinical response.
Zheng <i>et al</i> [48], 2016	Meta-analysis	4 RCTs of topiramate augmentation	Significant benefits of topiramate augmentation in reducing overall, positive, and negative symptom severity.
Veerman <i>et al</i> [49], 2014	Meta-analysis	6 RCTs of lamotrigine and 4 RCTs of topiramate augmentation	No benefit of lamotrigine and topiramate augmentation on reduction in overall, positive, and negative symptom severity.
Sommer <i>et al</i> [30], 2012	Meta-analysis	7 RCTs of lamotrigine ($n = 4$) and topiramate ($n = 3$) augmentation	Benefits of lamotrigine and topiramate augmentation for total and positive symptoms based on single RCTs that did not persist on further analysis.
Tiihonen <i>et al</i> [47], 2009	Meta-analysis	5 RCTs of lamotrigine augmentation	Evidence for benefit of lamotrigine augmentation in reducing overall, positive, and negative symptom severity.

RCT: Randomized controlled trial.

Methodological lacunae: One of the principal reasons for the inability to find effective 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 turn affected the methodological quality of meta-analytic examinations of the evidence. For example, in a systematic review of 21 meta-analyses only one was judged to have “very little 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 of these RCTs were conducted in China and are not easily accessible[53]. As shown in Table 4, there are only two small RCTs of ECT augmentation of clozapine response. The first showed that the clozapine-ECT combination was more effective than clozapine alone in TRS[54], whereas the second did not find the combination to be more effective in CRS[55]. The rest of the evidence consists of non-randomized 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 on low-quality evidence, obtained mainly among patients with TRS, and

Table 4 Electroconvulsive therapy and recurrent transcranial magnetic stimulation augmentation in clozapine-resistant schizophrenia

ECT			
Ref.	Study/review	Details	Results
Masoudzadeh <i>et al</i> [56], 2007	Controlled trial, (non-randomized, non-blinded)	18 patients with TRS; 3 groups of clozapine-ECT treatment, only clozapine and only ECT treatment (<i>n</i> = 6 each)	Significant differences between the clozapine- ECT combination and monotherapy groups in reduction of PANSS scores.
Petrides <i>et al</i> [54], 2015	Single-blind cross-over RCT	39 patients with TRS randomized to clozapine-ECT (<i>n</i> = 20) and clozapine only treatment (<i>n</i> = 19)	Significantly greater response on BPRS psychosis & CGI scores in the clozapine-ECT combination group.
Melzer-Ribeiro <i>et al</i> [55], 2017	Single-blind sham-controlled RCT	23 patients with CRS randomized to treatment with clozapine-ECT (<i>n</i> = 13) and clozapine-sham ECT (<i>n</i> = 10)	No significant differences between the groups on PANSS total and positive symptom scores and CGI scores.
Kupchik <i>et al</i> [57], 2000	Systematic review	Case reports of 36 patients with TRS and clozapine non-responders	67% of the patients on the clozapine-ECT combination showed good response.
Braga <i>et al</i> [58], 2005	Systematic review	12 case reports or chart reviews of patients with TRS and clozapine non-responders	The clozapine-ECT combination was efficacious.
Havaki-Kontaxaki <i>et al</i> [59], 2006	Systematic review	One open trial and 6 case studies of patients with CRS	73% patients on the clozapine-ECT combination showed marked improvement.
Pompili <i>et al</i> [60], 2013	Systematic review	31 studies examining indications for ECT in schizophrenia	The clozapine-ECT combination was efficacious in patients resistant to medications.
Grover <i>et al</i> [61], 2015	Systematic review	40 studies, mainly case reports of patients with CRS	Short-term response rates of the clozapine-ECT combination varied from 37%-100%.
Lally <i>et al</i> [62], 2016	Systematic review and meta-analysis	Pooled analysis of patients with TRS treated with clozapine and ECT based on 4 open trials, 2 controlled trials (1 RCT) ¹ , 2 chart reviews, 6 case series, and 15 case reports	Pooled response rate with the clozapine-ECT combination was 54% on meta-analysis. Systematic review showed 76% overall response rate with clozapine-ECT treatment and a relapse rate of 32%.
Manubens <i>et al</i> [63], 2016	Systematic review and meta-analysis	6 systematic reviews of ECT in TRS including 6 controlled trials of the clozapine-ECT combination in clozapine non-responders (1 RCT) ¹	Modest effect of ECT in augmenting clozapine response with low certainty of evidence.
Ahmed <i>et al</i> [64], 2017	Systematic review and meta-analysis	9 studies of the clozapine-ECT combination in TRS including 2 controlled trials (1 RCT) ¹ , 3 open trials, and 4 case series/chart-reviews <i>vs</i> 9 studies of ECT-non-clozapine antipsychotic combination	The ECT-clozapine combination was significantly better than the ECT-non-clozapine antipsychotic combinations in reducing positive symptoms on the PANSS and the BPRS.
Wang <i>et al</i> [52], 2018	Meta-analysis	18 RCTs of clozapine augmentation in CRS (17 from China and 1 from the United States) ¹	Adjunctive ECT was superior to clozapine monotherapy in reducing positive symptoms after 1–2 wk but with moderate effect size.
rTMS			
Wagner <i>et al</i> [66], 2020	Meta-analysis	Pooled data from 10 RCTs for 131 patients with persistent positive and negative symptoms being treated with clozapine	No differences between active and sham rTMS in improving clinical response and reducing PANSS scores. No benefit of rTMS augmentation for patients with persistent symptoms on clozapine.

¹The RCT from United States is by Petrides *et al*[54].

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression scale; CRS: Clozapine-resistant schizophrenia; ECT: Electroconvulsive therapy; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized controlled trial; rTMS: Recurrent transcranial magnetic stimulation; TRS: Treatment resistant schizophrenia.

limited to the short-term efficacy of ECT augmentation. Though the combination appears to be relatively safe, about 20% of the patients develop adverse effects, and there is some evidence of greater cognitive impairment[52,57,59,62,63]. Nevertheless, augmentation with ECT may result in a faster response, which is particularly useful 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, augmentation with recurrent transcranial magnetic stimulation appears to be largely ineffective in CRS despite promising results from recent trials[66,67].

Psychosocial augmentation strategies

Two systematic reviews of psychosocial interventions have concluded that CBT can be effective among patients with poor response to clozapine[33,68]. As shown in Table 5, the evidence-base for CBT until recently had consisted of a few trials with small

Table 5 Psychosocial augmentation strategies in clozapine-resistant schizophrenia

Ref.	Study/participants	Interventions	Results
Studies			
Pinto <i>et al</i> [69], 1999	Single-blind RCT of 41 patients with TRS started on clozapine	CBT and social skills training <i>vs</i> supportive therapy for 6 mo.	Significant reductions in positive and negative symptom severity in the CBT group.
Buchain <i>et al</i> [70], 2003	Single-blind RCT of 41 patients with TRS started on clozapine	Occupational therapy and clozapine <i>vs</i> clozapine alone for 6 mo.	Significant improvements in the occupational performance and interpersonal relationships with OT.
Barretto <i>et al</i> [71], 2009	Single-blind RCT of 21 patients with CRS	CBT <i>vs</i> supportive treatment (“befriending”) for 21 wk.	Significant reductions in overall symptom severity and improvement in quality of life with CBT.
Morrison <i>et al</i> [75], 2018	Double-blind RCT of 425 patients with CRS	CBT <i>vs</i> usual treatment for 9 mo. Follow-up for 21 mo.	Significant reductions in PANSS scores with CBT at 9 mo but no differences at 21 mo.
Sensky <i>et al</i> [72], 2000; Valmaggia <i>et al</i> [73], 2005; Edwards <i>et al</i> [74], 2011	RCTs of patients with TRS (<i>n</i> = 48-90) including patients on clozapine or clozapine non-responders	CBT <i>vs</i> supportive treatment or clozapine alone or comparisons with combinations of CBT with other antipsychotics.	Significant reductions in positive, negative, and depressive symptom severity, improvement in clinical response and functioning with CBT; benefits at end of treatment usually maintained during follow-up.
Reviews			
Ranasinghe <i>et al</i> [33], 2014	Systematic review	Review of the 2 CBT and 1 OT trial mentioned above.	Benefits of psychosocial interventions noted for overall symptom severity, quality of life, and social functioning.
Polese <i>et al</i> [68], 2019	Systematic review & meta-analysis	Review of all the above trials and meta-analysis of 4 RCTs including Morrison <i>et al</i> [75].	Benefits of psychosocial interventions noted for overall and positive symptom severity.

CBT: Cognitive-behavioural therapy; CRS: Clozapine resistant schizophrenia; PANSS: Positive and Negative Syndrome Scale; OT: Occupational therapy; TRS: Treatment resistant schizophrenia; RCT: Randomized controlled trial.

numbers and inadequate study designs[69-71] or RCTs that included some patients with CRS[72-74]. However, interest in the effects of CBT augmentation has been reawakened with a large, well-designed RCT among patients with CRS[75]. This was the largest trial among all RCTs of clozapine augmentation. It employed standardized definitions of CRS and trained therapists who administered manual-based CBT to patients from routine clinical settings. After 9 mo of active treatment, the total Positive and Negative Symptom Scale scores, positive symptoms, emotional distress, and excitement had reduced significantly in the CBT group compared to the usual treatment group. However, at the end of 21 mo, there were no significant differences in the Positive and Negative Symptom Scale scores between the two groups, leading to the conclusion that CBT augmentation was not effective in CRS. Nevertheless, other indices suggested that CBT might be useful for a proportion of patients, and patients' ratings of recovery were greater 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 emphasize 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 9 mo of treatment.

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 largely ineffective. Any favourable outcome for augmentation is usually based on low-quality or limited evidence, and the clinical significance of the small effects obtained in some meta-analyses is unclear. Moreover, because of the inconsistent results and methodological uncertainties, the

evidence offers no definite conclusions about the most effective augmentation strategies. 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 there may be considerable variability in individual responses of the patients comprising 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 considered to be a realistic option in clinical practice.

To reduce the disparity between the evidence-based findings and clinical practice, 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: personalizing doses to reach plasma levels ≥ 350 ng/mL; a 3 mo trial for patients with positive symptoms; shorter treatment trials for those with violence or self-harm (2 mo) and longer 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 while adding antidepressants, antipsychotics, mood stabilizers, 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 useful. 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 augmentation of clozapine with a second antipsychotic, low-quality evidence or single RCTs have suggested that risperidone, aripiprazole, and amisulpride may be beneficial (Table 2). The group also relied on naturalistic studies showing that the clozapine-aripiprazole combination may have positive effects[77]. Similarly, 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 stabilizers and ECT was recommended despite the acknowledgement that the evidence for these strategies is insufficient (Tables 3 and 4). The recommendation for using CBT if other treatments failed was based on the recent CBT trial[75], which concluded that certain individuals with CRS may benefit from a practical trial of CBT augmentation. Clozapine augmentation was preferred 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, cautious monitoring of all patients for the duration of the augmentation trial was also recommended.

Trying newer options for augmentation

Augmentation with long-acting antipsychotic injections: Apart from problems of resistance, non-adherence is a major 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 frequently[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 mostly of series of patients and observational studies[92-102]. However, mirror-image studies that are 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 hospitalizations has also been replicated consistently. Lastly, it appears that lower doses of both medications are required,

Table 6 Augmentation of clozapine with long-acting antipsychotic injections in clozapine-resistant schizophrenia

Ref.	Study details	Results
Kim <i>et al</i> [92], 2010	4 patients treated with clozapine and risperidone LAI for 1 yr	Reduction in number and length of hospitalizations and improvement in social skills after LAI addition. Fewer side effects with the combination.
Malla <i>et al</i> [93], 2013	One patient with poor response to clozapine treated with clozapine and an LAI	Improvement in symptoms and social functioning without any increase in side effects with combination treatment.
Baruch <i>et al</i> [94], 2014	8 patients, 6 with TRS. Treated with olanzapine LAI and clozapine or other antipsychotics up to 2 yr	Reduction in aggression in all 8 patients and in symptom severity in 6 patients.
Maia-de-Oliveira <i>et al</i> [95], 2015	2 patients with CRS treated with clozapine and paliperidone LAI for 9-10 mo	Remission of positive symptoms after LAI augmentation.
Kasinathan <i>et al</i> [96], 2016	9 patients with TRS and comorbid personality disorders/substance use and violence; 1 on clozapine but non-adherent treated with olanzapine LAI combination	1 yr of retrospective pre- and post-LAI comparisons showed significant improvements in psychotic symptoms, violence, and reduction in number and length of hospitalizations and emergency visits.
Sepede <i>et al</i> [97], 2016	One patient with poor response to clozapine treated with clozapine and aripiprazole LAI for 1 yr	Symptoms reduced by 50% with the combination without any increase in side effects.
Oriolo <i>et al</i> [98], 2016	Retrospective observational of 23 patients with TRS in whom paliperidone LAI was added to clozapine	Significant reductions in severity of global, positive, negative, depressive, and cognitive symptoms with the combination. Significantly lower doses of clozapine and paliperidone LAI required with combination treatment <i>vs</i> monotherapy.
Souaiby <i>et al</i> [99], 2017	Retrospective observational study with a mirror-image design of 20 patients with TRS treated with clozapine and LAIs for 32 mo	Significant reductions in number and length of hospitalizations during 32 mo of combination treatment <i>vs</i> 1 yr of monotherapy. No increase in side effects with the combination.
Grimminck <i>et al</i> [100], 2020	Retrospective observational study with a mirror- image design of 20 patients with poor response to clozapine or LAIs treated with clozapine and LAI combinations for 2 yr	Significant reductions in hospital admissions and emergency visits during 2 yr of combination treatment <i>vs</i> 2 yr of monotherapy. Overall improvement in behaviour and social functioning but no change in symptoms.
Bioque <i>et al</i> [101], 2020	Retrospective observational study with a mirror- image design of 50 patients with TRS treated with clozapine and paliperidone LAI for 6 mo	Significant reductions in BPRS scores, emergency visits, number and length of hospitalizations, and number and severity of adverse effects as well as significant improvements in social functioning during 6 mo of combination treatment <i>vs</i> 6 mo of monotherapy.
Caliskan <i>et al</i> [102], 2021	Retrospective observational study with a mirror- image design in 29 patients with TRS treated with clozapine and LAI combinations for 1 yr	Significant reductions in number of relapses and number and length of hospitalizations during 1 yr of combination treatment <i>vs</i> 1 yr of monotherapy. No differences in side effects with the combinations.

BPRS: Brief Psychiatric Rating Scale; CRS: Clozapine resistant schizophrenia; LAI: Long-acting antipsychotic injection; TRS: Treatment resistant schizophrenia.

while side effects are either less, or no more common with the combination than with clozapine monotherapy.

Indirect evidence for the effectiveness of clozapine-LAI combinations also comes from several Scandinavian nationwide cohort studies of antipsychotic treatment summarized in Table 7[77,82,105-109]. These provide the strongest support for the notion that clozapine and LAIs are the two most effective treatments for patients with both 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.

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, 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. Moreover, symptomatic remission appears to be faster with CBT augmentation, and the benefits obtained may persist longer[71,72,74]. CBT augmentation early in the course of clozapine treatment may further enhance its benefits[68-70,74].

Table 7 Scandinavian nationwide cohort studies of antipsychotic treatment

Ref.	Study details	Results
Tiihonen <i>et al</i> [105], 2006, Finland	2230 inpatients followed up for 3.6 yr	Significantly lower risks of rehospitalization or treatment discontinuation in patients on perphenazine LAI, clozapine, or olanzapine <i>vs</i> those on oral haloperidol.
Tiihonen <i>et al</i> [106], 2009, Finland	66881 outpatients followed up for 11 yr	Clozapine was associated with a substantially lower mortality than any other antipsychotics singly or in combination, with perphenazine as a comparator.
Tiihonen <i>et al</i> [107], 2011, Finland	2588 inpatients followed up for 2 mo after discharge	Significantly lower risks of rehospitalization with LAIs than oral medications. Clozapine and olanzapine were associated with significantly lower risk of rehospitalization than risperidone.
Tiihonen <i>et al</i> [108], 2017, Sweden	29823 patients followed up for 5.7 yr	Significantly lower risks of rehospitalization and of treatment failure ¹ with LAIs and clozapine <i>vs</i> no antipsychotic treatment.
Taipale <i>et al</i> [109], 2018, Finland	62250 inpatients followed up for 20 yr	Significantly lower risks of rehospitalization with LAIs and clozapine <i>vs</i> no antipsychotic treatment in first episode and chronic schizophrenia.
Tiihonen <i>et al</i> [77], 2019, Finland	62250 inpatients on antipsychotic monotherapy or antipsychotic combinations followed up for 14 yr	Combination of clozapine and aripiprazole was associated with significantly lower risk of rehospitalization and mortality than clozapine alone in first episode and chronic schizophrenia. Clozapine monotherapy was associated with the most favourable outcomes compared to other antipsychotics.
Luykx <i>et al</i> [82], 2020, Finland	2250 patients on clozapine treatment followed up for more than 1 yr before discontinuation	Compared to no antipsychotic treatment, significantly lower risks of rehospitalization with re-institution of clozapine alone, oral olanzapine, and antipsychotic combinations. Significantly lower risks of treatment failure ¹ with aripiprazole LAI, re-institution of clozapine alone, and oral olanzapine.

¹Treatment failure included re-hospitalization, suicide attempt, treatment discontinuation, medication switch, or death.

LAI: Long-acting antipsychotic injection.

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[33,110,111]. 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]. Psychoeducation and family interventions are also effective for schizophrenia[113], but they have not been tried out as augmenting strategies in TRS or CRS[20,68]. Lastly, psychosocial augmentation might be useful in other ways, for example in improving adherence to clozapine. An RCT that compared CBT with psychoeducation among patients with TRS on clozapine showed that both treatments led 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.

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 instituted 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, especially negative symptom severity, poorer functioning, and non-paranoid subtypes could predict clozapine non-response[117,118]. Low cerebrospinal homovanillic acid to 5-hydroxyindoleacetic acid ratios and normal structure and

function of the prefrontal cortex have also emerged as reliable predictors of good response in some studies[117,119]. Consequently, 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].

Optimizing clozapine treatment

Ensuring adequate treatment with clozapine may thus be the best option to prevent clozapine resistance. The necessary steps for optimizing clozapine treatment are listed in Table 8. Personalized dosing is a key 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, and results are often inconsistent[122]. This is particularly true for response to clozapine treatment. Though the response is usually poorer in women[116,117,122], research on clozapine's effectiveness has also found better outcomes among women, although 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 of clozapine than men because of differences in the 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. 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, and 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 hyperglycaemia and diabetes and increases in weight and body mass index[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 commoner among women[122,125,128,129].

Unlike the influence of gender, ethnicity does not appear to have any impact on 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 dose of clozapine required 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 dose. Despite these pharmacokinetic dissimilarities, ethnic differences seem to have minimal impact on the prevalence of adverse effects of clozapine[129]. Nevertheless, non-White ethnicity is a risk factor for metabolic syndrome, and certain 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]. This again emphasizes the fact that the best way to individualize 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. Standardized dosing schedules could be used in such instances[132].

Many of the side effects encountered with clozapine are dose-dependent including 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 with lipid levels and weight gain[140,141]. Risk factors for metabolic syndrome include higher baseline weight or body mass index, gender, non-White, possibly Asian ethnicity, and several genetic and peptide markers [126,127,136,139,142]. Somewhat paradoxically, metabolic disturbances are also associated with a reduction in symptoms[126,127].

Table 8 Steps for ensuring optimal clozapine treatment[65,81,110,111,120,123,132]

Steps for ensuring optimal clozapine treatment	
Adequate assessment	Diagnosis should be established properly. Comorbid conditions should be looked for. Adherence should be determined. Symptoms and other outcome domains should be preferably rated using validated instruments. Caregiver burden and coping should be assessed. Stressors and adverse circumstances should be evaluated.
Proper dosing	Inter-individual and ethnic variability in optimal doses should be considered. If facilities for serum levels are available, doses should be titrated to ensure plasma levels > 350 ng/mL. Doses should be increased slowly with careful monitoring of side effects to reduce the burden of dose-dependent side effects.
Adequate duration	A minimum of 2-3 mo is considered necessary. Durations could be shorter in those with high risk of aggression or self-harm. Durations could be longer in those with negative or cognitive symptoms and in partial responders.
Managing side effects	Many of the common side effects of clozapine can be managed by slow titration, using the least effective dose, reducing doses when side effects develop, adding medications, or adopting lifestyle changes to counter side effects. Additionally, careful monitoring should be carried out for the more serious and idiosyncratic adverse reactions such as agranulocytosis and cardiopulmonary complications.
Managing non-adherence	Careful monitoring of adherence based on multiple sources is necessary. Managing side effects, educating patients to deal with negative attitudes to clozapine, developing a trusting alliance to improve motivation, caregiver education and support to increase their involvement in the patient's care may help. These measures should ideally be initiated right at the beginning of treatment. Use of long-acting antipsychotic injections may be considered.
Collaboration with patients and caregivers	Both patients and caregivers should be the focus of treatment. Measures should be tailored according to their needs. Goals of treatment should be reduction of symptoms and distress, improving support, forging effective alliances, and promoting patient and caregiver engagement. Simple psychosocial measures including cognitive or behavioural strategies, psychoeducation, and emotional and practical support should be implemented at the start of treatment or as early as possible. More structured interventions can be tried depending on availability of resources and expertise.
Addressing clinician related barriers	Clinicians' lack of awareness and experience of clozapine treatment and negative attitudes towards clozapine use should be addressed by proper education, dissemination of information, and dedicated facilities.

Optimizing clozapine doses is the principal way of managing most dose-dependent side effects. Using the lowest effective dose, slow increase in doses, and dose adjustments to minimize side effects is always recommended[81,120,123]. Discontinuation of concomitant medications that might not be essential also reduces the side effect burden[120]. Only serious 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 require temporary discontinuation followed by re-initiation of clozapine[81]. In most other situations, the dose of clozapine should be reduced very gradually to avoid worsening of clinical state or emergence of withdrawal symptoms[120]. When side effects persist despite optimizing 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 of 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].

Minimizing 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 of adherence based on all available methods including caregiver 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 optimizing clozapine treatment that is 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 underutilization 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 main 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.

CONCLUSION

Clozapine resistance is probably one of the most difficult 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 optimize 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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