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Electroconvulsive therapy as an adjunctive treatment for clozapine resistant schizophrenia

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Thesis

**ELECTROCONVULSIVE THERAPY AS AN ADJUNCTIVE TREATMENT FOR
CLOZAPINE RESISTANT SCHIZOPHRENIA**

by

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ABSTRACT

Schizophrenia is a psychotic disorder that affects millions of people worldwide. Modern treatment options involving antipsychotics have improved outcomes, but a significant portion of those affected show insufficient reduction in their symptoms. Electroconvulsive therapy is a promising adjunctive therapy to resistant cases and has been shown by several studies to be significantly more effective at reducing the symptoms of schizophrenia, with minimal side effects. To date there have been very few randomized clinical studies, with most having been performed with small sample sizes.

This proposed study is ambitious in its scale of both recruitment of subjects, as well as its aim of following the patients for six months after the treatments. This will be performed to better understand not just the efficacy of ECT on reducing symptoms of schizophrenia, but also the therapeutic duration. This will be performed with the aim of developing better maintenance programs and reducing the relapse rate that is so detrimental to the schizophrenia community.

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LIST OF ABBREVIATIONS

BRPS.....	Brief Psychiatric Rating Scale
CBT.....	Cognitive Behavioral Therapy
CGI.....	Clinical Global Impression of cognition in schizophrenia
CRS.....	Clozapine Resistant Schizophrenia
DSM.....	Diagnostic and Statistical Manual of Mental Disorders
ECT.....	Electroconvulsive Therapy
EEG.....	Electroencephalogram
HAM-D.....	Hamilton Depression Rating Scale
IRB.....	Institutional Review Boards
ITT.....	Intent to Treat
LOCF.....	Last-Observation-Carried-Forward
MMSE.....	Mini-Mental Status Exam
PANSS.....	Positive and Negative Syndrome Scale
TRS.....	Treatment Resistant Schizophrenia

INTRODUCTION

Background

Schizophrenia is a debilitating psychiatric disorder that affects millions of people worldwide. For a person to be diagnosed they must meet criteria established by in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) as presenting with at least two of the following symptoms: delusions, hallucinations, disorganized speech, disorganized movements, or negative symptoms for at least one month, and the symptoms must cause social or occupational dysfunction.²

The symptoms of schizophrenia fall into several different clusters including positive symptoms, negative symptoms, cognitive deficits, and comorbid conditions that together lead to social and occupational dysfunction.²⁴ Positive symptoms are the symptoms that are associated with the disease and include delusions, and hallucinations. Negative symptoms are associated with a decrease in motivation, blunted affect, decreased verbal communication, and a general withdrawal from interactions with society. Cognitive deficits involve decreased attention and memory, and poor insight. Poor insight can lead to treatment complications because if a person doesn't recognize that they have a disease then they can be noncompliant with therapy. Comorbid conditions include anxiety and depression syndromes, as well as there is a high rate of substance abuse in people with schizophrenia.

The current treatment paradigm consists of relying on first or second-generation antipsychotics. Antipsychotics are very effective in some cases at alleviating the positive symptoms of schizophrenia but there are currently not very good treatment options for

the negative symptoms, or the cognitive dysfunction. Even with the success of currently pharmacotherapies there is still a significant portion of the population that is diagnosed with Treatment-Resistant Schizophrenia (TRS). TRS is defined as failure of two different trials of antipsychotics over the course of 6 weeks each to reduce the symptoms of the disease.¹⁷ There is one second-generation antipsychotic that is reserved for the treatment of TRS, clozapine. Clozapine is the most effective antipsychotic for treating schizophrenia, but it can produce life-threatening side effects in some people, including leukopenia, thrombocytosis, agranulocytosis, which is why it is reserved for TRS.²⁵ Unfortunately, many people's disease is also resistant to clozapine and they are diagnosed with Clozapine-Resistant Schizophrenia (CRS). For these cases additional non-antipsychotic drugs can be administered to treat specific symptoms such as a lithium as a mood stabilizer, or an antidepressant such as a SSRI.¹² Electroconvulsive therapy (ECT) can also be administered to a clozapine regimen as an adjunct therapy in situations where patients are not responsive to combination pharmacologic therapies.

ECT is one of the oldest treatment options for schizophrenia but has somewhat fallen out of favor due to a stigma associated with it that derives from its early, and sometimes barbaric history. Modern ECT protocols have changed dramatically from the past currently utilizing anesthesia, so the patient doesn't feel any discomfort during that procedure, and virtually eliminating any physical trauma that was sometimes associated with past protocols. Today the most common immediate side effects being headaches, nausea, muscle aches, and short-term disorientation and confusion. Impaired memory is the most common long-term side effect, which usually resolves itself days to weeks after

treatment.²⁶ Current research has found that despite its reputation that it might be the most effective treatment for TRS and CRS, and that it should be adopted more readily as standard of care.

Statement of the Problem

Despite the relative success of modern schizophrenia treatments, based on first and second-generation antipsychotics, there are limitations that must be accounted for and remedied. Antipsychotic regimens are most successful at treating the positive symptoms associated with the disease such as auditory and visual hallucinations, and delusions which are critical to control in the acute phase of the disease, but several studies have found that Treatment-Resistant schizophrenia (TRS) occurs in approximately 30% of individuals.¹⁷ The current standard of care for those afflicted with TRS is clozapine with a 40% response rate of reducing symptoms significantly, but current data shows that 12-20% of these patients don't respond effectively to clozapine and are diagnosed with Clozapine-Resistant schizophrenia (CRS).²⁷ Electroconvulsive therapy (ECT) has been shown to be an effective adjunctive therapy with clozapine for TRS and CRS but is currently being underutilized due to negative perceptions by patients, providers, and a lack of resources to actually meet potential demand.²³ Most of the data on the efficacy of ECT is derived from meta-analysis of smaller studies. A larger, blinded study into the efficacy of ECT must be performed, and those patients should be followed the treatment to determine the duration of the therapeutic effect.

Hypothesis

ECT in conjunction with clozapine will result in decreased symptoms of schizophrenia when compared to clozapine monotherapy in those afflicted with CRS, and that the benefits of the procedure will continue after the treatments have concluded.

Objectives and specific aims

Despite modern advances in the treatment of schizophrenia it is still considered to be one of the most devastating diseases. The current standard of care relies on pharmacologic treatment with antipsychotics and psychotherapy. There currently is a significant percentage of the population that is unresponsive to current pharmacologic regimens resulting in significant individual and societal damage. ECT has shown promise as an effective adjunctive treatment for patients with CRS but is underutilized as a therapy do to negative conceptions that derive from archaic notions of ECT. There has not been a large-scale study that has been able to definitively show the efficacy of ECT in a controlled and blinded way, as well as follow-up to determine the duration of the therapeutic effect after the treatments have concluded. Specifically this study aims to:

- Determine the efficacy of ECT in patients diagnosed with CRS
- Determine the duration of therapeutic effect after therapy is completed

REVIEW OF THE LITERATURE

Overview

Schizophrenia affects millions of people world-wide and is considered one of the most debilitating, and costly to both the individual and their community. It has a global prevalence of roughly 0.28%,¹ affecting men more than women, and generally arises during the late teens or early twenties. It is a devastating disease that has an annual cost of \$150 billion in the US.⁶ In addition to the monetary cost there is a dramatic human cost as well with an average decreased life expectancy of 15 years, with a 5-10% increased rate of suicides.⁶

Symptomology of schizophrenia

Schizophrenia is characterized by the DSM-V (Diagnostic and Statistical Manual of Mental Disorders) as presenting with both positive symptoms, negative symptoms, and cognitive impairment.

Positive symptoms are what are most associated with schizophrenia such as delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior.² Hallucinations can be auditory, the most commonly reported, visual, somatic, and/or olfactory/gustatory.⁴

Negative symptoms are a spectrum of symptoms that are associated with a decrease or complete absence of normal behaviors associated with motivation, interest, and expression. Negative symptoms are composed of five features: blunted affect, alogia

(lack of speech), avolition (decreased of motivation), withdrawing from social interaction, and anhedonia (reduced experience of pleasure).³

Cognitive impairment is a core component of the debilitating nature of schizophrenia. Global dysfunction is common with different aspects of cognition, affected, such as attention, working memory, verbal learning, flexible thinking, and self-control.¹⁵ These deficits often begin to take effect before the first acute psychotic event. Some studies have found that treatment with atypical antipsychotics can improve some of the symptoms of cognitive impairment, but the results are moderate at best.¹⁵

Schizophrenia tends to present in late adolescence and early adulthood. While the course of the disease can vary from one individual to another traditionally it is thought to follow three phases: prodromal, active, and residual. The prodromal phase is composed of a series of symptoms that can include cognitive impairment and mood changes. Cognitive impairments can manifest as deficits in memory, attention, concentration, and a lack of interest in school, while mood changes can present as depression, irritability/anxiety, anger, and changes in sleep patterns.⁷ The symptoms of the prodromal phase can be subtle and occur over time, so it is not common for a patient for the disease to be diagnosed in this stage. From there patients can enter the active or acute phase of the disease. This is the phase most associated with psychosis and is when positive symptoms, such as hallucinations, delusions, and disorganization, will manifest.⁷ If the patient does not receive treatment for their disease, then they can remain in this phase, often resulting in very poor person and social outcomes. If the patient does receive treatment and they are receptive to the therapy, they can enter the residual phase

which is where the positive symptoms are better controlled or completely subside. It is important to note that even with well controlled positive symptoms there are currently few effective treatment options for negative symptoms, and cognitive impairment. Poor insight can lead to nonadherence of a patient's treatment regimen and results in high relapse rates, even when treatment has been discontinued for a short duration.²⁸

Pathophysiology of schizophrenia

While the pathophysiological cause of schizophrenia is not well understood, there are several hypotheses that attempt to explain the mechanisms of the disease. The most commonly proposed mechanisms involve the dysregulation of dopamine and glutamate, with many researchers also believing that serotonin contributes.^{8,16}

Dopamine is a neurotransmitter that is strongly associated with the striatum, the reward center of the brain, and is associated with learning and memory. The theory is that increased signaling of dopamine -- through increased production of the neurotransmitter, increase in the number of receptors, or through increased receptor binding -- can lead to the positive symptoms commonly associated with schizophrenia. This theory is supported by the observation that amphetamine use causes increased dopamine release in the brain and can produce psychotic symptoms in people not afflicted with the disease, as well as exacerbating the positive symptoms in those previously diagnosed with schizophrenia.⁸ The current standard of care for the treatment of schizophrenia is through the administration of antipsychotic medications many of which are dopamine receptor antagonists.⁸

Glutamate is the predominant excitatory neurotransmitter in the brain, and it is thought that decreased production of the neurotransmitter, or the receptors could be a cause of the negative symptoms. There have been several studies performed that found that glutamate antagonism can lead to positive, negative, and cognitive symptoms in both humans and animal models.⁸ Currently, there are no efficacious treatment options for the glutamate hypothesis. Glutamate is globally important for neuroregulation, and it is theorized that dysregulation of specific areas of the brain are responsible for the symptoms of disease.⁸

Serotonin is known to be involved in the modification of dopamine transmission, and with decreased serotonin levels the dopamine system could become hyperactive. There are several postmortem studies that suggest an increase in the 1A receptors and a decrease in 2A receptors in schizophrenia, but other imaging studies refute this theory.¹⁶ More research is currently needed to elucidate the role of serotonin in the disease.

Treatment of schizophrenia

Treatment for schizophrenia is currently being actively researched and while the efficacy of the treatments varies from patient-to-patient, psychiatry has advanced from the days when people would be relegated to a life in an asylum. Treatment options fall into three main categories: nonpharmacological therapy, pharmacological therapies, and augmentation/combination therapies.

The foundation of nonpharmacological treatments is psychotherapy with the most studied being cognitive behavioral therapy (CBT). CBT was originally developed to treat

depression and anxiety and is based on the theory that a person's thoughts, feelings, and behaviors are all linked, and that the severity of symptoms can be reduced through learning coping mechanisms. CBT has been used to help treat patients with schizophrenia by attempting to develop a relationship based on trust where the patient and the therapist can explore the patient's symptoms and normalize the experiences. There have been some metanalytic studies that have been performed that have found improvement in positive symptoms, negative symptoms, and social functioning, while other studies that found that there is only moderate improvement seen in positive symptoms.⁹ One of the most significant advantages for CBT is that by establishing a trusting relationship the therapist is able to monitor the efficacy of the patient's therapeutic regimen and adjust as necessary.

Pharmacological treatments include two main categories first-generation antipsychotics also known as typical antipsychotics, and second-generation antipsychotics also known as atypical antipsychotics. While the exact mechanisms of antipsychotics is not currently known, it is thought that the typical antipsychotics, such as perphenazine, chlorpromazine, haloperidol, and chlorpromazine have relatively strong antagonistic effects for D₂ dopamine receptors and relatively low affinity for serotonin receptors.¹⁰ Atypical antipsychotics such as aripiprazole, risperidone, olanzapine, and clozapine have variable antagonistic effects for D₂ receptors, depending on the particular medication and high antagonistic effects on serotonin receptors.¹⁰ There have been several studies performed to investigate the difference in efficacy between typical and atypical antipsychotic medications with one of the most famous being the CATIE

(Clinical Antipsychotic Trials for Intervention Effectiveness) trials. In phase I of the trials the efficacy of atypical antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) were compared to that of perphenazine (a typical antipsychotic) and were found to have little difference in therapeutic effect.²⁹ In phase 2 of the trial the efficacy of clozapine was compared to other atypical antipsychotics (quetiapine, risperidone, olanzapine) and found that clozapine was significantly more effective at reducing symptoms associated with schizophrenia.²⁹ Clozapine usage in rare cases can result in life threatening side effects such as leukopenia, thrombocytosis, and agranulocytosis which is why it is reserved for patients that are diagnosed with TRS.²⁵ To monitor these effects a complete blood count must be performed weekly when initially beginning treatment with clozapine, which can eventually be reduced to every four weeks after one year of monitoring.¹²

When treatment is resistant to pharmacological and nonpharmacological treatments, it is suggested that only then should augmentation or combination therapy be attempted. Augmentation therapy can refer to nonpharmacologic therapies such as electroconvulsive therapy (ECT), or the addition of another class of pharmacologic such as a mood stabilizer like lithium to an already existing antipsychotic regimen.¹⁰ Combination therapy is when multiple antipsychotics such as a typical and an atypical, or multiple atypical antipsychotics, are used congruently to treat a patient. Combination therapy is less desirable due to the potential increased risks of adverse side effects.

For ECT the exact mechanism of action is not fully understood. Currently there are several hypotheses for a proposed mechanism, and they range from the induction of

genetic changes to transiently increasing the permeability of the blood brain barrier and several different proposed neurobiological changes that range from the upregulation and/or downregulation of several different neurotransmitters and receptors. Even though the exact mechanism is not known ECT is the oldest effective treatment for schizophrenia and has been used with varying degrees of popularity since the 1930's.

There are several different treatment algorithms for how a practitioner should approach the treatment of schizophrenia. The American Psychiatric Association in 2019 released their approved recommendation for treatment guidelines. The APA guidelines recommend that after the initial evaluation and diagnosis with schizophrenia the patient should be treated with an antipsychotic and monitored for side effects. If the patient shows improvement and the side effects are manageable then to continue the antipsychotic.¹¹ If the patient displays treatment-resistant schizophrenia, which is defined as positive symptoms being unresponsive to 2 different trials of antipsychotics for greater than 6 weeks each,¹⁷ or if the patient has an increased risk of suicide, then clozapine should be attempted.¹¹ ECT should be reserved for patients that are determined to have clozapine resistant schizophrenia and should be used as an adjunct with clozapine. The APA also recommends that psychotherapy and education services be utilized with the aim of increasing the patient's integration into society.¹¹

Existing research

ECT as a treatment for schizophrenia is actively being researched with many studies finding that it is an effective adjunctive treatment for the treatment of

schizophrenia. One attempt at determining the efficacy of the different treatment options was performed by A. Masoudzadeh et al. Their paper entitled “Comparative Study of Clozapine, Electroshock and the Combination of ECT with Clozapine in Treatment-Resistant Schizophrenic Patients” was published in 2007 and was an attempt at a blinded study that could measure and compare the efficacy of clozapine alone, ECT alone, and ECT plus clozapine on patients with TRS. This study was small with a total of only 18 patients studied, all selected from admitted patients in Zareh hospital in Sari, Iran, between May and November of 2006.²⁰

There were three groups each consisting of six patients. Each group was screened by gender, and subtype of schizophrenia, resulting in each group consisting of three males, three females, three paranoid schizophrenics, two disorganized schizophrenics, and one undifferentiated. One group was treated with clozapine and placebo ECT (consisting of sedation without induction of seizure). One group was treated with 12 sessions of ECT and received a clozapine placebo. The final group was treated with 12 sessions of ECT and was administered clozapine. All of the patients that were administered clozapine began with dosages of 200mg, which was increased as deemed necessary by a psychiatrist, and their dosage was ensured to be stable and appropriate for 8 weeks prior to beginning the study.²⁰ For the patients that were administered ECT they all received sessions three times per week for four weeks, resulting in a total of 12 sessions.²⁰

Response to therapy was evaluated using the PANSS (Positive and Negative Syndrome Scale) criteria,²⁰ and analysis of variance (ANOVA) was utilized to determine

significance.²⁰ PANSS was used to evaluate the patients at the very beginning of the study and was continued biweekly throughout the study to evaluate the patient's response to treatment.

The PANSS is a practitioner administered tool that includes 30 items rated from one (absent), to seven (extreme), resulting in a scale from 30-210.¹⁹ A score of 58 considered is considered mildly ill, 75 moderately ill, 95 markedly ill, and a score of 116 being "severely ill".¹⁹ A reduction in the PANSS score over the course of treatment denotes a reduction in disease severity. Over the course of 4 weeks if the score decreases by 26% it is considered minimally improved, 51% it is much improved, and 82% it is very much improved.¹⁹

The total mean PANSS scores at baseline before the study began were 96 for the clozapine group (23 positive and 32 negative), 99 for the ECT group (31 positive and 25 negative), and 99 for the combined group (33 positive and 26 negative). The differences in PANSS scores between the groups at baseline were not considered to be statistically significant.²⁰

After the study concluded the PANSS scores of the clozapine only group were reduced by 46% (96 to 52), 40% for the ECT only group (99 to 60), and 71% in the combination clozapine plus ECT group (99 to 29).²⁰ These results indicate that combination therapy with clozapine and ECT was statistically significant and was much more effective at reducing the symptoms of TRS than either of the individual treatments alone. Of note, the authors reported that there were no significant adverse effects reported by any of the patients.

This study has some significant limitations associated with it. The population size of the study was very small with only 18 participants, from only one hospital raising the question of generalizability. The patients were not followed up after the treatments concluded so there is no data on their outcomes after the treatments concluded.

While the study used a very small sample size, and only patients from one city in Iran the data definitively showed that ECT in conjunction with clozapine was significantly superior at treating the symptoms of schizophrenia when compared to either therapy alone.

It must be noted that the use of “sham” or placebo ECT is questionably unethical due to subjecting patients to the increased risks associated with the use of anesthesia without performing a procedure.

To evaluate the benefits of combined ECT and clozapine, when compared to clozapine alone, G. Wang et al. performed a meta-analysis of randomized controlled trials (RCT) entitled “ECT augmentation of clozapine for clozapine-resistant schizophrenia: A meta-analysis of randomized controlled trials” published in 2018.²¹ Large databases were utilized for study searches revealing 410 potentially relevant studies, of which 18 met the inclusion criteria of being RCTs. Of the 18, 17 were conducted in China and one was performed in the USA with a total of 1769 participants which were all diagnosed with TRS.²¹

Primary outcomes in the studies were measured using standardized scales such as PANSS or BPRS (Brief Psychiatric Rating Scale). Clinical outcomes were based on the intent-to-treat (ITT) and last-observation-carried-forward (LOCF).²¹

Clozapine dosages across all the groups ranged from 50-700mg per day with a median dosage of 337.5mg per day. ECT sessions ranged from 6-24 sessions with a median of 10.8 sessions over 4-12 weeks with a median of 5.8 weeks per study.²¹

Evaluating for early symptomatic improvement, 8 of the studies assessed the efficacy of the treatments in the first 1-2 weeks of their studies. In these studies, there was a reduction in symptoms of -0.54 standard mean difference (SMD) in the combined group (n=384) when compared to the monotherapy group (n=355) (Table 1).²¹

The superiority in symptom reduction continued for the combined group when comparing to the monotherapy group. As seen in figure 1, the post-ECT assessment (performed directly after the last treatment) the symptom improvement showed a SMD of -0.88 when comparing the combined group (n=386) compared to the monotherapy group (n=317). Even after the treatment concluded, the endpoint assessment performed 1-10 weeks after treatment (mean 5.3 weeks), showed a SMD of -1.44 for the combined group (n=646) when compared to the monotherapy group (n=589).²¹

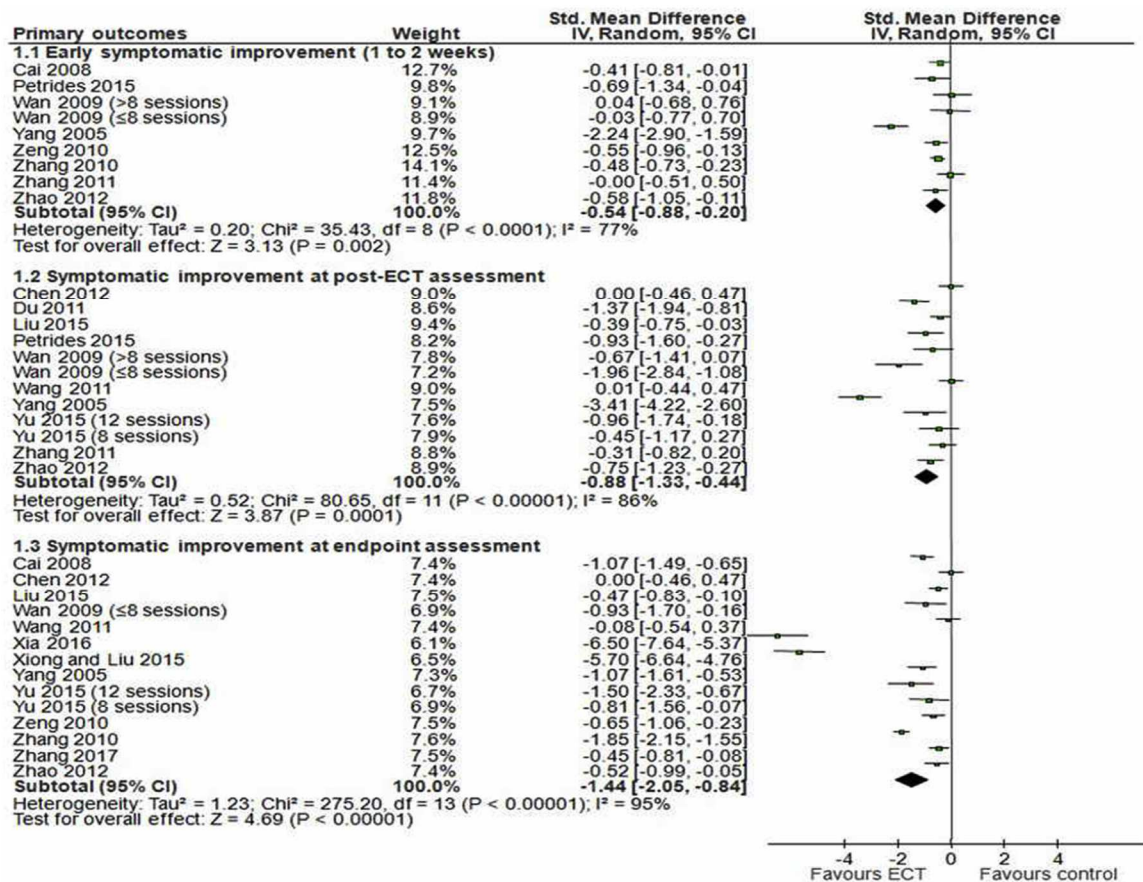


Figure 1. Global Symptomatic Improvement adopted from Wang et al.²¹

There were some adverse effects that were reported from the different studies.

The combined group reported an increase in headaches (14% in combined compared to 1.6% in monotherapy) and an increased prevalence in impaired memory occurring in 24.2% in the combined group and no incidences reported in the monotherapy group. The study did not indicate the duration, severity, or if the memory impairment resolved.²¹

This meta-analysis of RCTs found a significant improvement in the reduction of symptoms from the combination therapy of ECT and clozapine when compared to clozapine alone, and from a large sample size. This was consistent during treatments and

after the treatments had concluded, which is important because this could help reduce the relapse rate that is so common in schizophrenia.

There are several limitations of this study that must be addressed. Being a meta-analysis, it is comparing results from different studies with different methodologies automatically introducing an element of error. Additionally, 17 of the 18 studies that were analyzed were performed in China and that leads to potential issues of generalizability of the study.

Since the combination therapy of ECT and clozapine has been shown to be more effective than clozapine alone S. Ahmed investigated whether ECT can be just as efficacious with a different antipsychotic in “Combined use of electroconvulsive therapy and antipsychotics (both clozapine and non-clozapine) in treatment resistant schizophrenia: A comparative meta-analysis”.¹⁴

The author focused on 23 studies where 9 evaluated the efficacy of clozapine and ECT, and 14 where ECT was evaluated with other antipsychotics. Six of the studies were double-blind with ECT and placebo (two clozapine and four other antipsychotics), sixteen were open-label clinical trials (six with clozapine, and one utilizing other antipsychotics), and there was one retrospective case study included. All of the studies reported improvements in symptoms based on BPRS or PANSS scores.

A total of 1179 patients were included in the study, with 95 composing the clozapine and ECT group and the remaining 1084 composing the ECT and another antipsychotic group. The other antipsychotics that were utilized in the studies were flupentixol, chlorpromazine, risperidone, olanzapine, sulpiride, and loxapine.¹⁴

The meta-analysis in Figure 2 shows that clozapine and ECT were significantly more effective at treating TRS when compared to ECT and all other antipsychotics.¹⁴ This is not overly surprising because clozapine has been shown to be the most effective antipsychotic for the treatment of schizophrenia and is, thus, the standard of care for TRS, only being reserved for TRS due to the potential for agranulocytosis and neutropenia.

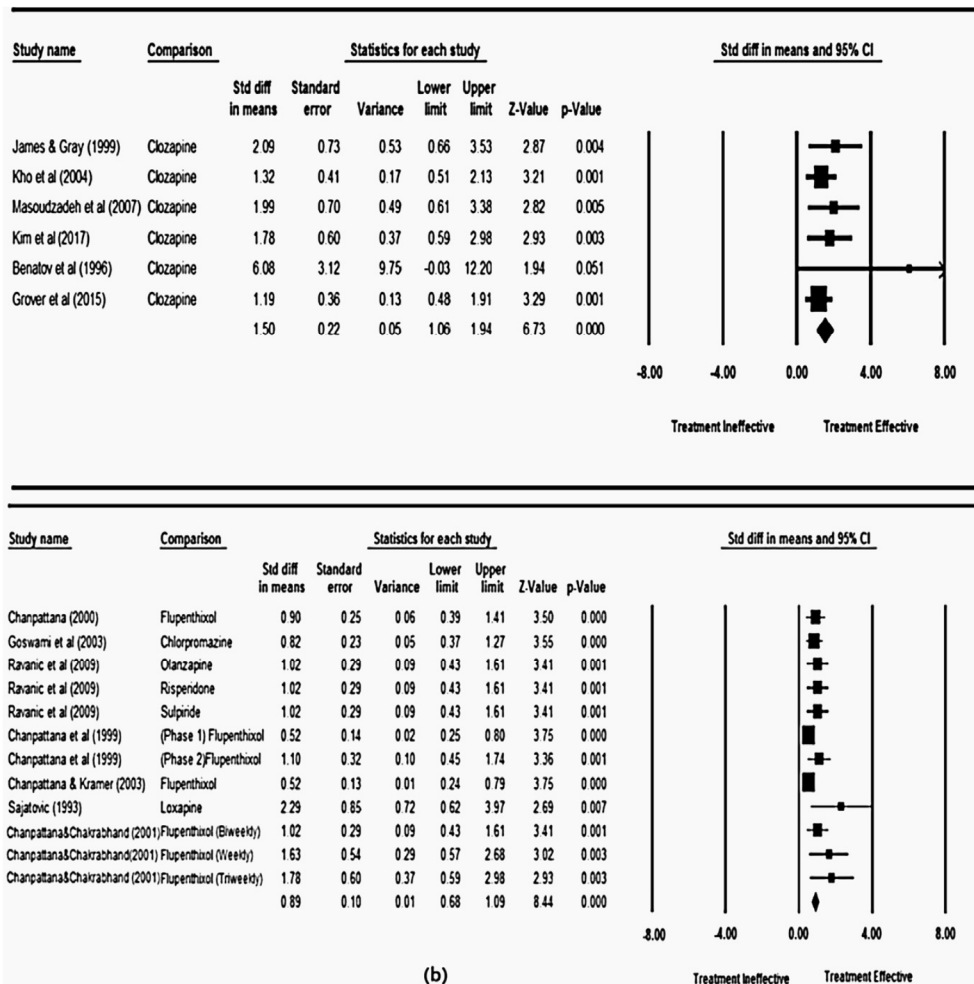


Figure 2. Forest plot (a) non-clozapine plus ECT, (b) clozapine plus ECT adopted from Ahmed et al.¹⁴

The study also addressed the potential for side effects with ECT which from prior studies have ranged from prolonged seizures, cardiovascular complications, headaches, changes in cognition, and increased blood pressure. The authors reported that there were no incidents of significant side effects reported from ECT.

This study is also limited by the fact that it is a meta-analysis, which is attempting to compare different studies with different methodologies. For instance, the different studies used either PANSS or BPRS to assess symptomatic improvement. The author attempted to account for this by converting all the BPRS scores to PANSS, which is adequate but not as strong as if all the studies originally had used the same scale.

The previous meta-analyses and the blinded study found that ECT plus clozapine was the most effective therapeutic option for the treatment of TRS but they all suffered from limitations. The meta-analyses were comparing different studies with different methodologies and the study performed by A. Masoudzadeh et al. was severely limited by a very small sample size. Dr. Georgios Petrides, MD attempted to perform a more thorough evaluation of the combination of ECT and clozapine in his paper entitled “Electroconvulsive Therapy Augmentation in Clozapine-Resistant Schizophrenia: A Prospective, Randomized Study”.²²

This study was conducted at The Zucker Hillside Hospital of the North Shore-LIJ Health System. It was an eight-week randomly assigned study with non-blinded treatment and blinded assessments. Two groups of patients that had been diagnosed with clozapine-resistant schizophrenia (CRS) were either assigned to the clozapine only group, or the ECT plus clozapine group. CRS for this study was defined as persistent psychotic

symptoms after a minimum of a 12-week trial of clozapine with a serum level greater than or equal to 350ng/mL.²²

For most medication studies, response criteria are set as a 20% reduction in symptoms but, for this study, the criteria were set as a reduction of symptoms greater than 40%. Patients were evaluated utilizing several different scales including the BPRS, CGI, HAM-D, Schedule for Assessment of Negative Symptoms, and the Treatment Emergent Side Effects Scale. Patients were evaluated at baseline before the treatment began, and weekly through the trial. Patients were required to undergo neuropsychological testing performed at baseline and week nine utilizing the Mini-Mental Status Exam (MMSE), the Rey Auditory Verbal Learning test, and six others to determine if there were any adverse effects related to ECT.

There were 92 patients that were screened and 54 met inclusion criteria. Of those 13 refused participation, 41 consented to enter the study, and 39 were selected and randomized: 20 for the ECT plus clozapine group and 19 for the control clozapine monotherapy group. They were matched according to variables such as sex, ethnicity, and psychopathology, shown in Table 1.²²

Table 1. Demographic and Clinical Characteristics of Patients with Clozapine-Resistant Schizophrenia adopted from Petrides et al. ²²

Variable	ECT Plus Clozapine Group (N=20)		Clozapine Group (N=19)	
	N	%	N	%
Sex				
Male	15	75	13	68.4
Female	5	25	6	31.6
Race/ethnicity				
Caucasian	11	55	10	52.6
African American	5	25	6	31.6
Hispanic	2	10	3	15.8
Other	2	10	0	0
	Mean	SD	Mean	SD
Age (years) ^a	35.70	2.27	42.78	1.82
Brief Psychiatric Rating Scale (BPRS) total score	45.68	1.87	46.42	2.55
BPRS psychotic symptom subscale score	16.58	0.86	16.89	0.9
Clinical Global Impressions-severity score	5.35	0.02	5.53	0.22
Hamilton Depression Rating Scale score	14.90	1.64	16.79	1.58
Mini-Mental State Examination (MMSE) score	22.60	1.2	22.2	1.0
Modified MMSE score	44.78	1.89	39.76	39.76
Clozapine level (ng/mL)	854.8	278.1	828.9	267.5

^aThe p value was calculated using Wilcoxon rank-sum test (p=0.03; W=269).

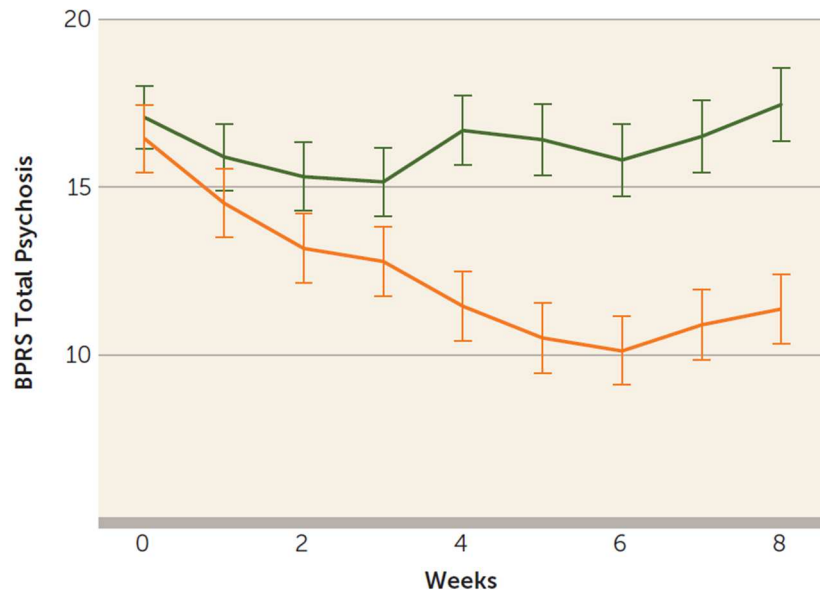
The clozapine group and the ECT group were administered clozapine and were brought to a stable dosage for 12 weeks before the trial began and were unable to change the dosage during the trial. Mean clozapine dosage for the ECT group was 525mg/day, and the mean dosage of the monotherapy group was 511.1mg/day.²² The differences between the dosages were not determined to be statistically significant.

Once the trial began, the ECT group were scheduled to be administered ECT treatments three times per week for the first four weeks, and biweekly for the subsequent four weeks. There was also a crossover trial that was performed where patients from the

clozapine monotherapy group were allowed to begin the ECT protocol at the completion of the eight weeks, for an additional eight weeks. The average number of ECT treatments were 15.8 for the ECT group and 14.3 for the crossover group.²²

Of the original 20 participants in the ECT group 17 completed the study and, of the original 19 in the clozapine monotherapy group, 16 completed the study.

Figure 3 shows that decrease of BPRS scores were significantly more for the ECT group when compared to the clozapine monotherapy group and that the reduction in symptoms occurred shortly after the trial began. 50% of the ECT group (10 of 20) met the criteria of a 40% reduction of symptoms, while none of the clozapine monotherapy group met criteria.²² The author notes that this was anticipated considering that all the participants in the study had been selected for CRT. He notes that if the response criteria had been an accepted 20% reduction in symptoms, then 12 of the 20 (60%) would have met criteria. Participants showed statistically significant improvements in symptoms by week 3 and this continued for the duration of the eight-week trial. After the original eight-week trial concluded, all 19 of the original clozapine monotherapy group consented to join the crossover group and, of those, 9 (47.4%) met the criteria of 40% reduction in symptoms.²²



^a The graph shows the changes in psychosis symptoms in the clozapine group (blue line; phase 1) and the ECT plus clozapine group (red line; phase 1). Treatment-by-time interaction: $F=5.38$, $df=8, 238$, $p<0.0001$. The degrees of freedom for mixed-models analysis were obtained using Satterthwaite's method. Error bars represent standard deviations.

Figure 3. Changes in BPRS Psychosis Subscale Results Over Time adopted from Petrides et al. ²²

As for side effects, one participant in the ECT group was removed from the study because of a recurrence of involuntary movements that the patient had experienced in the past. This raised concerns about potential seizure activity, but this was not corroborated by a subsequent EEG study. Overall, there were no significant side effects noted. Two other patients from the ECT group did have transient experiences of mild confusion, and treatment was postponed for a day, but not suspended.

Results of this study corroborated what other studies had found previously, that ECT is not only an effective treatment for patient that have CRS but also that it is safe with minimal side effects.

Limitations for this study were that first there was no ECT placebo group because the author notes that so called “sham” ECT studies are considered unethical. The sample size was small with only 39 participants but compared to other studies it is quite large.

Despite the efficacy of ECT and clozapine combination therapy access to treatment is unwanted or unavailable to many in the country. Why ECT is not utilized more regularly was addressed by Dr. Samuel Wilkinson, MD in the paper entitled “Barriers to the implementation of Electroconvulsive Therapy (ECT): Results from a Nationwide Survey of ECT Practitioners”.²³ The first part of this study was a qualitative interview that was performed on 17 ECT providers where their conversations were recorded, and then analyzed by coding the categories and subcategories discussed in the interview. The results from the interview identified 22 barriers to expanding ECT services and a quantitative survey was developed where ECT practitioners were asked to rank the barriers based on importance.

Results from qualitative interview suggested that, within hospitals, providers felt that hospital administration, stigma associated with the procedure, and lack of understanding of the treatment were the biggest barriers to expanding ECT services. Providers felt that ECT was not valued by hospital administration due to relatively low reimbursement rates when compared to other hospital procedures. Additionally, support staff such as anesthesiologists and nurses had other duties that would take precedence over the ECT procedures. Providers that had favorable experiences within a hospital setting had someone that realized the benefit of a fully functional and supported ECT program and advocated for the program resulting in dedicated space and staff and

resulting in a good reputation within the hospital and the surrounding community.

Providers also reported that due to a limited number of ECT services nationally there are few trained experts and opportunities for training. This lack of opportunities for treatment leaves many in the country without adequate education about ECT and there is a stigma that persists due to this lack of education.²³

The quantitative survey was sent to 690 ECT providers that were identified through the Medicare Provider Utilization and Payment Database. Respondents to the survey were 192 physicians at 142 hospitals, 81% of which were male (n=155). The top 8 ranking of the barriers for expanding an existing ECT program were: 1. Lack of physical space; 2. Stigma on part of patients; 3. Transportation; 4. Lack of administrative support and bureaucratic issues; 5. Lack of adequately trained ECT practitioners; 6. Potential side effects not acceptable to patients; 7. Lack of knowledge on part of referring providers; and 8. Poor reimbursement rates.²³ Most prominent barriers to initiating a new ECT program were: 1. Lack of well-trained colleagues and ECT practitioners; 2. Lack of a champion; 3. Lack of physical space; 4. Lack of administrative support and bureaucratic issues; 5. Lack of well-trained support staff (nursing); 6. Stigma on part of patients, 7. Poor reimbursement; and 8. Patient transportation and geographic barriers.²³

Lack of physical space was identified as a prominent barrier in both the interview and the survey and is believed to be tied to relatively low reimbursement rates. If space in a hospital was shared, it was often with surgical services which are considered more profitable and consisted of recovery areas like the PACU. This led to issues with scheduling such as limiting appointments to the early mornings and ECT patients were

often required to leave the shared space as surgical procedures completed. In hospitals where there is dedicated space for ECT procedures then scheduling is much easier and can continue throughout the day. The author suggests that this can be remedied by increasing reimbursement by insurance providers, which they admit will be difficult, and allowing for reimbursement for ECT in ambulatory surgical centers. The Centers for Medicare and Medicaid Services currently do not allow for reimbursement in ambulatory surgical centers.

Stigma associated with ECT is another important barrier to expanding services. The author reported that most media representations of ECT are negative or inaccurate, thus giving the general population misguided notions of what ECT is, and its efficacy for the treatment many disorders.

Evaluation of ECT providers by population showed that there is a mean of 2.97 and a median of 2.23 per million people nationally.²³ By state, the number of providers varies dramatically, ranging from 0 in Alaska to 12.8 per million in Maine. The greatest concentration of practitioners was in New England at 6.4 per million, and the lowest concentration was in the Central Southwest with 1.1 per million.²³

To increase the number of well-trained providers the author reported that of the 200 psychiatry residency programs in the US, 12 have produced almost one-third of the ECT physicians. He suggests that increasing the emphasis on ECT in the training process would produce more practitioners, increasing education to the general public and services provided while decreasing the stigma associated with ECT.

Limitation of this study are that it was a quantitative survey derived from a qualitative interview which is susceptible to the biases of the respondents. Compounding this is that only 28% of the physicians that were asked to fill out the survey responded.

In summation, the studies above found that the combination of ECT and clozapine was the most efficacious treatment option for patients with resistant schizophrenia.

Masoudzadeh et al. found that the combination of ECT and clozapine was more efficacious than ECT or clozapine alone, but the study was limited by the fact that the sample size was very small with only 18 participants. The meta-analysis of randomized control trials by Wang et al. confirmed the findings of Masoudzadeh with a much larger sample size. The study was limited by the fact that 17 of the 18 studies that were analyzed were performed in China leading to question of generalizability. Ahmed et al. attempted to understand if ECT and another antipsychotic would be as efficacious as ECT and clozapine. They had a very large sample size of 1179 participants and found that ECT and clozapine was significantly more efficacious than ECT and any other antipsychotic, but due to the inclusion of multiple different study designs there was the potential introduction of error. Petrides et al. designed a randomized controlled and blinded study that confirmed the original findings of Masoudzadeh with a larger sample size and found that there were very few negative side effects associated with ECT.

Despite several studies finding that the combination of ECT and clozapine was the most efficacious current treatment option of CRS Wilkinson found that there are currently many barriers preventing the ECT becoming more accessible to patients across the country. It was found that a stigma existed in the public based on an inaccurate

understanding of modern ECT treatment, as well as a lack of prioritization by most of the psychiatry residency programs (resulting in too few trained providers), and many hospital systems due to relatively low reimbursement rates.

METHODS

Study design

This study will be an expansion of Petrides et al.²² and will be a multicenter randomly assigned, controlled study with non-blinded treatment and blinded assessments studying the efficacy of electroconvulsive therapy (ECT) as an adjunctive therapy to a regular clozapine regimen compared to patients in a clozapine only monotherapy group. Participants will have a previous diagnosis of clozapine resistant schizophrenia (CRS) and will be monitored throughout the treatment which will span twelve weeks, as well as being regularly monitored through a six-month follow-up phase.

Study population and sampling

Participants will be recruited over a 24-month period from inpatient psychiatric facilities throughout the greater Boston region. They will have a previous diagnosis of CRS, defined as a failure to resolve the symptoms of schizophrenia after a minimum of 12 weeks with a blood level of clozapine greater than or equal to 350ng/mL.

Inclusion criteria will consist of a current diagnosis of schizophrenia utilizing DSM-V criteria, age 18-60, duration of illness for greater than two years, CRS defined as insufficient reduction of symptoms of schizophrenia for greater than twelve weeks after administration of clozapine with a minimum serum level of 350ng/mL, and a baseline PANSS score of greater than 75 indicating moderately ill.

Exclusion criteria include non-schizophrenia psychosis diagnosis (such as schizoaffective disorder, delusional disorder, or substance-induced psychotic disorder), receiving ECT treatments within six months prior to the study and a past medical history

of epilepsy, cardiovascular, pulmonary disease, or other condition that would be contraindicated for the use of anesthesia.

An estimated sample size of 50 patients would be required based on the sample size calculator from the UCSF Clinical and Translational Science Institute with an alpha of 0.05, a beta of 0.20, an even distribution of patients in both the experimental and control group, and the clinical outcomes of P_1 being 0.50 and P_0 being 0.10 based on the work of Petrides et al. This study will attempt to recruit 200 patients with active CRS in order to better capture statistical relevance, account for subgroups, and due to an anticipated attrition rate of at least 20%. Patients will then be randomly assigned to either the ECT plus clozapine group, or the clozapine monotherapy group. Attempts will be made to maintain heterogeneity with respects to age, gender, ethnicity, and severity of disease measured by PANSS.

Treatment

Once the groups have been randomly assigned then both will have to maintain a stable dosage of clozapine prior to beginning the study. If participants are also taking other medications, they will be permitted but must also have a stable dosage for the 12-week period before the study begins and must be maintained throughout the 12-week study. ECT will be administered three times per week for the first six weeks, and then will be reduced to twice a week for the remaining 6 weeks of the study.

Study variables and measures

The primary outcome will be the reduction of symptoms of schizophrenia measured by the PANSS (Positive and Negative Syndrome Scale). The PANSS is a

practitioner administered tool that includes 30 items: seven for positive symptoms, seven for negative symptoms, and 16 for general psychopathology. Each item can be rated 1-7 with the scale ranging from 30-210 with a score of 58 considered “mildly ill”, 75 “moderately ill”, 95 “markedly ill”, and a score of 116 being “severely ill”.¹⁹ The PANSS will be administered at the beginning of the trial to establish a baseline then weekly throughout the duration of the 12-week study. The PANSS will then be administered monthly after the completion of trial for six months to assess the duration of the therapeutic effect. Reduction criteria will be established as a reduction of 40% or more of symptoms of schizophrenia during the 12-week trial.

Secondary outcomes will be the duration of reduction of the symptoms after ECT is discontinued after the 12-week trial. The duration of the therapeutic effect will be established during the follow up phase by determining when a patient’s symptoms have increased by 20% after the conclusion of treatments. Additionally, patients will be monitored for adverse events and side effects to attempt to quantify their prevalence with ECT treatment.

Recruitment

Patients with CRS will be recruited from inpatient psychiatric facilities by psychiatrists throughout the greater Boston region and if they meet the inclusion criteria will be asked to join the study. Recruitment will occur over a 24-month period because it is believed that it will take a significant amount of time and resources to attain the sample size of 200 participants. Prospective participants will be informed of the potential benefits of the ECT therapy as well as potential side effects such as drowsiness,

confusion, headache, and nausea. Additionally, they will be screened for cardiovascular dysfunction, pulmonary dysfunction, severe neurological dysfunction because these can increase the risks associated with ECT and anesthesia. After the patient has been medically cleared and expresses an interest in joining the trial they will sign a consent form and will be registered for the study by one of the participating psychiatrists.

Data collection

Prior to beginning the therapy all participants will undergo evaluation of their symptoms utilizing the PANSS which will be administered by trained professionals and will establish their baseline. Each week throughout the study, and every month during the follow up phase, the PANSS will be performed, and the results will be recorded. To limit bias, the practitioners that are administering the PANSS will be blinded to which group the participants are in, and their evaluations will be recorded. The recordings will then be evaluated by third parties to ensure the PANSS is being administered and rated in the same manner for all of the participants.

Data analysis

Chi-square test will be performed on all categorical variables to determine statistical significance. The median and mean of the therapeutic duration (in months) will be calculated from the end of the 12-week treatment phase until a participant's symptoms increase by 20%.

Each facility will be responsible for its own data collection, which will then be reported. All of the data will then be evaluated by a statistician, after the conclusion of the study.

Timeline and resources

IRB submission and approval will occur in the fall of 2022. After approval patient recruitment and treatment intervention will occur at the different psychiatric facilities from January of 2023-January 2025. During the 12-week treatment phase each psychiatric facility will require psychiatrists to administer the treatments and monitor the patients throughout the trial, trained professionals to administer the PANSS who are blinded to which group the participants are in. Video recording equipment will need to be available at each facility to monitor the administration of the PANSS, and then those recordings will then be reviewed weekly by other trained professionals who are also blinded to ensure consistency of the administration of the PANSS.

During the six-month follow-up phase trained professionals who are blinded will be necessary every month for the administration of the PANSS to all participants. The protocol will remain the same as during the trial phase, except for the frequency being reduced to once a month.

Data analysis will occur at the conclusion of the study and will be compiled and analyzed by a statistician at Boston University Medical Campus.

Institutional Review Board

The protocol for the study will be evaluated for full board review by IRB at Boston University Medical Campus under INSPIR II, as well as IRB at all the participating facilities.

CONCLUSION

Discussion

This is an ambitious study that would attempt to perform one of the largest and most thorough evaluations of electroconvulsive therapy (ECT) as a treatment for clozapine resistant schizophrenia. If it is able to be performed it will offer a large amount of data on the efficacy of ECT as a treatment, as well as ascertain the therapeutic duration after conclusion of the therapy, which would be very helpful in adopting maintenance regimens that could help prevent the high levels of relapse that are associated with treatment-resistant schizophrenia.

This study is not without limitations. It is designed to be performed exclusively in the greater Boston area, where there are significantly more ECT practitioners and facilities than in most of the rest of the country. This could raise questions about the generalizability of this extensive of a treatment in other parts of the country. Additionally, studies involving psychosis are often hindered by a lack of compliance by the participants which is one reason that some many have such small sample sizes. However, a large sample size is essential to elucidate the potential benefits of ECT amongst patients with CRS. Another limitation of this study is the lack of a ECT placebo. It will be difficult to recruit and maintain participants to this study if it were to include a “sham” ECT procedure. This population is historically distrusting of many people, and the nature of the disease can cause paranoia. Developing trust and a good therapeutic relationship will be essential to prevent attrition. Additionally, it is often

considered unethical to introduce the risks associated with anesthesia to a patient without performing the treatment.

Summary

There is a growing amount of research that ECT is an effective adjunctive treatment for patients with CRS. With the incidences of TRS estimated to be 30% of all patients with schizophrenia,¹⁷ and clozapine resistance occurring in up to 20% of those patients,²⁷ it is important to seek improved therapeutic options, especially with how devastating the disease is to the individual when inadequately treated.

The proposed study would be one of the largest randomized controlled studies performed evaluating the efficacy of ECT in CRS. This would help determine the true value of ECT as a therapeutic regimen for a population desperately in need. Additionally, it would help determine the therapeutic duration posttreatment so that effective maintenance protocols could be developed to prevent relapse into the acute phase of schizophrenia and better manage symptoms long-term.

Additional research will be necessary to further elaborate about the specific mechanism of therapy for ECT and schizophrenia, as well as different protocols. This study proposes three sessions per week for six weeks and then two per week for an additional six weeks. It is possible that fewer treatments could be just as efficacious, or that increased frequency in treatments, or increased duration would be more efficacious.

Clinical and/or public health significance

ECT has shown that it is potentially a very useful tool in the treatment of schizophrenia, but to date it is underutilized nationwide. If this proposed study is

successful at illustrating the efficacy of ECT then it can potentially gain favor by psychiatric residency programs leading to an increase in the number of physicians that are trained with ECT, leading to the further adoption. This could lead to hospital administrators realizing the importance of ECT as a therapy and lead to an increased allocation of resources.

LIST OF JOURNAL ABBREVIATIONS

AJP	American Journal of Psychiatry
JCP	Journal of Clinical Psychiatry
JPR	Journal of Psychiatric Research
WPA	World Psychiatric Association

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