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ELECTROCONVULSIVE THERAPY AS AN AUGMENTATION STRATEGY IN CLOZAPINE-RESISTANT SCHIZOPHRENIA

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ABSTRACT

Aims: This narrative review evaluates the efficacy, tolerability, and clinical applicability of electroconvulsive therapy (ECT) as an augmentation strategy in clozapine-resistant schizophrenia (CRS), a particularly severe subtype of treatment-resistant schizophrenia (TRS) unresponsive to clozapine. It also aims to summarize current evidence from clinical studies and highlight unresolved challenges in the use of ECT for this population.

Methods: A comprehensive literature search was conducted in PubMed, Cochrane Library, Embase, and Web of Science for English-language publications from 2014 to 2024. The search focused on studies addressing clozapine-resistant schizophrenia and electroconvulsive therapy. Inclusion criteria comprised clinical relevance, focus on ECT as augmentation, and sufficient methodological quality. A total of 191 publications, including clinical studies, reviews, and meta-analyses, were selected and synthesized to evaluate efficacy, tolerability, and clinical application.

Results: The majority of studies suggest that ECT augmentation improves positive symptoms and overall clinical outcomes in patients with clozapine-resistant schizophrenia. Reported adverse effects are typically mild and transient, including headache and short-term cognitive impairment. Maintenance and continuation ECT (M/C-ECT) appear beneficial in sustaining remission and reducing relapse risk. Nevertheless, the overall strength of evidence is limited by methodological heterogeneity, small sample sizes, and the scarcity of randomized controlled trials.

Conclusions: ECT represents a promising adjunctive intervention for clozapine-resistant schizophrenia, particularly in cases unresponsive to pharmacological strategies alone. Despite encouraging clinical data, its routine implementation is constrained by limited high-quality evidence. Further well-designed trials are needed to define patient selection criteria, optimal treatment protocols, and long-term outcomes, and to support the integration of ECT into standardized treatment guidelines.

Keywords: schizophrenia, clozapine-resistant, electroconvulsive therapy, augmentation, antipsychotic resistance

1 INTRODUCTION

SCHIZOPHRENIA – OVERVIEW

Schizophrenia is a severe, chronic, and complex psychiatric disorder affecting approximately 1% of the global population over their lifetime [1,2]. This debilitating illness is characterized by a heterogeneous symptomatology encompassing positive symptoms (e.g. hallucinations and delusions), negative symptoms (e.g. social withdrawal, apathy, and blunted affect), and cognitive deficits, such as impaired memory and executive functioning [3,4]. The disorder's course is highly variable, with some individuals experiencing full recovery after an initial episode, while most endure a relapsing-remitting course [5,6].

The etiology of schizophrenia is multifactorial and encompasses genetic predispositions [7], infections [8], autoimmune processes [9], as well as social and psychological influences [10]. Comorbid conditions, including cardiovascular, metabolic, and infectious diseases, contribute to a mortality rate 2–3 times higher than that of the general population [11,12].

Functionally, schizophrenia leads to profound disability, with 80–90% of patients unable to maintain employment and a significant proportion requiring long-term support for daily activities [13,14]. The financial burden is substantial, covering direct healthcare costs and indirect costs due to lost productivity [15,16].

Treatment strategies primarily rely on antipsychotic medications, beginning with the introduction of chlorpromazine in the 1950s, alongside non-pharmacological therapies tailored to individual patient needs [17,18]. Despite advances in pharmacotherapy, the variability in treatment response and disease trajectory highlights the ongoing challenges in managing this disabling condition [19,20].

TREATMENT-RESISTANT SCHIZOPHRENIA AND CLOZAPINE-RESISTANT SCHIZOPHRENIA

While many individuals with schizophrenia achieve symptom control with antipsychotic medications, a significant proportion experience inadequate treatment response, leading to what is classified as "treatment-resistant" or "treatment-refractory" schizophrenia (TRS). The most widely accepted minimum criterion for TRS includes a failure to respond to at least two different, non-clozapine antipsychotic drugs [16,21–27]. However, various definitions have been proposed, with some suggesting stricter diagnostic criteria to ensure precision and consistency in identifying treatment resistance. In 2017, the Treatment Response and Resistance in Psychosis (TRRIP) Working Group established treatment resistance criteria based on a global expert consensus. According to their definition, TRS is characterized by at least moderate symptom severity and functional impairment linked to schizophrenia, along with insufficient improvement following two or more trials of antipsychotic medications. Each trial must meet specific standards, including an adequate dosage (equivalent to at least 600 mg of chlorpromazine daily), a minimum duration of six weeks, and a patient adherence rate of at least 80% of the prescribed doses [22].

The prevalence of TRS varies significantly across studies, ranging from 10% to 70% of individuals diagnosed with schizophrenia. Most authors agree that approximately 30% of patients with schizophrenia meet the criteria for TRS [16,26,28–41].

Clozapine, developed in 1958 as the first dibenzodiazepine atypical antipsychotic, has established itself as the most effective treatment for patients with treatment-resistant schizophrenia [42,43]. Initially withdrawn in the 1970s due to concerns about agranulocytosis [42], clozapine was reintroduced in the late 1980s following a pivotal study by Kane et al. (1988) that demonstrated its superiority in treating this challenging patient population [27]. Clozapine offers significant benefits, including symptomatic improvement in both positive and negative symptoms, reduced hospitalization and mortality rates, cost-effectiveness, and enhanced social functioning [19,21,44–47]. It also has an unique advantage of mediating addictive behaviors and reducing suicide rates in patients with comorbid substance use disorders [48]. Conversely, clozapine is associated with adverse effects such as neutropenia, agranulocytosis, sedation, constipation, sialorrhea, orthostatic hypotension, chest pain, nocturnal enuresis, increased seizure risk, and metabolic syndrome. However, most of aforementioned are monitorable and manageable [49–52]. Routine hematologic monitoring is required to mitigate the rare but serious risk of agranulocytosis [16,53–55].

"Clozapine-resistant" schizophrenia (CRS) represents a particularly challenging subset of treatment-resistant schizophrenia cases, where patients fail to respond to clozapine despite its established efficacy as the gold-standard treatment for TRS [19,21,53,56–60]. While clozapine has shown remarkable success in managing TRS, approximately 40–70% of patients either do not achieve sufficient therapeutic response or are unable to tolerate the medication due to adverse effects [27,53,56–59,61–71]. The TRRIP Working Group has proposed that CRS should be classified as a distinct subtype of TRS, termed "ultra-treatment-resistant schizophrenia" (UTRS), characterized by persistent symptoms after at least three months of clozapine treatment at adequate doses (400–

500 mg/day) and therapeutic plasma levels of 350 ng/mL or higher [21,22]. This condition is also referred to as "super-refractory" or "ultra-resistant schizophrenia" in the literature [72–74].

TRS and, especially, CRS are associated with profound clinical and societal burdens. These groups of patients exhibit significantly poorer daily functioning, lower quality of life, and higher unemployment rates compared to those who respond to treatment [28,66,75–77]. Furthermore, treatment resistance substantially increases the frequency of hospitalizations, reflecting both the severity and persistence of symptoms. The financial impact is also notable [76,78]. The costs associated with TRS are estimated to be 3–11 times greater than for patients whose schizophrenia is in remission [76].

The treatment of clozapine-resistant schizophrenia remains one of the most challenging areas in psychiatry, with limited evidence-based interventions available [79]. Augmentation strategies are often employed, involving the addition of other pharmacological agents, such as antipsychotics, antidepressants, mood stabilizers, anxiolytics, or glutamatergic agents [19,21,80–85]. Despite these efforts, meta-analyses of placebo-controlled trials have demonstrated little or no consistent benefit from pharmacological augmentation in CRS [86–89]. Moreover, the use of polypharmacy carries a higher likelihood of adverse effects compared to monotherapy, highlighting the importance of investigating non-pharmacological augmentation strategies [16]. Alternative approaches, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and cognitive behavioral therapy (CBT), have been proposed for addressing CRS [21]. However, the overall lack of unequivocal evidence underscores the significant public health burden of managing CRS, highlighting the need for continued research and innovation in treatment approaches [63,90,91].

This narrative review aims to synthesize current evidence on the use of electroconvulsive therapy (ECT) as an augmentation strategy in clozapine-resistant schizophrenia (CRS), focusing on its clinical efficacy, tolerability, and mechanisms of action. The novelty of this paper lies in its comprehensive integration of recent clinical trials, meta-analyses, and consensus statements, providing an updated and critical perspective on the evolving role of ECT in treatment-resistant cases. Additionally, a more multifaceted view is presented than has been emphasized in prior research.

2 METHODOLOGY

A comprehensive literature search was conducted using electronic databases, including PubMed, Cochrane Library, Embase, and Web of Science. The search employed a specific query designed to identify studies focusing on clozapine-resistant schizophrenia and electroconvulsive therapy. The query comprised the keywords: "clozapine-resistant", "clozapine-refractory", "CRS", "treatment-resistant", "TRS", "schizophrenia", "electroconvulsive", "electroshock", "shock" and "ECT" in the title or abstract fields. Inclusion criteria were original clinical or observational studies, systematic reviews, and meta-analyses addressing ECT in clozapine- or treatment-resistant schizophrenia, published within the last 10 years (2014-2024). Exclusion criteria included editorials, letters, conference abstracts without full-text availability, non-English papers, and studies not involving human subjects.

The primary search yielded 53 articles that were screened based on titles and abstracts, resulting in the selection of 47 papers comprising randomized controlled trials (RCTs), cohort studies, retrospective analyses, meta-analyses, and systematic reviews. Additionally, a manual search of related references identified and reviewed 423 articles. Although no formal quality appraisal tool was applied, methodological rigor, sample size, outcome clarity, and peer-reviewed publication status were considered in evaluating the quality and relevance of each study.

Ultimately, a total of 191 studies were included in this review, and their findings were synthesized to address the objectives of the article. This multi-step process ensured a comprehensive and rigorous selection of relevant literature.

FINDINGS

3 ELECTROCONVULSIVE THERAPY AS A FORM OF TREATMENT

HISTORY AND EVOLUTION

Electroconvulsive therapy, introduced by Cerletti and Bini in the 1930s, is the oldest biological treatment in modern psychiatry and has been used in schizophrenia treatment for nearly 90 years [80,92,93]. Its application initially declined after the introduction of antipsychotic medications in the 1950s but still continues to play a significant role in the management of schizophrenia, especially in regions with limited access to pharmacological therapies, such as Asia, Africa, and South America [80,94,95]. Since the reintroduction of clozapine in the 1990s, ECT has increasingly been explored and utilized as an augmentation strategy [96,97].

Early ECT practices often resulted in side effects, such as muscle damage, fractures and memory impairment, due to the lack of anesthesia and the use of sine-wave devices. Modern techniques, including anesthesia and brief-

pulse wave devices, have markedly improved electroconvulsive therapy's safety profile [19,98]. While now most commonly used for depression, ECT remains a key neurostimulation tool for severe psychiatric disorders, demonstrating enduring value within psychiatry's therapeutic armamentarium [80,92].

MECHANISM OF ACTION

During the procedure, a controlled electrical current is delivered to the brain to induce therapeutic seizures while the patient is under anesthesia and muscle relaxation [99,100]. Depending on electrode placement, the treatment can be administered bilaterally, affecting both hemispheres of the brain, or unilaterally, targeting the non-dominant hemisphere [101]. Among the variations of bilateral ECT, bifrontal ECT has demonstrated superior clinical outcomes and fewer side effects compared to bitemporal ECT, the latter being more frequently associated with cognitive impairments [102,103]. Another term often used in the literature is "sham-ECT," which refers to the procedure involving all steps except the electrical stimulation [101].

Although the exact mechanisms remain unclear, ECT has been linked to alterations in neurotransmitter levels, increased neuroplasticity, and changes in regional cerebral blood flow [70,104–106]. It has also been suggested that enhanced blood-brain barrier permeability allows therapeutic drugs to reach the brain more effectively [107,108]. However, positive effects of ECT may partly result from placebo mechanisms, including patient expectations, attention from medical staff, or the intensive nature of the care process [109,110].

PSYCHIATRIC IMPLICATIONS

Electroconvulsive therapy is effective in treating various psychiatric conditions but remains controversial due to potential side effects, particularly memory loss [111]. While there is no conclusive evidence linking ECT to brain damage [112,113], it can still cause cognitive impairments, prolonged seizures, and cardiovascular complications [19]. Moreover, ECT is a resource-intensive treatment that often involves multiple sessions over weeks and may require inpatient care, which adds to the financial and time-related burden for patients and their families [37,114]. Furthermore, ECT's underutilization is influenced by factors such as stigma, negative media portrayals, and unclear treatment guidelines [111,115–118].

Before delving into considerations regarding ECT augmentation in schizophrenia treatment, the authors of this review first examined the most recent recommendations from the American Psychiatric Association (APA). The 2025 guidelines highlight ECT as a highly efficacious treatment for acute catatonia, supported by robust expert consensus and observational evidence. Regarding schizophrenia, the APA recommends ECT as a treatment option in combination with antipsychotic medications when there is a history of positive response to ECT, when symptoms are resistant to antipsychotic treatment (including clozapine), or when symptoms are severe, such as in cases of violence or significant disability [119]. These guidelines, while not exhaustive, underscore the continued relevance of ECT in managing schizophrenia in specific, often challenging, clinical scenarios.

4 AUGMENTATION OF ECT

Some studies focus on ECT augmentation in treatment-resistant schizophrenia in general, while others specifically examine cases where clozapine, the gold standard for treatment resistance, has also failed. Although this paper primarily addresses the use of ECT as an augmentation strategy in clozapine-resistant schizophrenia, it also includes an analysis of studies on TRS. This broader perspective provides valuable context for understanding the potential benefits of ECT supplementation in CRS.

ECT AUGMENTATION IN TRS

To assess the effectiveness of ECT augmentation in treatment-resistant schizophrenia, various psychiatric rating scales are used, with the Positive and Negative Syndrome Scale (PANSS) being the most common. This 30-item scale measures positive, negative, and general psychopathology symptoms, with higher scores indicating greater severity [97,120]. A clinically significant reduction is typically defined as a 20% decrease, though stricter thresholds are also used [121]. Brief Psychiatric Rating Scale (BPRS), another tool for evaluating psychiatric symptoms, assesses 18 items, where higher scores again reflect more severe symptoms [122]. Both scales are essential in measuring treatment response and provide standardized means of assessing symptom changes, offering valuable insights into the efficacy of ECT as an augmentation strategy.

The literature on ECT augmentation in treatment-resistant schizophrenia generally supports the efficacy of combining ECT with pharmacological treatments. Studies consistently report that augmenting antipsychotics with ECT is often more efficacious than relying on medications alone in managing symptoms of schizophrenia [19,35,77,95,123–125], with clozapine being shown to offer superior symptom reduction and greater cost-effectiveness compared to alternative antipsychotic options [19,53,54,59]. Additionally, studies indicate that ECT may result in fewer relapses and higher rates of hospital discharge compared to sham-ECT, further supporting the potential benefit of ECT in treatment-resistant populations [17,118,126].

In studies by Pawełczyk et al. (2014) [127,128], 29 and 34 patients with prominent negative symptoms of schizophrenia, respectively, were treated with ECT and antipsychotics. Response to AP+ECT therapy was defined as a reduction of at least 25% in the total PANSS score. In the first study [127], the results showed a 32% reduction in the total PANSS score, with the most significant improvement in the positive symptom subscale (37.5%) and the least in the negative symptom subscale (23.8%). Overall, 60% of participants demonstrated a response to the treatment. The other study [128] found a 30.8% mean decrease in PANSS total scores, with a significant 38.09% reduction in positive symptoms and a 23.01% reduction in negative symptoms. 58.8% of patients responded to the AP+ECT therapy. Another study supporting the efficacy of ECT in conjunction with clozapine in TRS was conducted by Masoudzadeh and Khalilian (2007) [77], who compared ECT, clozapine, and the two treatments together. The ECT-clozapine combination was significantly more effective, showing a 71% reduction in PANSS scores, compared to 40% for ECT alone and 46% for clozapine alone. Positive symptom reduction was also greatest in the combination group, reaching 80%. Finally, Lally's systematic review and meta-analysis (2016) of 71 patients from five clinical trials found a 54% response rate to the combination of clozapine and ECT in patients with TRS, with the rate increasing to 66% when case reports and retrospective data were included [118].

However, not all studies agree on the effectiveness of ECT added to antipsychotic treatment. Nieuwdorp et al. (2015) [129] reviewed nine RCTs that compared real ECT to sham-ECT in conjunction with antipsychotic treatment. Data from seven trials, involving a total of 172 participants, were accessible. Of these, four studies reported a significant advantage of real ECT over sham-ECT, while three studies found no difference in symptom severity between the two groups.

Based on the available evidence, ECT augmentation may offer significant benefits for patients with treatment-resistant schizophrenia, particularly when combined with antipsychotic treatments, though the results across studies are not entirely consistent. Additional studies are required before ECT can be incorporated into the standard treatment protocols for TRS.

ECT AUGMENTATION IN CRS

Although clozapine remains the gold standard for managing treatment-resistant schizophrenia, it fails to achieve adequate symptom control in a subset of patients, classified as having clozapine-resistant schizophrenia. While certain authors examine the role of ECT within the broader framework of treatment-resistant schizophrenia, others have concentrated specifically on its utility in clozapine-resistant schizophrenia, which constitutes the primary focus of this article. One study specifically addressed both TRS and CRS. Grover et al. (2017) [130] reported that 63% of patients with TRS, including CRS cases, achieved a significant symptom reduction of more than 30% with the combination of clozapine and ECT. In the case of clozapine non-responders, 69% benefited from the addition of ECT.

Randomized controlled trials, meta-analyses, open-label studies, case reports and reviews have been analyzed, with the vast majority of studies indicating that electroconvulsive therapy augmentation with clozapine in clozapine-resistant schizophrenia yields positive effects and demonstrates greater therapeutic benefit compared to clozapine monotherapy [70,80,85,97,131–135]. In studies by Kim et al. (2018) [134] and Kim et al. (2017) [97], response rates were 42.9% and 71.4%, respectively, both based on a 20% reduction in PANSS. Petrides et al. (2015) [80] found a 60% response rate with a 20% reduction, and Grover et al. (2017) [130] observed the highest response rate at 85% with the same threshold. Kho et al. (2004) [133] reported a 72.7% response rate, though using a more stringent 30% reduction criterion. Furthermore, studies show that electroconvulsive therapy tends to have a more pronounced impact on positive symptoms of clozapine-resistant schizophrenia than on general or negative symptoms [70,80,85,133–135]. However, it has been suggested that improvements in negative symptoms may require prolonged treatment [136]. In a comprehensive analysis of 35 randomized controlled trials, Yeh et al. (2023) [135] evaluated the most effective augmentation strategies for clozapine-resistant schizophrenia. Among the interventions, ECT emerged as one of the top three approaches for improving overall symptoms, alongside mirtazapine and memantine. Notably, for addressing positive symptoms, ECT was identified as the most effective option.

Petrides et al. (2015) [80] conducted one of the most frequently cited studies on ECT augmentation in clozapine-resistant schizophrenia. In an 8-week, single-blind, randomized controlled trial with a crossover phase, ECT plus clozapine (N=20) was compared to clozapine monotherapy (N=19). Using a stringent response criterion (≥40% reduction in psychotic symptoms on the BPRS, CGI-severity <3, and CGI-improvement ≤2), 50% of the ECT group responded, while none in the clozapine group met this threshold. This well-designed study highlights the efficacy of ECT augmentation in CRS, though no significant benefits for negative symptoms were observed.

Conversely, studies by Melzer-Ribeiro et al. have raised doubts about the efficacy of ECT as an augmentation strategy for clozapine-resistant schizophrenia. In randomized controlled trial from 2017 [137], 23 patients with partial clozapine response were randomized to receive either 12 sessions of real ECT or sham-ECT. The study

found no significant differences between the groups in PANSS total scores or its subscales, indicating that ECT did not outperform sham-ECT in symptom reduction. Recently, subsequent double-blind RCT [138] further evaluated the effectiveness of 20 sessions of ECT compared to sham-ECT in CRS patients. In this study, 19 patients in the ECT group and 17 in the sham-ECT group completed the trial. Results showed that only one patient (5.26%) in the ECT group achieved a ≥50% reduction in PANSS total score, compared to none in the sham-ECT group. A similar proportion of patients in both groups experienced moderate improvements (≥20% but <40% reduction), while 42% of the ECT group and 47% of the sham-ECT group had minimal improvements of ≤10%. Moreover, increases in PANSS scores were observed in 26% of ECT patients and 23.5% of sham-ECT patients. The findings suggest that ECT may not provide a clear advantage over sham-ECT in CRS, as no significant differences were observed in total PANSS score reductions, subscale improvements, or specific symptom dimensions.

In light of the current evidence, ECT has emerged as a promising augmentation strategy for CRS, with most of studies reporting favorable outcomes, particularly for positive symptoms. However, some studies have failed to show a clear benefit over clozapine monotherapy, particularly in terms of negative symptoms. Furthermore, a subgroup of CRS patients may not respond to ECT, a phenomenon referred to as ECT-resistant schizophrenia, which remains a topic of ongoing debate. There is currently insufficient evidence to guide clinicians in selecting the optimal treatment for this subset of patients [139]. While ECT augmentation remains a promising option, further research is essential to validate its role in management of CRS.

Table 1 provides a comparative summary of selected clinical studies evaluating the efficacy and tolerability of ECT as an augmentation strategy in treatment- and clozapine-resistant schizophrenia. The table highlights differences in study design, patient populations, treatment protocols, and reported outcomes, illustrating both the therapeutic potential of ECT and the heterogeneity of existing evidence.

Table 1. Summary of selected studies on ECT augmentation in TRS and CRS

Study	Design	Sample Size	Patient population	Intervention	Outcome Measures	Main Findings
Grover et al., 2017	Retrospective	59	TRS, CRS	Clozapine + ECT (mean 13.95 sessions)	PANSS, BFCRS	63% of TRS patients and 69% of CRS patients responded to treatment (PANSS score reduction ≥ 30%); ECT relatively safe
Kim et al., 2017	Retrospective	7	CRS	Clozapine + ECT (mean 13.4 sessions)	PANSS	71.4% of patients achieved clinical remission (PANSS score reduction ≥ 20%); mean PANSS reduction 25.5%; no improvement in negative symptoms; no persistent adverse effects
Kim et al., 2018	Retrospective	30	TRS	Clozapine + ECT vs. clozapine alone (mean 14.9 sessions)	PANSS	Response rate by acute ECT 42.9% (PANSS score reduction ≥ 20%); statistically

						significant decrease of negative symptoms, but the effect size the lowest among PANSS total and subscale factors; no severe adverse effects
Petrides et al., 2015	Prospective, randomized, single-blind	39	CRS	Clozapine + ECT vs. clozapine alone	BPRS, CGI-S	Combined group had greater symptom reduction; ECT well tolerated
Kho et al., 2004	Open-label	11	CRS	Clozapine + ECT	PANSS	8 patients achieved remission (PANSS score reduction ≥ 30%); ECT well tolerated
Zheng et al., 2016	Meta-analysis	818	TRS	ECT + non-clozapine AP vs. AP monotherapy	PANSS, BPRS, remission rate	Adjunctive ECT superior to pharmacologic monotherapy; ECT relatively tolerable; some cases of memory imparirment and headache
Wang et al., 2015	Systematic review and meta-analysis	1394	TRS	ECT + non-clozapine AP vs. AP monotherapy	Multiple (including PANSS, BPRS)	ECT augmentation superior to monotherapy; higher frequency of headache and memory impairment in combination group
Braga et al., 2019	Pilot	14	CRS	C-ECT (10 sessions)	BPRS-PS, CGI	Gains achieved with the acute course of ECT sustained; well tolerated
Pawełczyk et al., 2014	Pilot	34	TRS + dominant negative symptoms	AP + ECT (mean 12.3 sessions)	PANSS, CDSS, CGI	58.8% response rate (PANSS score reduction ≥ 25%);

						greatest improvements in positive symptoms; smallest in negative symptoms; ECT relatively safe
Lally et al., 2016	Systematic review and meta-analysis	192	TRS	Clozapine + ECT (mean 11.3 sessions)	PANSS, BPRS, CGI	An overall response of 66%; adverse events reported in 14% of identified cases
Vuksan et al., 2018	Prospective, open-label	31	TRS	AP + ECT (mean 10.2 sessions)	Multiple (including PANSS, CGI)	Significant improvement in verbal memory and executive functioning; no worsening in other cognitive domains
Melzer-Ribeiro et al., 2024	Randomized, double-blind, sham-controlled	40	CRS	ECT vs. sham-ECT	PANSS, CDRS	ECT augmentation of clozapine tolerable but not more efficacious than sham-ECT

PREDICTORS OF RESPONSE

Several studies have investigated factors that may predict response to electroconvulsive therapy in TRS/CRS. Clinical, neuroimaging, neurophysiological, and genetic markers have been proposed as potential predictors [140]. Findings from Chanpattana & Sackeim (2010) research [141] involving 138 patients with TRS suggest that younger age, shorter illness duration, absence of comorbid substance use disorder and cognitive impairments, fewer failed treatments, and the presence of prominent positive symptoms are associated with better outcomes. Negative symptoms, on the other hand, predict poorer outcomes [141,142]. In contrast, Chan et al.'s (2019) analysis [37] of 50 patients found no clear association between treatment response and factors such as age, sex, duration of untreated illness, or prior clozapine failure. While these findings provide useful insights, the connections remain inconsistent, emphasizing the need for further research to better understand predictors of ECT response.

ECT FREQUENCY AND RELAPSE PREVENTION

Although ECT is effective in inducing remission, its effects are often transient, with many patients experiencing a return of psychotic symptoms after treatment is abruptly discontinued [143–146]. Relapse rates within one year can reach as high as 63.6%, with the majority of recurrences occurring within the first six months [133,145,147,148]. One study found a median relapse-free period of 21.5 months following acute ECT [148]. Factors that increase the risk of symptom return include a history of multiple psychotic episodes, higher post-ECT BPRS scores, and a greater number of ECT sessions [149].

One approach to reduce the risk of relapse after initial ECT (index ECT) is continuation or maintenance ECT (C/M-ECT) [150,151]. Continuation ECT (C-ECT) is administered after the acute phase to prevent relapse within the first six months, while maintenance ECT (M-ECT) is used to prevent recurrence of symptoms after six months of remission [152,153].

Maintenance ECT has been shown to maintain clinical remission and improve the quality of life for patients with TRS, and therefore, its employment is recommended by many authors [43,57,80,146,154–164]. What is more, the procedure is reported to help reduce hospital re-admissions [150,159,165–167], with one study noting an 80% decrease in annual hospitalizations for chronic schizophrenia [167].

Combining antipsychotic drugs with M/C-ECT seems to be more effective than drug-only treatment [161,168,169]; for instance, in a study of Chanpattana (1999) [168], the use of neuroleptics alongside C-ECT resulted in a relapse rate of 40% within 6 months, compared to 93% for either C-ECT or neuroleptics alone.

There is no conclusive evidence on the optimal duration of M-ECT in schizophrenia patients [134,161,163]. However, Sackeim et al. (2001) [170] suggest that to prevent symptom recurrence, M-ECT should be administered at least every two months. To determine the appropriate frequency and titration of the treatment, it is recommended to monitor symptom severity using standardized scales such as PANSS or BPRS [159]. Further research is needed to establish clearer guidelines for the long-term administration of maintenance electroconvulsive therapy and its combined use with other treatments.

IMPACT ON QUALITY OF LIFE

The impact of electroconvulsive therapy on the quality of life (QOL) in patients with treatment-resistant schizophrenia or clozapine-resistant schizophrenia is complex, with improvements often occurring at a slower rate than symptom reduction [37]. While some studies indicate significant QOL improvements following ECT, particularly in domains such as physical capacity, health, and environmental satisfaction [171,172], others report no significant changes in overall QOL [37,173]. This variability highlights the multifaceted nature of QOL, which is influenced by a range of factors. Notably, the relationship between cognition and QOL is inconsistent. While improvements in cognition have been linked to better QOL in some studies [174], other research suggests that cognitive gains may sometimes result in lower QOL scores, potentially due to increased insight into the illness that may lead to feelings of depression or distress [37,175,176]. Furthermore, the severity of psychotic symptoms has shown weak or no correlation with QOL outcomes in some studies [177,178]. Additionally, factors such as re-admission rates have been found to negatively impact QOL, with patients experiencing more frequent hospitalizations reporting lower satisfaction with treatment and diminished quality of life [179]. Overall, while ECT has demonstrated efficacy in reducing symptoms in TRS/CRS, its effects on QOL remain inconsistent and appear to be influenced by a variety of psychological, clinical, and contextual factors.

IMPACT ON COGNITION

Cognition, alongside quality of life, is often discussed in the context of ECT. Around 80% of individuals with schizophrenia face significant neuro- and sociocognitive deficits [180,181]. At the same time, concerns about potential cognitive side effects remain a major consideration in the use of ECT [134]. Therefore, investigating the true relationship between ECT augmentation and cognitive function in schizophrenia is of particular importance.

Evidence indicates that ECT does not result in persistent cognitive impairments [146,182,183]. While temporary issues with cognition, such as disorientation of time or memory difficulties, may occur shortly after treatment, these effects are typically mild and resolve within days to weeks [85,97,128,130,184]. Notably, no significant changes in global cognition, as assessed by tools such as the MMSE, have been observed in well-designed trials [77,80]. In fact, several studies reported cognitive improvements following ECT [37,185], including enhanced verbal memory, executive functioning, and cognitive flexibility [121]. On the whole, while transient side effects related to cognition may occur, the long-term cognitive profile of ECT appears favorable.

ADVERSE EFFECTS

Like any treatment, ECT augmentation in TRS/CRS is associated with potential side effects, aforementioned cognitive impairments being one of them. Among identified studies, headaches [35,85,127,128,134,138,169] and indeed mild, transient cognitive impairments (particularly affecting memory) [35,85,128,130,138,169] were mentioned most commonly. Other frequently reported adverse effects include nausea [127,128,134,138] and prolonged seizures [130,186,187]. Additionally, cardiovascular manifestations like risen blood pressure, tachycardia, or bradycardia were highlighted in a few studies [130,186,188,189]. Less commonly recorded adverse effects include delirium [37,130], muscle soreness [128], drowsiness [138] and dizziness [138]. Importantly, most undesired events were manageable with conventional treatments. Furthermore, many studies found no evidence of persistent or serious adverse effects following ECT [19,21,77,80,97,127,133,146,159,163,190,191]. Based on the findings of Lally et al.'s meta-analysis, side effects may occur in up to 14% of cases, highlighting the relatively low incidence of adverse reactions to ECT augmentation in the discussed population [118]. These results suggest that incorporating ECT in TRS/CRS treatment is relatively safe and well-tolerated, with adverse effects being uncommon and generally manageable.

5 DISCUSSION AND LIMITATIONS

Treatment-refractory schizophrenia, particularly when unresponsive to clozapine, is characterized by high disability rates, frequent hospitalizations, and substantial financial strain, all of which create significant challenges for patients, their families, and healthcare providers. Managing clozapine-resistant cases is demanding. Limited evidence for the effectiveness of pharmacological augmentation and an increased risk of adverse effects from polypharmacy underscore the need of seeking alternative treatment modalities.

Electroconvulsive therapy has shown promise in augmenting antipsychotic treatments, particularly clozapine, with studies consistently reporting superior symptom reduction and cost-effectiveness compared to pharmacological monotherapy. ECT appears to be particularly effective in alleviating positive symptoms of schizophrenia, while its impact on general or negative symptoms may be less pronounced. Continuation or maintenance ECT further shows potential in reducing relapse rates and sustaining symptom remission. Importantly, ECT augmentation seems to be generally well-tolerated, with adverse effects such as headaches and mild, transient cognitive impairments being rare and manageable.

The conclusions of this review are generally consistent with previous research. Nevertheless, there are several limitations and the interpretation of the current findings requires caution. The literature on ECT augmentation in clozapine-resistant schizophrenia provides limited high-quality evidence, as only a small number of large, well-designed randomized controlled trials have been conducted. Many analyzed studies involved small samples, single-center designs, or lacked blinding, increasing the risk of bias. Moreover, the available evidence is marked by notable methodological variation across studies, including differences in patient selection, response criteria, concurrent therapeutic interventions, electrode placement, treatment frequency, and total number of sessions, which may also contribute to the differing conclusions reported in some studies. That heterogeneity limits the ability to adequately compare the results. Finally, the current work synthesizes findings narratively and without advanced statistical or visual synthesis, which constrains the ability to precisely estimate the strength of the provided evidence.

6 CONCLUSIONS AND FUTURE RESEARCH PERSPECTIVES

This review integrates current clinical data on ECT augmentation in clozapine-resistant schizophrenia and highlights unresolved aspects of its implementation.In summary, ECT represents a valuable therapeutic option for clozapine-resistant schizophrenia, yet its use should be guided by individualized risk-benefit assessment and further supported by high-quality clinical evidence.Future research should aim to:

- conduct large-scale, well-controlled trials assessing the short- and long-term efficacy and safety of ECT-clozapine combination;
- identify clinical or biological predictors of ECT response in CRS patients;
- determine the optimal frequency and duration of maintenance or continuation ECT;
- evaluate cognitive and functional outcomes over time;
- assess cost-effectiveness and quality-of-life benefits;
- and address persistent misconceptions about ECT through public health communication.

DISCLOSURES

AUTHORS' CONTRIBUTIONS

Conceptualization: Aleksandra Zagajewska; methodology: Aleksandra Zagajewska, Magdalena Cyrkler; analysis and investigation: Aleksandra Zagajewska, Aleksandra Giba, Aleksandra Krygowska; resources: Aleksandra Zagajewska, Aleksandra Giba, Aleksandra Krygowska, Aleksandra Reda; data curation: Aleksandra Zagajewska, Aleksandra Giba, Michał Wąsik; writing – original draft: Aleksandra Zagajewska, Aleksandra Giba, Aleksandra Krygowska, Michał Wąsik, Dorota Słupik, Aleksandra Reda; writing – review and editing: Aleksandra Śledziewska, Magdalena Cyrkler, Kamila Sieradocha; visualization: Michał Wąsik, Dorota Słupik; supervision: Aleksandra Zagajewska; project administration: Aleksandra Zagajewska, Aleksandra Śledziewska

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CONFLICTS OF INTEREST

Authors have no conflict of interest to declare.

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