# Efficacy of electroconvulsive therapy augmentation for partial response to clozapine: a pilot randomized ECT – sham controlled trial

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## Abstract

**Background:** Thirty percent of schizophrenia patients are treatment-resistant. **Objective**: This is a single-blinded sham-controlled trial to assess the efficacy of electroconvulsive therapy (ECT) as augmentation strategy in patients with clozapine-resistant schizophrenia. **Methods**: Twenty three subjects were randomly assigned to 12 sessions of ECT (N = 13) or placebo (Sham ECT) (N = 10). The primary outcome was improvement on psychotic symptoms as measured by the mean reduction of the PANSS positive subscale. The assessments were performed by blind raters. **Results:** At baseline both groups were similar, except for negative and total symptoms of the PANSS, which were higher in the Sham group. At the endpoint both groups had a significant decrease from basal score. In the ECT group the PANSS total score decreased 8.78%, from 81.23 to 74.75 (p = 0.042), while the positive subscale had a mean reduction of 19% (19.31 to 16.17, p = 0.006). In the Sham group, the mean reduction of PANSS total score was 15.27% (96.80 to 87.43; p = 0.036), and the PANSS positive subscale decreased 27.81% (22.90 to 19.14, p = 0.008). The CGI score in ECT group decreased 23.0% (5.23 to 4.17; p = 0.001) and decreased 24.31% in the Sham ECT group (5.80 to 4.86; p = 0.004). **Discussion:** In this pilot study, we found no difference between the groups.

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**Keywords:** Schizophrenia, electroconvulsive therapy, ECT, single-blinded sham-controlled trial, partial response to clozapine.

## Introduction

The use of antipsychotics represented a considerable advance in the treatment of schizophrenia but since the introduction of these agents, it was observed that a certain percentage of patients continues to exhibit psychotic symptoms despite adequate treatments either using first or second generation antipsychotics[1]. These patients are termed "refractory" or "treatment-resistant" and various guidelines and algorithms established operational criteria to define these patients as, for example, lack of response to two antipsychotic trials with adequate doses and at least six weeks duration each[2-4]. It is well established that clozapine is the drug of choice for such condition[1,2,4].

Nevertheless, about 30% of patients with treatment resistant schizophrenia (TRS) also do not respond satisfactorily to clozapine and remain predominantly psychotic and such patients are termed incomplete responders, partial responders or having super-refractory schizophrenia (SRS)[4,5].

There is a general agreement that patient with SRS have persistence of psychotic symptoms after adequate treatment with adequate doses of clozapine at least for 6 months[3]. However, to our knowledge, only Mouaffak *et al.*[6] have proposed an operationalized definition, using multidimensional criteria, as follows: 1) At least 8 weeks treatment with clozapine with plasma levels of >350 micrograms/L and failure to improve by at least 20% in total BPRS score; 2) Persistent psychotic symptoms as defined as ≥ 4 (moderate) on at least 2 to 4 positive symptoms items of the BPRS (18 items, graded 1-7); 3) Current presence of at least moderately severe illness on the BPRS score (≥ 45) and a score of ≥ 4 (moderate) on the Clinical Global Impression Scale.

For this population various augmentation strategies have been proposed using compounds such as anticonvulsants, antipsychotics, antidepressants and glutamatergic agents[5] for clozapine augmentation. However, with the exception of the modest effect of lamotrigine, there is no evidence that any pharmacological intervention is really efficacious in terms of clozapine augmentation for such patients[7].

Electroconvulsive therapy (ECT), has been used for treatment of schizophrenia before the advent of antipsychotics[8] and there is evidence of its efficacy when used in combination with antipsychotics, improving patients with schizophrenia who show limited response to medication alone[9]. ECT showed to be effective for patients with TRS in some uncontrolled trials[10,11] as well as retrospective studies[12]. Additionally ECT is recommended in guidelines[3] and algorithms such as the International Psychopharmacology Algorithm Project (www.ipap.org). The use of ECT has been proposed for this population of patients resistant to clozapine with good tolerability in case series with small number of patients, case reports or open label trials which vary considerably in terms of the definition of TRS, ECT techniques and outcome measures[13].

There are only 2 controlled trials which tested the efficacy of ECT in patients resistant to clozapine as is the case of Masoudzadeh and Khalilian[14] who treated 18 patients with TRS. Resistance was defined as lack of response to two antipsychotics trials with 8 weeks duration with adequate doses. Clozapine plasma levels were not evaluated. Eighteen treatment-resistant schizophrenic patients were assigned to three equal groups: one group received clozapine, one group was treated with ECT and one group was treated with the combination of clozapine and ECT. The treatment response was evaluated using the PANSS criteria and results showed that combination therapy was superior to single modality therapy. There were no significant adverse effects with combination treatment.

In another randomized controlled trial[15] patients with partial response to clozapine where assigned to receive ECT and compared

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with patients who received treatment as usual. Patients who were considered non responders to clozapine received an 8-week open trial of ECT (crossover phase). ECT was performed three times per week for the first 4 weeks and twice weekly for the last 4 weeks, 20 sessions. Response was obtained with a 40% reduction in psychotic symptoms on the BPRS[15].

However to the best of our knowledge, there are no studies which tested the efficacy of ECT in comparison with Sham ECT in patients with partial response to clozapine.

Thus, the aim of the present study is to compare clozapine augmentation with ECT as with Sham ECT through a randomized control trial in patients with schizophrenia resistant to clozapine.

Despite the fact that ECT was considered superior to placebo[9] there are no studies which compared ECT versus placebo (Sham) in patients with SRS[13].

## Methods

This was a pilot, randomized, placebo-controlled, single blinded, single center trial to assess the efficacy of electroconvulsive therapy (ECT) as augmentation strategy in patients with partial response to clozapine or Super Refractory Schizophrenia (SRS), as compared to placebo (Sham ECT). Patients were recruited at the Institute of Psychiatry of the University of São Paulo Medical School and all the assessments and treatment procedures were carried out at the same site. The study was conducted in accordance with the Declaration of Helsink[16], was approved by the local Internal Review Board of University of São Paulo General Hospital (protocol 0364/09) and was registered in the Clinicaltrials.gov site (NCT02049021). All subjects or a legal tutor signed an informed consent form.

*Inclusion criteria:* patients of both genders, between 18 to 55 years old were included. Patients fulfilled criteria for a DSM IV-TR[17] diagnosis of schizophrenia or schizoaffective disorder based on clinical interview and follow-up of experienced psychiatrist of the Schizophrenia Research Program of the Institute of Psychiatry of University of São Paulo (Projesq). Severity of symptoms was evaluated by the Positive and Negative Syndrome Scale (PANSS)[18] and Clinical Global Impression scale (CGI)[19]. Generally patients were using clozapine at least for 6 months and had to have a total PANSS ≥ 60 and the CGI ≥ 4. Clozapine plasma levels should be equal or higher than 350 ng/mL[20].

*Super refractoriness definition:* patients were defined has having an unsatisfactory response to clozapine (super-refractory) using modified criteria[6]: 1) At least 8 weeks treatment with clozapine with plasma levels of > 350 micrograms/L and failure to improve by at least 20% in total BPRS score; 2) Persistent psychotic symptoms as defined as ≥ 4 (moderate) on at least 2 to 4 positive symptoms items of the BPRS (18 items, graded 1-7); 3) Current presence of at least moderately severe illness on the BPRS score (≥ 45) and a score of ≥ 4 (moderate) on the Clinical Global Impression Scale. We used BPRS items contained in the PANSS scale to evaluate patients.

*Blindness:* raters were blinded for the ECT/Sham procedures and patient's group status.

*Medications:* all patients were on clozapine either in monotherapy, or in combination with other psychotropic drugs such as antipsychotics, antidepressants or anticonvulsants.

*Exclusion criteria:* if they showed evidence of any unstable clinical condition in the last three months before the inclusion in the study as well have received ECT treatment for six months before the initiation of study. In case of childbearing potential, women were requested to use contraceptive methods.

*Randomization:* patients were randomized to either ECT or Sham ECT using tools provided by the researchrandomizer.com site.

*Patient's follow-up:* patients were assessed at baseline and after 12 sessions by raters who were completely blinded throughout the study. Clozapine serum blood levels were measured before the initiation of the trial, in order to assure that they were within the therapeutic range[20].

*ECT procedures:* ECT or Sham ECT was administered three times a week, with a total of 12 sessions. ECT was delivered using either a MECTA SpECTrum 5000Q or a MECTA SpECTrum 4000Q (Mecta Corp., Lake Oswego, Oregon, USA). The bitemporal electrode placement technique was used with a standard brief pulse stimulus threshold titration and dosing[21,22]. As routine procedure all patients received anesthesia either by hypnotic induction with Etomidate (0.15 to 0.3 mg/kg) or Propofol (1 to 2 mg/kg), Suxamethonium (0.5 mg/kg) was used for muscle relaxation with Atropine 0,5 mg intravenously. Sham ECT consisted in using the same setting and hypnotic sedation, but without muscle relaxation or electrical stimulus. Therefore all patients received the same procedures.

*Measures of efficacy:* the primary outcome was the response rate on psychotic symptoms as measured by the mean reduction at PANSS positive subscale. Response rates were defined according to three levels: a 20% reduction, which is generally considered the minimum level of response[23] and 30% reduction, which correspond to "minimally improved" CGI level[24], and 40% reduction, which correspond to the "much improved" CGI level adequate level[24] and considered an adequate level for ECT trials[15]. Secondary outcomes were clinical improvement on other PANSS subscales as well as the CGI.

### Statistical analysis

At baseline groups were compared with Pearson's chi-square test for categorical variables or Student's t-test for continuous variables. Response rates were calculated as usual: (Baseline score – Endpoint score)/Baseline score. Pre- and post-treatment comparisons between groups was carried out with a linear mixed effects model to accommodate the dropouts[25]. The goal was to compare the pre and post treatment difference in scores with the interaction effect. Assumption of normality of residuals was assed inspecting the QQ plot. Analyses were carried out on SPSS version 22 and significance level was set at 5%.

## Results

Twenty-three patients participated in the study. Only patients with the diagnosis of schizophrenia were included. They were randomly assigned to the ECT group (13 patients) or the Sham group (10 patients). At baseline these groups were comparable in terms of age, gender, educational level, dose of clozapine and blood levels of clozapine. Nineteen patients completed the trial. There were four dropouts: three of them from the Sham ECT group, as can be depicted by the Consort diagram displayed in Figure 1. Reasons for the dropouts: one patient had an infectious orchitis (ECT group) and three other patients could not attend the sections for other reasons not related to the study (Sham group).

Despite the fact that there were more dropouts in the Sham group, demographic variables showed no statistical differences between both completers groups. Patients receiving Sham showed higher degrees of psychopathology than patients receiving ECT as measured by the PANSS and CGI, but only the total score was significantly higher at baseline: PANSS positive subscale (22.9 vs 19.3, p = 0.15), PANSS negative subscale (29.0 vs 23.15, p = 0.08), PANSS General Psychopathology (44.9 vs 38.7, p = 0.13), PANSS total score (98.8 vs 81.2, p = 0.023) and CGI (5.8 vs 5.2, p = 0.14) (Table 1).

In terms of efficacy response rates the 20% reduction on the PANSS positive subscale was achieved by two ECT patients as well as two Sham ECT patients; one ECT patient and two Sham ECT patients had a 30% reduction and only one ECT patient met 40% reduction. Comparing pre and post treatment in terms of the improvement of all other PANSS subscales as well as the CGI no differences were found between active or Sham ECT, since all scores decreased significantly in both groups and no interaction effects were significant, except for the PANSS negative subscale (Table 2 and Figure 2).

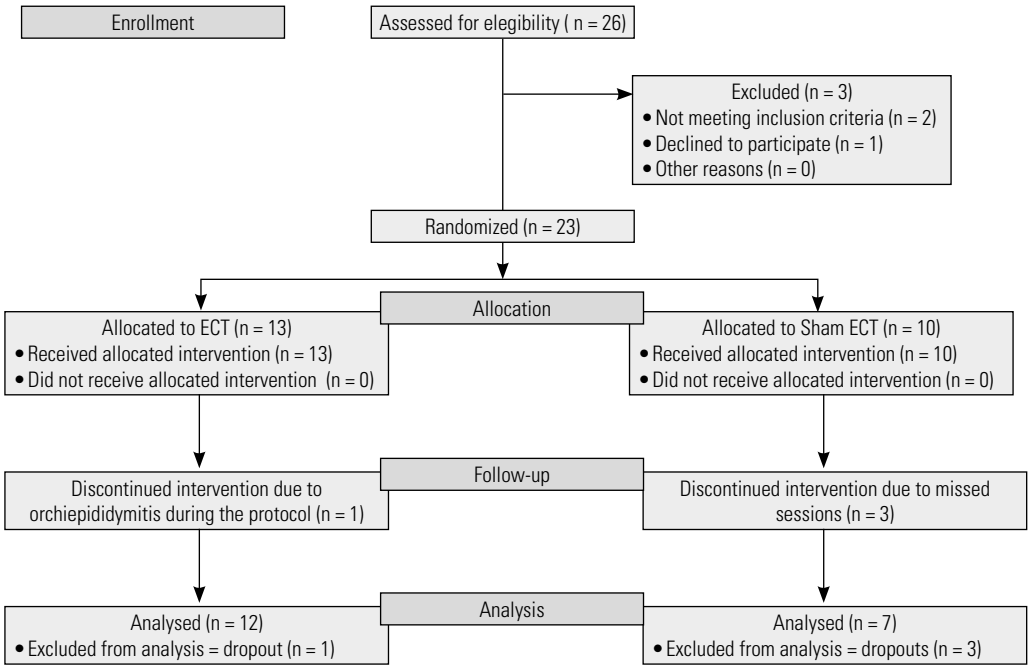


**Figure 1.** Consort diagram.

**Table 1.** Baseline data

| | ECT | Sham | Statistics | *p* |
|---|---|---|---|---|
| Gender | 9 male; 4 female | 7 male; 3 female | $\chi^2(1) = 0.002$ | 0.97 |
| Age (years) | 36.63 (9.95) | 37.60 (9.56) | t(21) = -0.24 | 0.81 |
| Education (years) | 10.15 (2.54) | 10.00 (2.86) | t(21) = 0.13 | 0.89 |
| Number of hospitalizations | 3.33 (2.74) | 4.00 (1.32) | t(21) = -0.70 | 0.51 |
| Age at first hospitalization | 20.15 (5.92) | 22.20 (8.51) | t(21) = -0.68 | 0.50 |
| Clozapine plasma levels (ng/ml) | 644.30 (253.71) | 747.82 (397.66) | t(21) = -0.76 | 0.45 |
| Clozapine dose (mg) | 532.69 (168.75) | 505.00 (130.06) | t(21) = 0.43 | 0.67 |
| PANSS total | 81.23 (14.56) | 98.80 (19.86) | t(21) = -2.45 | 0.023 |
| PANSS positive | 19.31 (3.56) | 22.90 (6.70) | t(21) = -1.54 | 0.15 |
| PANSS negative | 23.15 (7.69) | 29.00 (7.61) | t(21) = -1.81 | 0.08 |
| PANSS general | 38.77 (9.37) | 44.90 (9.33) | t(21) = -1.56 | 0.13 |
| CGI | 5.23 (0.60) | 5.80 (1.14) | t(21) = -1.55 | 0.14 |

**Table 2.** Comparison between Treatment (ECT) (N = 13) and Placebo (Sham) (N = 10) using Mixed Model Analysis

| | | Pre-treatment | | Post-treatment | | *p*-values | | |
|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | | Group | Time | Interaction |
| PANSS Total | ECT | 81.23 | 14.56 | 74.75 | 12.17 | 0.046 | 0.006 | 0.668 |
| | Sham | 96.80 | 19.27 | 87.43 | 24.76 | | | |
| PANSS Positive | ECT | 19.31 | 3.57 | 16.17 | 4.11 | 0.121 | < 0.001 | 0.646 |
| | Sham | 22.90 | 6.71 | 19.14 | 6.28 | | | |
| PANSS Negative | ECT | 23.15 | 7.69 | 23.42 | 5.82 | 0.041 | 0.995 | 0.610 |
| | Sham | 29.00 | 7.62 | 30.14 | 8.38 | | | |
| PANSS General | ECT | 38.77 | 9.36 | 35.17 | 7.61 | 0.193 | 0.023 | 0.501 |
| | Sham | 44.90 | 9.33 | 38.14 | 11.71 | | | |
| CGI | ECT | 5.23 | 0.60 | 4.17 | 0.72 | 0.149 | < 0.001 | 0.908 |
| | Sham | 5.80 | 1.14 | 4.86 | 1.46 | | | |

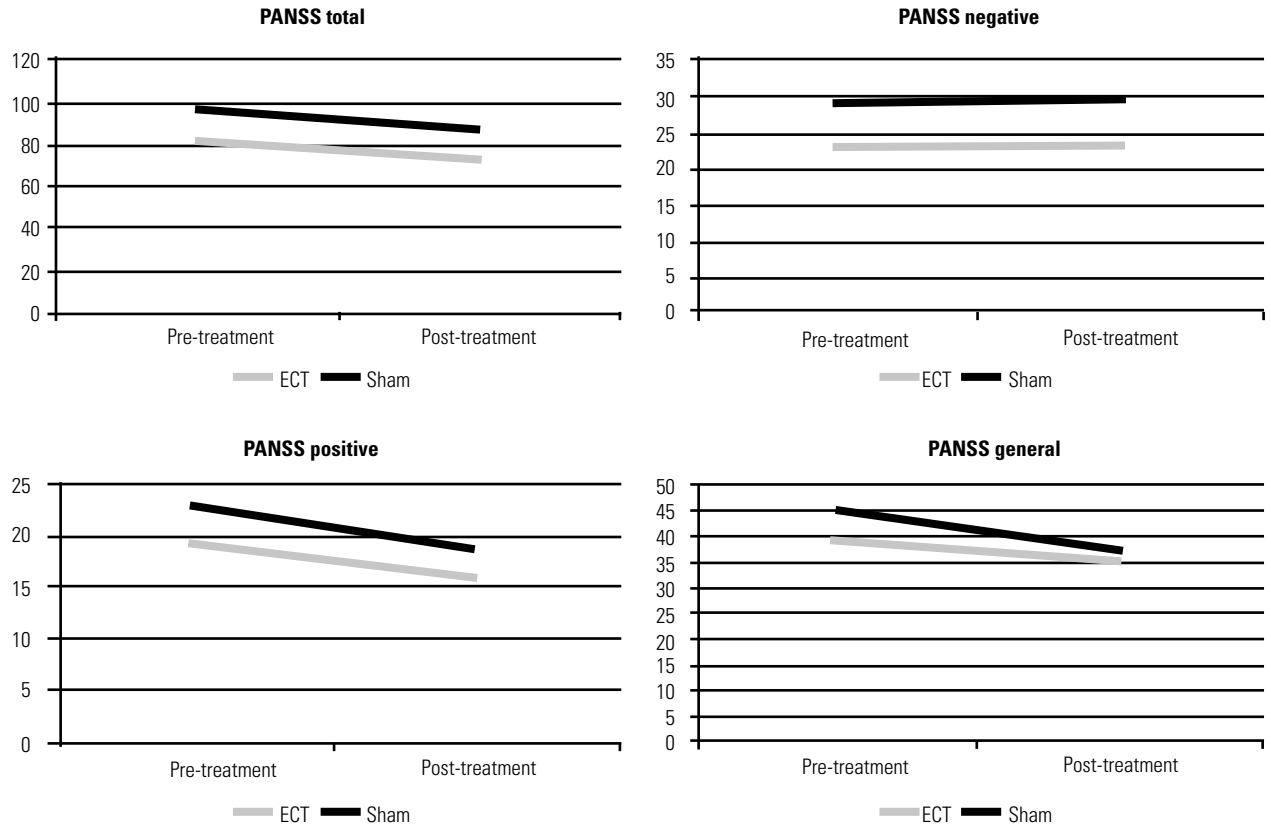


**Figure 2.** Comparison of PANSS (total and subscale scores) change over time between groups.

## Discussion

The present study found that patients with schizophrenia with partial response to clozapine who were treated with ECT as an augmentation strategy showed no benefit when compared with those patients who received Sham ECT either in terms of the primary outcome (i.e. PANSS positive subscale) as well as secondary outcomes (other PANSS subscales and CGI).

As previously mentioned the majority of clozapine augmentation studies with ECT were case reports or open label studies[26] and therefore it is difficult to compare the this study with others, except for the Petrides *et al.*[15] to which the present study bears some similarities such as age range, degree of severity of illness, monitoring clozapine plasma levels and maintenance of concomitant medication with clozapine. However, the mentioned study differs substantially from ours since it was a cross-over trial, employed a higher number and frequency of ECT sessions, used the BPRS which is a scale with less number of items than the PANSS but, mainly, the ECT intervention was compared with treatment as usual.

In fact even in non-pharmacological procedures like ECT, it is well known that the gold standard for the establishment of therapeutic efficacy is the randomized placebo-controlled trial[27] and we think that this aspect represents an important strength of the present study since several reviews have shown that there are no Sham ECT controlled studies of clozapine augmentation strategies in patients with schizophrenia[26,28,29].

The monitoring of adequate plasma levels of clozapine is, to our point of view, another important issue of the present study since it allows to infer that patients are adequately treated and are true clozapine partial responders. This is pointed out by some reviewers who observed that the lack of response to ECT may related to low clozapine oral doses[30] and that the majority of published studies on the efficacy of ECT augmentation strategy for patients with partial response to clozapine did not report their clozapine doses or plasma levels[31].

As reported in other studies the procedure showed to be tolerable and safe since the dropouts in the ECT or Sham groups seems to be not related to the procedure. However there are several limitations that must be considered. The first issue to be considered is the small sample size, of 23 subjects and 19 completers. The high rates of dropouts, three of them from Sham group, (i.e. 50% of the final sample), by no means represents a possible source of bias. We could speculate that lower therapeutic effects associated to difficulties to keep regularity to the complex procedure contributed to these higher rates in this group.

The placebo (or Sham) group had a significant improvement in this study. Indeed, placebo effect was comparable to ECT effect at the endpoint, with no statistical differences (last PANSS and CGI assessments were carried out until seven days after the last procedure)[32-34]. One possible explanation could be the cumulative factors that can increase placebo effect, also described and found in other clinical trials, such as: small sample sizes, smaller placebo groups, higher severity of psychopathology at baseline, lower mean age of participants, as well as the briefness of intervention[32-34].

Moreover, the last structured assessment was carried out until seven days after the last procedure, probably the best point to detect positive symptoms improvements, but still under post-ictal cognitive side effects, which may have an impact on the PANSS scores. Given the short-lived nature of placebo effect, we hypothesize that a long term observation could increase discrimination capacity. Another factor described about placebo effect concerns the nature of intervention itself: complex procedures, using active substances (such as anesthesia), and engaging patients in therapeutic environment, can lead to response rates as high as 70%[35]. This finding of lower differences between control (placebo) and active groups has been reported to be growing, concerning research centers and the industry,

not just in antipsychotic development, but also in mood disorders research[36].

Scales such as the PANSS scale were used as primary outcome measure and CGI as secondary outcome measure. We concluded that these two tools could not confirm that ECT is superior to placebo (Sham ECT) as augmenting therapy to clozapine in SRS, in part due to the small sample size, and other factors discussed above. However the present study is a work in progress. It is an ongoing research and the increasing number of participants we will probably improve statistical power to detect significant effects between groups.

Other aspects should also be considered as for example the fact that recent literature on clinical trials focusing the treatment of schizophrenia have shown a progressive increase in the placebo effect. For example, observing placebo-controlled studies which used the PANSS between 1983 and 2007 studies, it was found a progressive increase of improvement in the placebo group as compared to almost no placebo effect in the earlier decade of the 1980s[34]. In fact the placebo effect of ECT is not understood and may be underestimated[37].

It is well documented that patients with TRS are amongst the most severe cases of schizophrenia[4] and those with partial response to clozapine have higher degrees of psychopathology and current psychopharmacological augmentation strategies showed no superior benefit as compared to placebo[7] while some psychological trials showed small benefits for patients[38]. As previously mentioned contemporary clozapine pharmacological augmentation strategies are considered not better than placebo[7] and in this sense further placebo controlled trials with larger samples are warranted since ECT still represent the single non pharmacological therapeutic alternative for patients with partial response to clozapine.

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