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Comparing Clozapine and Electroconvulsive Therapy in Refractory Schizophrenia

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by

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Abstract

Schizophrenia is a complicated problem that millions of Americans struggle with and unfortunately, about 50 percent of schizophrenics become resistant to medication. It is common practice to try multiple drugs to combat this resistance and many patients are placed on clozapine or given electroconvulsive therapy (ECT) as a last resort. Research has shown that many are not receiving the benefits of these treatments due to adverse effects, negative public opinion, and difficulty executing high quality research studies particularly when it comes to ECT. As a result, a significant number of patients that would benefit from these interventions are suffering with uncontrolled schizophrenia. More data is required on the use of these interventions as much of the research is low quality due to the unpredictable nature of schizophrenia and many patients not completing trials. This study analyzed the literature available for the efficacy and safety of both clozapine and ECT in order to understand its benefit versus risk in refractory schizophrenics. After analyzing the quality and results of many peer-reviewed studies, it was found that ECT and clozapine are both effective and safe for patients. Clozapine was shown to have more serious and long-term side effects than ECT, but both were shown to be effective. ECT was also shown to be effective for patients that were refractory to clozapine. Finally, the data showed combined therapy to be the most effective and I can conclude that it should be used far more often than is currently reported.

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Comparing Clozapine and Electroconvulsive Therapy in Refractory Schizophrenia

Schizophrenia effects an estimated .25 to .64 percent of the United States and despite being relatively low prevalence, it represents a staggering burden to both patient and society. (NIH, 2018) It consistently ranks in the top 15 leading causes of disability and has a staggering suicide rate of 4.9 percent. In addition, the economic costs are severely disproportionate to the pervasiveness of the disease in the United States. The direct healthcare costs amount to about $37.7 billion per year and when added to the estimated indirect costs such as unemployment and caregiver burden that number skyrockets to about $155.7 billion (AJMC, 2020). The purpose of this study is to evaluate and compare the efficacy and safety of a controversial but long-standing treatment for this disease known as electroconvulsive therapy or ECT to the gold standard medication for treatment clozapine.

Statement of the Problem

Electroconvulsive therapy was invented in the 1930s and used to treat various mental illnesses including depression, catatonia, and mania. The treatment involves sending electric current through the brain causing a seizure which stimulates the microbiome and increases metabolic activity. Though it replaced many unsafe and ineffective biological treatments at the time of conception, a stigma has been developed over the years due to injuries suffered and possible memory loss. Modern ECT is far more humane than that of the mid 1900s, but public opinion is still very low. Despite popularity issues, providers need to know if this treatment is both safe and effective or if medication alone is the better choice.

Research Question

Psychiatry is still a relatively novel science and many of its treatments can be considered controversial. Both new and old treatments rightfully undergo severe and unrelenting scrutiny

over the years. It is necessary we routinely evaluate and reevaluate treatments in order to choose the intervention that is best for our patients. This repeated evaluation of data and protocol not only ensures safety but provides providers with an arsenal of information to provide patients when they question their treatment plans. This article is meant to answer the question: Is electroconvulsive therapy both safe and effective in patients with schizophrenia that is refractory to treatment with medication?

Methods

A comprehensive review of literature was performed using multiple electronic databases including Pubmed, AccessMedicine, Clinical Key, Embase, and Google Scholar. The search was aided by keywords clozapine, ECT, Electroconvulsive Therapy, augmented, schizophrenia, refractory, efficacy, effectiveness, and safety. Studies were further limited to meta-analysis, randomized trials, control trials, head-to-head trials, prospective trials or versus placebo. Articles were excluded if they did not specifically deal with clozapine, ECT, or schizophrenia. Articles evaluating ECT as a treatment for depression or any other mental illness were excluded as well. The eight remaining studies were then evaluated on their trial process, strength of evidence, presentation of significant data, results, and limitations.

Literature Review

The effects of electroconvulsive therapy are well-documented in the treatment of depression, but less so in the case of refractory schizophrenia. The American Psychological Association's protocol for treatment of schizophrenia was updated in September of 2020 and recommends first quantitatively measuring severity of symptoms and "person-centered treatment" including both medication and non-pharmacological interventions. Initial treatment has a 1A evidence rating to treat with an antipsychotic medication. If schizophrenia is treatment

resistant, then clozapine is recommended (1B). Electroconvulsive therapy is then available as a second line treatment if patient is refractory to pharmacological interventions. However, the New York Office of Mental Health states that ECT can be used as either a primary treatment in cases of acute mania, severe depression, mood disorder with psychosis, and catatonia depending on severity of symptoms (2020).

Safety and Efficacy of Clozapine

Antipsychotics are a relatively new class of medication and so can be quite controversial. One of the first antipsychotics developed in 1951, chlorpromazine was initially used as an antihistamine until its sedative effects were noticed by psychiatrist Pierre Denker. Denker began to trial chlorpromazine on his patients with great success. Its calming effects were proven quite efficacious in treatment of psychosis and it was approved by the Food and Drug Administration in 1954 (Kane, 2010).

Since chlorpromazine, many additional medications have been developed or repurposed as anti-psychotics. These medications are classified as typical and atypical groups and initially replaced non-medical treatments for psychosis used at the time such as electroconvulsive therapy. (Ramachandraiah, 2009) Typical anti-psychotics consist of phenothiazines like chlorpromazine as well as butyrophenones like haloperidol and atypical antipsychotics which includes but is not limited to benzamides.

The medications that followed chlorpromazine were found to be relatively equal in efficacy but were uniquely prescribed based on both symptom and side effect profiles. haloperidol, for example, was found to be very effective for not only treating agitation, but hallucinations as well. Though less invasive than previous interventions such as frontal lobotomy and insulin coma, these medications all have a large profile of adverse effects. Butyrophenones

and phenothiazines produced at the time both had extrapyramidal side effects and could cause catalepsy or “a trancelike state marked by loss of voluntary motion in which the limbs remain in whatever position they are placed” (Mirriam-Webster, 2021). These side effects were so pronounced that the scientific community of the time believed that increased extrapyramidal side effects translated to increased efficacy (Ramachandraiah, 2009).

In 1958, the tricyclic antidepressant clozapine was first synthesized and found to be a very effective atypical anti-psychotic that had little extrapyramidal side effects and did not cause catalepsy in patient population studies. Many ground-breaking studies were performed and confirmed the efficacy of clozapine as well as the lack of neurological adverse effects of the drug. Unfortunately, in 1975 a Finnish research company found a steep increase in the blood dyscrasia agranulocytosis associated with clozapine use which caused it to be temporarily removed from the market.

However, studies involving clozapine continued and it was shown to be so much more effective than chlorpromazine in many diseases including refractory schizophrenia and Tourette’s syndrome in children that it regained favor in the scientific community. Despite its severe adverse effects, it is considered the gold standard medication for refractory Schizophrenia. In fact, many studies including many of those cited show that fear of side effects has made Clozapine underutilized in the psychiatric community.

The study Clozapine Use in a Cohort of First-Episode Psychosis by Doyle et al sought to determine both how often clozapine was utilized as well as its efficacy (2017). It did so by studying a sample of patients who suffered a first episode of psychosis between 1995 and 1999. Paper charts and electronic records were compiled and data points for age, gender, weight, blood work, diagnosis, admission, service, medications provided, etc. were recorded. The sample used

a total of 171 individuals in which 57.9 percent were male an average age was 29. Of the 171 individuals, twenty-eight were prescribed clozapine of which the most prevalent diagnosis in those that received clozapine was schizophrenia. Four of these individual's data were not included bringing the total followed to 24 patients

Twenty-one of twenty-four patients complained of documented adverse physical symptoms. These symptoms included 13 (54.1%) with weight gain, 12 (50%) with drooling, 9 (37.5%) complained of sedation. 8 (33.3%) with constipation, and 7 (29.1%) adverse effects were simply placed in an "other adverse effects" category. However, even more concerning health diagnoses were documented post-clozapine. 6 patients developed high blood pressure over 140/90 at some point during clozapine treatment. Two-thirds of the patients developed high cholesterol after initiation of clozapine therapy and 4 individuals had elevate ALT liver enzymes. Five of the 24 patients were diagnosed with diabetes. All but one of these diagnoses occurred post clozapine initiation.

In terms of efficacy, Doyle et al monitored through admissions to the hospital at a per year rate after clozapine initiation. This approach yielded positive results for the effectiveness of clozapine. Total hospitalizations decreased from 6.04 on average to .88 per year after patients began utilizing clozapine. The total days spent in hospital decreased from 257.8 to 42.6 post clozapine initialization. Which the study described as statistically significant using a Wilcoxon signed ranks test (z- -405, $p < 0.00$ for admissions per year and $z=-3.89$, $p < 0.00$ in days hospitalized).

The study points out a few issues in the discussion section. First, the population size was unexpectedly low given that 1/3 of schizophrenia patients have treatment resistance. They also admit to being unable to follow up on if patients. Furthermore, 11 of these participants had their

clozapine augmented with another medication such as a mood stabilizer, first generation or second-generation antipsychotic. This augmentation can potentially increase risk for adverse effects not caused by clozapine. In addition, many diseases that patients experienced over the 6 studies could not have been caused by clozapine at all, but it seems to be inferred. Finally, though the clozapine average dose was well into the normal maintenance dose range of 300-600 mg at 359.38 mg, The doses varied and had a standard deviation of 113.71. Most studies have shown that side effects are dose-dependent and this variable should be more accounted for.

The primary conclusion the authors drew from this study is that physicians are prescribing clozapine far less often than expected. He provides reasons such as physicians may have been reluctant to prescribe clozapine on an outpatient basis at time of data collection. In addition, clozapine guidelines did not come into effect until 2002 which is 3 years after this study's range. Finally, it is likely that clozapine commonly causes side effects, especially when it comes to weight gain and increased cholesterol.

A network meta-analysis or randomized trialed by Huhn et al compared 32 antipsychotics in trials both with placebos and "head-to-head." (2019) The meta-analysis consisted of all second-generation/atypical antipsychotics as well as benperidol, chlorpromazine, clopenthixol, clopenthixol [cis-isomer and trans-isomer], flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, molindone, penfluridol, perazine, perphenazine, pimozide, sulpiride, thioridazine, thiotixene, trifluoperazine, and zuclopenthixol [cis-isomer]. The analysis further increases its credibility by enlisting the assistance of 50 international schizophrenia experts cited later in the study.

Huhn et al primarily compared outcomes with use of the positive and negative spectrum scale (PANSS), brief psychiatric rating scale (BPRS), and other scales used by the studies. In

addition, the study looked at all-cause discontinuation, discontinuation due to inefficacy and responder rates (study defined), as well as change in positive, negative, and depressive symptoms, quality of life, and social functioning, measured by means of published rating scales. Side effects of all medications were evaluated including "measure of extrapyramidal side-effects, akathisia, weight gain in kg, 7% weight gain or more, prolactin levels, sedation or somnolence, QTc prolongation, and at least one anticholinergic side-effect" (Huhn, 2019). Once data was collected and processed the confidence of the evidence was rated as high, moderate, low, or very low depending on many factors such as study size and consistency. Then, of the 54,417 citations, 22,074 reports, and 2827 articles, the study excluded all but 550 reports 402 studies including a total of 53.463 participants. Average age of participants was 37-40 with an average illness duration of 11.9 years.

From the studies selected 218 with 40,815 contained usable results for change in symptoms. Twenty-six of the 32 antipsychotics tested were associated with significant improvement of symptoms. "The SMDs for drugs associated with significant improvement ranged between −0.89 (95% credible interval [CrI] −1.08 to −0.71) for clozapine to −0.26 (−0.39 to −0.12) for brexpiprazole" (Huhn et al, 2019). Of the drugs tested, clozapine, amisulpride, zotepine, olanzapine, and risperidone were most effective in reduction of symptoms. Other drugs were all similar, but equally less efficacious. Amisulpride, risperidone, olanzapine, paliperidone, and haloperidol were significantly more effective than many other drugs at reducing positive symptoms, but older drugs like clozapine have secondary efficacies reported far less often than the newer medications. For negative symptoms, lozapine, amisulpride, olanzapine, and zotepine and risperidone reduced negative symptoms significantly more than many other drugs. Zotepine and risperidone, though efficacious, were less so than the other drugs named. Other drugs

effectiveness in reducing negative symptoms were simply uncertain. Interestingly, only ten studies containing 3341 participants recorded quality-of-life data used in this study. When compared to a placebo with "SMDs ranging from −0.49 (95% CI −0.72 to −0.26) for aripiprazole to −0.18 (−0.34 to −0.02) for paliperidone." (Huhn et al, 2019).

In addition to efficacy, statistics for safety, side effects, and discontinuation were recorded. The data shows that 80 percent of participants discontinued the antipsychotics at some point for any cause. Of these 80 percent, more dropped out due to inefficacy (40%) than due to adverse effects of the medications (20%). Clozapine showed high evidence of severe weight gain of 0.36kg to 3.32 kg with a mean of 1.89 kg. The evidence also shows that there is a significantly higher risk for anticholinergic side effects in patients taking clozapine. Most other side-effects such as prolonged QTc and increased prolactin had very low evidence to show clozapine as a cause.

There were many controls, difficulties, and identified issues in this study. No individual items that were deemed to have a high risk of bias were used; however, 92 of the studies were rated as high for overall risk of bias based on allocation concealment, selective reporting, missing blinding for patient and personnel, missing outcomes a few other unexplained biases. Overall, the confidence in the evidence of most (75%) of the studies with placebos were considered low or very low. 92 percent of studies comparing two medications to each other were also deemed to provide evidence that was considered low or very low confidence. In addition, newer medications tended to provide date for positive or negative symptoms, while older medications did not provide these data points as frequently.

The study mitigated these issues as effectively as possible. A homogenous sample was taken from the data and inconsistency was moderated as best as possible. Interestingly, an

increase in placebo response was noted in the later years addressed in the study. The numbers had to be adjusted to accommodate this change. Data for positive and negative symptoms in older antipsychotics were published, but marked as likely less strong evidence or indeterminate of actual outcome.

Safety and Efficacy of Electroconvulsive Therapy

A study by Sinclair et al attempted to assess the benefits and harms of ECT for people with treatment resistant schizophrenia. In addition, they had secondary objectives seeking to compare unilateral versus bilateral, maintenance ECT, long or short course ECT, and if there is a differential response person to person. They performed a search based meta-analysis of randomized controlled trial studies found in the Cochrane Schizophrenia Group's Study-Based Register of Trials in September 9th, 2015 and August 4th, 2017. Their calculated risk ratio and the 95% confidence interval for binary outcomes and continuous date compared the means and estimated the mean difference with a 95% confidence interval. In addition, they used the GRADE framework to assess risk for bias and the fixed-effect model for analyses. This framework is used to judge bodies of evidence as a whole as either strong or weak. It also judges bias as either high risk, some concerns, or low risk.

15 studies were used with a total of 1285 participants diagnosed with treatment-resistant schizophrenia. 14 of these studies were considered high risk of bias due to blinding issues in either patient of personnel. They defined their outcomes of interest as:

"(i) clinically important response to treatment; (ii) clinically important change in cognitive functioning; (iii) leaving the study early; (iv) clinically important change in general mental state; (v) clinically important change in general functioning; (vi) number hospitalised; and (vii) death."

They used four comparisons for data including ECT plus standard care compared to sham-ECT with standard care, ECT plus standard care versus antipsychotic plus standard care, ECT plus standard care compared to standard care alone, and ECT alone compared to antipsychotic alone.

ECT plus standard care versus sham ECT plus standard care used two studies. One study focused on BPRS. It was labeled very low quality and concluded that there was no difference between the two. The other study measured number readmitted and clearly favored ECT over sham ECT (short term; RR 0.29, 95% CI 0.10 to 0.85; n = 25; studies = 1; low quality evidence). They then compared two additional studies on ECT plus standard care versus clozapine plus standard care. In the first study, no clear difference was found in clinically important response (low quality evidence). The second study found very low-quality evidence that ECT had a positive effect on short-term BPRS versus clozapine (MD ‐ 5.20, 95% CI ‐ 7.93 to ‐ 2.47; participants = 162; studies = 1).

ECT and standard care versus standard care alone were compared and more people that received ECT showed a positive clinically important response (medium term; RR 2.06, 95% CI 1.75 to 2.42; n = 819; studies = 9; moderate quality evidence). It also showed an increase in memory loss, but no change in acceptance of treatment or satisfaction. (Very low-quality evidence). The general functioning and BPRS were used to score end point outcome and found a decisively positive difference in scores that favored ECT (medium term; MD 10.66, 95% CI 6.98 to 14.34; n = 97; studies = 2; very low-quality evidence).

The author concludes that there is moderate quality evidence found and presented in this study to show that ECT has a positive effect on medium-term clinical response for those with medication resistant schizophrenia. Unfortunately, all other aspects of the study did not show enough evidence to state that adding ECT to standard care increases outcome or that ECT

outperforms sham ECT in this study. The author admits that the studies used did not contain the desired level or grade of evidence necessary and states the need for more "good-quality" evidence to be obtained before any true conclusion about the efficacy of ECT can be made.

Wang et al. (2018) performed a meta-analysis of control trials that used either clozapine or clozapine with ECT augmentation. The report begins by citing many previous studies that depict why clozapine is still the gold standard for schizophrenia that is refractory to medications as well as schizophrenia that is not refractory. The cited sources have revealed that clozapine is superior in both efficacy and side effect profile to traditional medications. It also states that despite this, clozapine is underutilized based on fear of its side effects of agranulocytosis. Serial blood-work has shown to greatly decrease the chance of morbidity and mortality caused by neutropenia or agranulocytosis, but still it is underutilized in therapy.

The study also gives a brief history of studies performed in the past comparing augmented therapy. These studies were labeled Chinese and non-Chinese in origin and the author states that few randomized control trials have been performed outside of China. This limited the author to a majority of Chinese trials. Though data is limited, the majority of trials have shown medication augmented with ECT is more effective than monotherapy alone.

The study compiled randomized control trials that reported efficacy, safety, or both when adding ECT to clozapine. Studies without data that could be analyzed and effectively incorporated into this study were excluded. The study used the PANSS or BPRS to measure overall psychopathology, but also measured secondary outcomes. These measured outcomes were as follows:

> 1) early symptomatic improvement (at 1–2 weeks), 2) study-defined response at post-ECT and endpoint assessments, 3) study-defined remission (using the definitions by

authors of included studies) at post-ECT and endpoint assessments, 4) specific response (⩾50% reduction in total PANSS or BPRS) and remission (⩾75% reduction in total PANSS or BPRS) at post-ECT treatment and endpoint assessments, 5) positive, negative, or general symptom scores assessed by PANSS or BPRS or the total scores of the Scale for the Assessment of Positive Symptoms and/or the Scale for the Assessment of Negative Symptoms (SANS) at post-ECT treatment and endpoint assessment, 6) patient-reported adverse events, 7) neurocognitive functioning, and 8) treatment discontinuation.

The study used various databases including PubMed, PsycINFO, Cochrane Library databases and Chinese databases (Chinese Biomedical database (CBM), China Journal Net and WanFang database). These were searched using both English and Chinese with various keywords. Three authors then independently extracted the data and various statistical analyses were performed once all data was collected. The statistical methodology was the Inverse-Variance method which compares multiple studies and calculates the weighted mean. In addition to the Inverse-Variance, standardized mean differences with 95% confidence intervals were reported and used. They then calculated the risk ratio.

The search yielded 254 English articles and 206 Chinese, but only 18 randomized control trials were used after extensive analysis to determine if they met study criteria. The 18 trials had 20 active treatment arms with an N=1769. Mean sample size was 88.5 and they lasted 4-12 weeks with 9.2 being the average. All participants had treatment resistant schizophrenia that had already failed at least 2 antipsychotics. The average age was 38.2 and dosages ranged from 50-800mg of clozapine in the medication only group and 50-700mg in the ECT treatment group. ECT treatment ranged from 6-24 sessions with a median of 10.8. In terms of quality, the studies were graded 16.7%, 43.3% moderate, 26.7% low, and 13.3% very low.

The data yielded for efficacy showed that the combined treatment was superior to clozapine. In early symptom improvement clozapine/ECT was shown more efficacious (2 weeks, 8 RCTs with 9 active treatment arms, SMD: 0.54, 95%CI: −0.88 to −0.20; I2 = 77%, p = 0.002). For overall symptom status after 4-12 weeks (average of 5.8 weeks) monotherapy was once again shown inferior to ECT augmentation (SMD: −0.88, 95%CI: −1.33 to −0.44; I2 = 86%, P = 0.0001). Two outlying studies were removes and still combined therapy's numbers were better in a statistically significant way. "Statistical significance changed to a statistical trend only for patients with failure to ⩾2 APs (P = 0.09), studies with male preponderance (P = 0.08) and electrode placement using bilateral (P = 0.06)." (Wang et al., 2018)

Meta-analysis was further broken down into positive symptom effects and found once again clozapine combined with ECT to be superior (SMD: −0.45, 95%CI: −0.68 to −0.22; I2 = 8%, P = 0.0001). The study also showed more instances of significant improvement defined as ⩾50% reduction in total PANSS in those with both therapies (RR = 1.61, 95%CI: 1.20–2.16; I2 = 0%, P = 0.002, NNT = 7, 95%CI: 3-∞). However, there was no definitive proof of increased incidence of remission when comparing the therapies.

The data for ECT-clozapine versus clozapine monotherapy was also processed revealing that two symptoms: memory impairment (RR = 16.10, 95%CI: 4.53–57.26; I2 = 0%, P < 0.0001, NNH = 4, 95%CI: 2–14) and headache RR = 4.03, 95%CI: 1.54–10.56; I2 = 0%, P = 0.005, NNH = 8, 95%CI: 4–50) were reported far more than clozapine alone. However, common clozapine complaints such as weight gain (RR = 0.61, 95%CI: 0.42–0.89; I2 = 0%, P = 0.01, NNT = 14, 95%CI: 8–100) and constipation (RR = 0.77, 95%CI: 0.61–0.99; I2 = 0%, P = 0.04, NNT = 14, 95%CI: 7–100) were significantly less common in ECT-clozapine therapy. All other symptoms including salivation, leukocytopenia, drowsiness, elevated liver enzymes,

nausea/vomiting, and tachycardia did not have a significant change in commonality (RR = 0.68–1.65, 95%CI: 0.22–4.27; I2 = 0%–41%, P = 0.05–0.74). Finally, there was no significant change in discontinuation rate due to all-causes.

The study states with confidence that ECT-clozapine combined treatment was superior to clozapine alone. The study states that despite many patients not responding to post and endpoint assessments, the data still showed favorable results in the most severe subgroup of those with schizophrenia. In terms of adverse reactions, ECT-clozapine patients did suffer headache and memory impairment. However, memory issues were reported as non-significant a week after therapy. Wang et al concluded these temporary symptoms to be significant of a generally safe and well tolerated side effect. Finally, they found no increase in other symptoms or discontinuation rates in general of the two therapies revealing they were likely similarly tolerated by patients.

The study identified 6 issues it faced in analysis. The first was differences in studies. Many studies differ in methodology, size, sampling, dosage, ECT technique, and random effects. Second, was a smaller sample size (n=1769) used after unusable dated was removed. Though this is considered a robust sample size (>1000), the author would like more data to further solidify the evidence. Third, the study being in China made access to non-Chinese patients for follow-up difficult. Also, none of the studies used the placebo of ECT known as sham ECT. The next issue identified was the fact that the mean duration of the studies was relatively short at 8-9 weeks. A longer study would be preferred for follow up and long-term data. Finally, the author believed that those performing the study should record more cognitive side effects of the ECT in their documentation.

Another study demonstrating the effects of ECT on hospital readmission in schizophrenic patients was performed by Ying et al in 2016 and recently published in 2021. This study examined the data recorded by Beijing Anding Hospital in China from January 1, 2016 to December 31, 2016. The study was limited to all patients with schizophrenia as their primary diagnosis and consent was received by either the patient or legal guardians prior to data use. Data collected included demographic information, diagnoses, length of stay (LOS), medications and other treatments, and other information related to the hospitalization. Other requirements for inclusion were patients that were post-hospitalization with a follow-up withing 3 to 6 months of discharge.

Patients were required to be hospitalized for over 24 hours to be eligible for this study and those that did not follow-up did not have their data used. The independent variable was described as receiving ECT or not. The study indicator was a binary yes or no in the three fields: the patient was admitted within 3 months, 6 months, or neither. Many variables could not be accounted for and 168 covariates such as age, sex, marital status, income, alcohol and tobacco use disorders, etc. were defined. Machine learning technology in the form of XGBoost was used to interpret results and predict the significance of variables. Chi-squared test was used to compare categorical variables and a t-test and Mann-Whitney test compared the continuous variables.

After removing ineligible participants, 2131 total patients were reviewed. Of these patients 886 (41.58%) received ECT. 642 ECT patients had follow-up visits within a t3-month period and 596 had follow-up visits within 6 months. Of the non-ECT group 457 had follow-ups in 3 months or less and 379 had visits withing 6 months. In addition, only 2 of the ECT patients received maintenance therapy for worsening symptoms. All patients were on some form of anti-

psychotic for this study. Type and dose of each anti-psychotic was recorded with demographic data. 48.43% of patients did not follow up at 3-months and 51.58% did not follow up at 6 months. Machine learning determined factors significant to failure to follow up were: income, alcohol abuse or dependence, LOS, medication use (paliperidone ER, haloperidol and perphenazine). Of these significant factors, age and duration of initial visit were determined to be by far the most significant factors.

Ying et al tried to mitigate the vast covariants by using a PSM or propensity score matching. This matched samples by certain factors such as medications. Prior to using PSM the data showed 11.37 percent of ECT group and 17.94% of the non-ECT group were readmitted within 3 months. In terms of 6-month hospitalization, 18.79% of the ECT group and 29.36% of the non-ECT group were readmitted within 6 months. Statistical analysis of this date showed significant differences between the two groups in readmission rates within 3 ($\chi2 = 3.100$, $p = 0.002$) and 6 months ($\chi2 = 4.000$, $p < 0.001$). The data was again processed after applying PSM technology and showed 66 (11.02%) in the ECT group and 62 patients (16.10%) in non-ECT group were readmitted within 3 months. 104 (18.24%) in the ECT group and 101 patients (27.37%) in non-ECT group were hospitalized again within 6 months. Again, a significant difference was still found for ECT versus non-ECT treatment and readmission in both the 3-month group's statistics ($\chi2 = 2.320$, $p = 0.02$) and 6-month statistics ($\chi2 = 3.320$, $p = 0.001$).

The data also showed an inverse relationship between the number of ECT treatments and the readmission rate. As number of treatments increased, the likelihood of readmission fell. This relationship continued until 9 total treatments and showed that more than 9 ECT sessions were not effective in further decreasing hospitalization. The study summarized the data by stating:

> In the 3-month cohort, the readmission rates within 3 months for the two groups were 8.4% (⩽9 ECT group) and 15.4% (>9 ECT group), respectively (p = 0.012). In the 6-month group, the 6-month readmission rates of the two groups were 14.6% (⩽9 ECT group) and 24.2% (>9 ECT group), respectively (p = 0.006). (Ying et al, 2021)

The study then compares its data and findings to other recent studies performed. Of the studies, Han et al. (2020) also showed that those who received 6-12 ECT treatments showed lower risk of hospitalization especially with schizophrenic patients. Goswami et al also showed 6-12 treatments of ECT significantly lowered readmission rates within 6 months of initial treatment. One study by Ma et al. did not disagree with the other studies but rather was unable to show statistically significant data to associate ECT and readmission. The author cites likely reasons to be different samples, rates of ECT utilization, and ECT treatment parameters including stimulation dosage, electrode placement, and number of treatments in the index course.

The author concludes that the combination of medication and ECT shows significantly better outcomes in terms of both 3 and 6-month readmission rates (p = 0.024 and p = 0.002, respectively). In addition, “Male, older age, being married, lower income, shorter inpatient length of stay (LOS), and receiving some specific antipsychotic medications, especially olanzapine, was significantly associated with risk of readmission” (Ying et al, 2021).

The author identified a few limitations of his study. The first limitation was the use of a single large hospital rather than multiple separate population samples. There is a chance that this hospital had some confounding factor to the overall data. Second, there were many patients lost to lack of follow-up which is unfortunately and issue with many psychiatric studies. Non-compliance with treatment plan and medication is a common issue among patients with schizophrenia. Another limitation was the fact that patient’s symptoms were not assessed or

recorded on initial discharge. Some patients could have felt more well overall than others upon initial discharge which could affect their reaction to treatment and overall wellness at home. The author also admits that some of these patients could have been admitted to other hospitals or treatment facilities and the study did not have the resources to follow-up at every possible hospital. Overall, this is another study that shows ECT as effective. As more and more studies of variable GRADES are performed, the evidence will continue to grow in strength.

Effectiveness of Combination Therapy

Petrides et al. (2015) performed a randomized single-blind study of traditional clozapine treatment versus ECT augmented clozapine treatment. The study as formatted as an 8-week random-assignment study in which one group was randomly assigned combined therapy and the other received clozapine only. All patients were classified as antipsychotic resistant and, in this case, resistant to clozapine as well. In addition, non-responders from the clozapine group received an open 8-week trial of ECT with the same schedule and procedures as the randomized ECT plus clozapine group.

Requirements for participation were age 18-60 with a minimum of 2 years duration of illness. Patients were also required to be resistant to at least 2 antipsychotics including clozapine and have a baseline BPRS score of at least four (which indicates moderate severity) in one of the four psychotic categories (hallucinatory behavior, suspiciousness, conceptual disorganization, and unusual thought content) or a combined score of at least 12 total on the BPRS. Women were required to take a pregnancy test and test negative prior to inclusion and also needed to be on an acceptable contraceptive for safety purposes.

Per the study “exclusion criteria were schizoaffective disorder; bipolar disorder; current affective episode; ECT within 6 months; history of epilepsy; severe neurological or systemic

disorder that could significantly affect cognition, behavior, or mental status (other than tardive dyskinesia or neuroleptic-induced parkinsonism); psychoactive substance dependence (other than nicotine or caffeine) within 1 month prior to entering the study; a score >18 on the 24-item Hamilton Depression Rating Scale (HAM-D); clinical determination that mood stabilizers that could not be discontinued were necessary; and pregnancy." Those with affective disorders and depression were excluded because it is already well documented that ECT has a positive effect on these patients. Data was measured by response rate in each group. A response was considered significant if it had greater than or equal to 40% improvement in psychotic symptoms, CGI severity of less than 3 and a CGI improvement of at least 2 points. Traditionally 20% is considered improvement, but the study chose 40% due to the complexity and increased effort that ECT requires.

The clozapine group remained on clozapine for at least 8 weeks without changing the dose. They were allowed additional antipsychotics and antidepressants as needed. Lorazepam and diphenhydramine were used to treat any anxiety, agitation, or insomnia. After the 8 weeks, if the patient had no response to clozapine, they were given ECT and placed in the combined therapy group as part of a crossover trial. As for the combined therapy, patients were given three treatments per week for the first week and 2 treatments per week for the remaining 4 weeks. If patient was decidedly in remission, treatment would be dropped to 1 treatment per week until 8 weeks had elapsed.

Patients were rated using BPRS, CGI, HAM-D, the Schedule for Assessment of Negative Symptoms, and the Treatment Emergent Side Effects Scale, and rating assessments were performed weekly. BPRS ratings in both the initial and final portion of the study were recorded in order to objectify findings. At initial assessment and week nine a focused neuropsychological

batter was performed to assess the neurocognitive effects of ECT. These tests included the standard and modified Mini-Mental State Examination (MMSE), the Rey Auditory Verbal Learning Test, the paired-word and story-recall measures subtests of the Randt Memory Battery, the letter-number span task, the Trail-Making Test, the Controlled Oral Word Association Test, the Competing Programs Test, and the Set Shifting Test.

The study used a combination of histograms, q-q plots, and the Shapiro-Wilk test to assess the distribution of continuous variables. To compare baseline continuous variables a t-test or Wilcoxon rank-sum test was used. A Chi-square test was employed for categorical variables. The rater reliability was assessed between those that performed the interviews and those who watched the videos and gave their ratings. The consistency intraclass coefficient between rating was 0.892 (95% confidence interval [CI]=0.783–0.948; F=17.5, df=28, 28, $p<0.0001$). The absolute agreement intraclass coefficient was 0.888 (95% CI=0.783–0.948; F=17.5, df=28, 28, $p<0.0001$).

54 patients met inclusion criteria, but 13 declined to participate. 39 individuals were randomly assigned clozapine (19) or combined therapy (20). Of the 20 assigned ECT and clozapine, 17 completed the full trial. Two dropped out and refused additional treatments and one was removed due to persistent involuntary movements. In the clozapine trial 16 of 19 participants completed the full trial. Three patients dropped out due to refusal to participate in the evaluation system. These three patients agreed to participate in the ECT combined therapy group instead.

Overall data showed that 10 of the 20 ECT augmented patients met the priori response criteria of 40 percent reduction in score while none of the clozapine group met this goal. Had the study used the traditional 20 percent reduction, 12 of 20 ECT patients would have met this goal

and still zero from the clozapine alone group would qualify. If they increased the threshold for response to 50%, 60%, or 70%; then 9, 6, or 3 subjects respectively would have met the response criteria. The study confidently states that there is a significant decrease in BPRS-psychosis subscale and CGI severity in those with ECT compared to clozapine alone. In addition, there were significantly less psychotic symptom subscale rating by week 3. This decrease in symptoms lasted for the full 8-week trial.

In the next part of the trial known as the crossover phase, the 19 patients in the non-ECT group underwent ECT after the initial 8-week trial concluded. Of the 19, nine patients met the 40% reduction in psychotic symptom response criteria. In total, 48.7 percent of the participants that received ECT reached the criteria threshold or better. In regards to negative symptoms there was determined to be no significant difference based on the Scale for the Assessment of Negative Symptoms on global measures for affective flattening ($F=0.98$, $df=1, 39.3$, $p=0.33$), alogia ($F=0.03$, $df=1, 40.1$, $p=0.87$), avolition-apathy, ($F=0.76$, $df=1, 39.3$, $p=0.39$), and anhedonia-asociality ($F=1.87$, $df=1, 39.7$, $p=0.18$). In terms of side effects, one patient had to be removed from ECT therapy due to “jerky” movements. These movements were preexisting, but researchers were concerned with possible seizure activity.

There were no side-effect differences noted between the two groups with exception of two instances of mild confusion in the ECT group which resolved in less than a day. Neurocognitive symptoms were assessed using the battery of tests described previously. The data yielded from these tests showed that neither group had a significant change in neurocognitive function. The mean MMSE scores for the ECT plus clozapine group were 22.6 (SD=1.2) at baseline and 23.1 (SD=1.2) at week 9, and mean scores for the clozapine group were 22.2 (SD=1.0) and 23.4 (SD=1.2), respectively. However, speed of processing was deemed to be

reduced and sensitive to the effects of ECT at week 9. This was short lived outside of the subacute (1-week) timeline.

The study summarizes that 50 percent of the initial ECT-clozapine group had a positive response rate versus 0 in the clozapine group. 47 percent of the crossover also experienced these positive results after failing 8 weeks of clozapine only and then receiving ECT. These effects were exclusively in positive symptoms of schizophrenia and no significant change was observed in negative symptoms. Interestingly, the study states that at the time this was one of the highest augmentation response rates ever recorded in a patient population with severe schizophrenia.

Petrides et al. (2015) did recognize a few limitations associated with this study. The first being a lack of a sham ECT placebo. Many countries do not find sham ECT ethical which makes it difficult to pin down the placebo effect. Also, the number of patients studied was low and only included inpatients. Third was the fact that the ECT group was on average younger. Though the patients were selected randomly, this coincides with current bias of practice in that many practitioners are less likely to advocate ECT for older patients due to documented cognitive effects. Lastly, the duration of the study was relatively short and no conclusion can be drawn for long-term or maintenance effects of the therapy.

Another study by Kim et al searched medical records of Dongguk University International Hospital from March 2012 to December 2016. Search criteria was defined as those diagnosed with schizophrenia between the ages of 20 and 65 that were treated with clozapine. Requirements were adequate clinical information, IQ of greater than or equal to 80, no comorbities, and no substance addiction. Symptoms of psychosis were assessed via the PANSS in the area of positive symptoms, negative symptoms, and overall psychopathology. In addition, possible adverse effects caused by ECT were also collected via observation notes.

The ECT procedure used was an acute course performed three time per week and eventually decrease to twice per week based on patient condition at the discretion of the provider. Bilateral electrode placement and brief pulse stimuli with MECTA spectrum 5000Q were applied. Initial seizure threshold was found in the first session via an upward titration. Patients received anesthesia and muscle relaxers prior to procedure for safety and comfort.

The data was collected over five years of observation and included 30 patients. 14 were undergoing ECT and 16 were given clozapine alone. Only patients that maintained blood levels at or above 350 ng/mL of clozapine were taken into consideration. Of the 14 long term patients, all were observed for the entire 5-year study duration with the exception of one who stopped visiting the hospital and was excluded. ECT sessions were described as:

> "The mean session number and duration of acute ECT were 14.9±4.6 and 44.9±15.4 days, respectively. The mean electrical charges were 147.4±69.7 mC as the initial seizure threshold and 236.9±142.4 mC at last session of acute ECT (t=2.35, p=0.035, by paired t-test). The total charge and total seizure duration in average were 2,981.2±2,029.6 mC and 687.4±296.6 seconds, respectively. There was no gender difference based on ECT parameters" (Kim et al, 2018).

The mean number of ECT sessions was 36.0 plus or minus 23.3 over a mean of 675.8 days plus or minus 498.5 days. ECT was performed at least one time every 1-4 weeks or intermittently when symptoms would worsen as an acute or rescue ECT therapy. Clozapine blood levels were monitored and averaged 367.9 mg in the ECT group prior to ECT and reduced to an average of 292.9 mg after initiation of ECT. The average in the non-ECT group was 265.6 mg.

The results found via PANSS changes were that in ECT the total score was significantly reduced from 101.7 on average to 82.7 with a p value found to be less than 0.001. This was an

average of 19.0 total points. Six of the 14 patients were considered in remission with a 20% or greater reduction in overall PANSS score. Another form of measurement used was Tuinier's cognitive domain which showed that all factors were significantly reduced by ECT. Though still significant, negative symptoms were considered least changed. In addition, "The effect sizes of the mean difference between before and after ECT were -1.213 for PANSS total score, -1.598 for positive symptom, -0.548 for negative symptom, -1.579 for general psychopathology, and -0.991 for Tuinier's cognitive domain." (Kim et al, 2018) The mean PANSS score in the non-ECT group was 76.6 total points. And all subscale factors including "positive symptom ($t=4.78$, $p<0.001$), negative symptom ($t=3.07$, $p=0.005$ by t-test), general psychopathology ($t=5.63$, $p<0.001$ by t-test), and cognitive domain ($t=5.17$, $p<0.001$ by t-test) were significantly higher in the ECT group than in the non-ECT group." (Kim et al, 2018) However, after ECT statistical differences appeared only in general psychopathology ($t=2.11$, $p=0.022$ by t-test) and cognitive domain ($t=2.14$, $p=0.042$ by t-test) compared to the non-ECT group.

The study found no "sustained severe adverse events related to ECT or general anesthesia." Adverse effects included mild postictal agitation, headache, and nausea were managed with conventional interventions and/or benzodiazepine medications and generally resolved within a few hours. The mean MMSE-KC (Mini Mental Status Examination) score before ECT was 24.9 and the mean after was 27.4 and deemed to be of no statistical difference by the study. However, there was statistically significant in the Tuinier's cognitive domain of the PANSS ($t=-3.66$; $p=0.003$; by paired t-test).

From the data, the study drew a few conclusions. The first is that the ECT group had a significantly higher PANSS score prior to ECT than that of the non-ECT group. This suggests that those with more severe symptoms are more likely to receive ECT therapy and those with

overall lower scores and less severe symptoms are more likely to be treated with clozapine alone. The study also concluded that the data demonstrated the efficacy of an acute course of ECT. ECT "rapidly and substantially" decreased symptoms and showed no observable serious or adverse events. Also "in this study, the response rate by acute ECT in patients with clozapine-resistant schizophrenia was 42.9% (6 of 14 patients) when applying the 1-7 scoring system based on the traditional criteria of 20% reduction in psychotic symptoms." (Kim et al, 2018) Though this is lower than previous reported response rates, it is still clinically significant. After excluding patients with pseudo-resistance to clozapine, the study found ECT augmentation to be highly effective in those that had inadequate response to clozapine therapy. Unfortunately, remission rate was limited and response was not consistent for individual patients. The study further provided evidence that ECT seems less effective on negative symptoms. Though it still provided significant improvement, the improvement was less significant than other sub-groups which is relatively in line with other studies showing little to no significant improvement.

There were many limitations stated in this study. For one, other medications used by patients were not controlled. This included other psychotropics. Another cited limitation was cognitive functions post-ECT were not completely tested with a full neurocognitive exam. The author also would have preferred more long-term follow-up examination after ECT to hopefully test if maintenance ECT was required in patients or if the acute ECT was effective long term. Though not cited in the limitations, sample size was relatively small and more high-quality evidence is still required.

Discussion

After considerable research it can be concluded that there is probably a statistical benefit to ECT augmented treatment including that it is likely safer than the current gold standard treatment of clozapine. It can also be concluded that pharmacological treatment augmented with ECT is more effective than either treatment alone. However, as with many incidents of polypharmacy there are increased side effects and safety issues versus single intervention treatment. Though side effects of ECT are usually temporary, they must be taken under consideration. It is interesting to note that use of multiple treatments actually seems to lessen the side effect intensity and profile of monotherapy with clozapine alone.

Unfortunately, due to low populations in studies, the subjective nature of these studies, and the unreliability of patients due to this disease; it is hard to grade the evidence above moderate quality. More research will likely increase this quality of evidence as well as provide more information on the best choice of therapy for patients with schizophrenia refractory to both typical and atypical antipsychotics. Due to the relatively low comparative risk to other schizophrenia treatments, electroconvulsive therapy actually seems relatively benign. Despite the high level of aversion to ECT therapy, it appears quite efficacious in the treatment of positive symptoms associated with schizophrenia in particular. However, the data shows low to no improvement of negative symptoms.

Applicability to Clinical Practice

The literature obtained and evaluated in this study should assist providers in their choice of intervention for a very complex and difficult disease. It is intended as an aid in the individualized treatment of medication resistant schizophrenia and assist the provider in increasing patient quality of life. It will provide evidence-based information about the utility and

safety of ECT. The provider will be able to use this information to both guide his decision for treatment as well as inform the patient of the positive and negative aspects of these treatments.

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