Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A systematic review and meta-analysis

Authors:

John Lally, John Tully, Dene Robertson, Brendon Stubbs, F Gaughran* J H MacCabe*

*Authors contributed equally and should be acknowledged as joint senior authors

Dr John Lally, MB MSc MRCPsych, Clinical Research Fellow,

Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience (IoPPN),

King's College London, London, United Kingdom and National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, United Kingdom.

Dr John Tully MB MRCPsych

NIHR Academic Clinical Fellow and Specialist Registrar in Forensic Psychiatry, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience

Dr Dene Robertson MRCGP MRCPsych,
Consultant Psychiatrist in Behavioural and Developmental Psychiatry, Clinical Academic Group with South London and Maudsley (SLaM) NHS Foundation Trust and Honorary Senior Lecturer Institute of Psychiatry, Psychology & Neuroscience (IoPPN) King’s College London.

Brendon Stubbs, MSc, MCSP, PhD

Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King’s College London, and Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom

Dr Fiona Gaughran MB, BCh, BAO, FRCPI, FRCP, FRCPsych, MD,

Lead Consultant Psychiatrist, National Psychosis Service, South London and Maudsley NHS Foundation Trust, Senior Lecturer, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, United Kingdom.

Dr James H MacCabe BSc MBBS FRCPsych MSc PhD

Reader in the Epidemiology of Psychosis, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King’s College London and Honorary Consultant Psychiatrist,
Abstract

The primary aim of this systematic review and meta-analysis was to assess the proportion of patients with Treatment Resistant Schizophrenia (TRS) respond to ECT augmentation of clozapine (C+ECT).

We searched major electronic databases from 1980 to July 2015. We conducted a random effects meta-analysis reporting the proportion of responders to C+ECT in RCTs and open-label trials. Five clinical trials met our eligibility criteria, allowing us to pool data from 71 people with TRS who underwent C+ECT across 4 open label trials (n=32) and 1 RCT (n=39). The overall pooled proportion of response to C+ECT was 54%, (95% CI: 21.8-83.6%) with some heterogeneity evident (I²=69%). With data from retrospective chart reviews, case series and case reports, 192 people treated with C+ECT were included. All studies together demonstrated an overall response to C+ECT of 66% (95% CI: 57.5-74.3%) (83 out of 126 patients responded to C+ECT). The mean number of ECT treatments used to augment clozapine was 11.3. 32% of cases (20 out of 62 patients) with follow up data (range of follow up: 3-468 weeks) relapsed following cessation of ECT. Adverse events were reported in 14% of identified cases (24 out of 166 patients). There is a paucity of controlled studies in the literature, with
only one single blinded randomised controlled study located, and the predominance of open label trials used in the meta-analysis is a limitation. The data suggests that ECT may be an effective and safe clozapine augmentation strategy in TRS. A higher number of ECT treatments may be required than is standard for other clinical indications. Further research is needed before ECT can be included in standard TRS treatment algorithms.

**Keywords:** Treatment resistant schizophrenia; clozapine; ECT; psychosis; schizoaffective disorder

**Conflict of Interest**
Dr Gaughran has received honoraria for advisory work and lectures from Roche, BMS, Lundbeck, and Sunovion and has a family member with professional links to Lilly and GSK;

The other authors declare no conflict of interest.

**Acknowledgement**
Dr Lally and Dr MacCabe are both supported by CRESTAR (CRESTAR project, [http://www.crestar-project.eu/](http://www.crestar-project.eu/)) EU-FP7 grant number 279227; Dr MacCabe is also supported by MRC grant nos. MR/L011794/, MR/L003988/1 and MC_PC_13065) and by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, Kings College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

The authors would like to thank Dr. Rohit Garg, M.D., Senior Research Associate, Department of Psychiatry, Government Medical College & Hospital, Chandigarh. India, 160036; Dr Tomasz Pawełczyk, MD, PhD, Department of Affective and Psychotic Disorders, Medical University of Lodz, Poland; Dr Itziar Flamarique MD, PhD, Child and adolescent psychiatrist, Clinical research fellow,
Schizophrenia is a chronic disabling illness, with a lifetime prevalence rate of 0.6-1% (Saha et al., 2005). Approximately 30% of people with schizophrenia do not respond to conventional antipsychotic therapy (i.e. first or second generation antipsychotics (FGAs or SGAs) and meet the criteria for treatment resistant schizophrenia (TRS) (Brenner et al., 1990; Conley and Buchanan, 1997; Meltzer, 1997).

Clozapine remains the only effective medication for TRS, and is the only licensed treatment. However, 30-40% of TRS patients fail to respond to clozapine (Meltzer, 1992). Those unresponsive to clozapine, are the most disabled of all patients with schizophrenia, with illnesses characterised by persistent...
symptoms, a poorer quality of life, increased disability and a greater economic cost than treatment responsive patients (Kennedy et al., 2014). Numerous pharmacological strategies have been explored, including the addition of a second antipsychotic, mood stabilisers, anxiolytics, antidepressants, anti-inflammatories and glutamatergic agents, but with no robust replicated evidence to support the efficacy of any of these strategies (Cipriani et al., 2009; Porcelli et al., 2012; Remington et al., 2005; Taylor et al., 2012; Tranulis et al., 2006).

The use of ECT in schizophrenia is supported by findings from a Cochrane review indicating that treatment with ECT is significantly more likely to result in clinical improvement than placebo or sham ECT (n=9 trials; n=400 patients), with ECT resulting in fewer relapses and increased rates of hospital discharge than sham ECT (Tharyan and Adams, 2005). However, recommendations for the use of ECT in schizophrenia are inconsistently reflected in current national clinical guidance. For example, the United Kingdom’s National Institute of Care Excellence (NICE) does not recommend ECT as a treatment for schizophrenia, unless prominent catatonia exists (NICE, 2014), whilst the American Psychiatric Association (APA) recommends that ECT should be considered when there is treatment resistance (APA, 2008).

There is clear evidence that many users of mental health services hold negative views regarding ECT, although there has been little research on the attitudes of patients with treatment refractory
schizophrenia to ECT (Rose et al., 2003; Rose et al., 2005). Rose et al., found that perceived coercion and a lack of information about ECT and potential adverse effects were highlighted by patients as problems with their ECT treatment (Rose et al., 2005).

A recent RCT of ECT augmentation in clozapine-resistant schizophrenia showed encouraging results (Petrides et al., 2015). This prompted us to conduct an up-to-date systematic and meta-analytic review of the literature, to assess the efficacy of C+ECT in TRS. We conducted a systematic review and meta-analysis to assess the pooled proportion of responders to C+ECT in people with TRS. Further, we sought to identify studies that have assessed the use of maintenance ECT in patients taking clozapine. We reported data on the safety and adverse effects of augmentation of clozapine with ECT, as well as patients’ perspectives of ECT, when any of these were reported in the identified studies. However, we did not systematically search for studies reporting these aspects.

**Methods**

We performed a literature search to identify all published case series/case reports, and all observational and interventional studies, both RCTs and open label studies up until January 2015, investigating or describing ECT as a clozapine augmentation strategy in treatment resistant schizophrenia (TRS) and/or schizoaffective disorder. This systematic review was conducted in
accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard (Moher et al., 2009).

**Inclusion criteria**

Studies were included in this systematic review if they: (1) included adult participants (>18 years, with no upper age limit) with a diagnosis of treatment resistant schizophrenia or schizoaffective disorder and (2) reported studies where ECT was used to augment clozapine treatment and (3) had been written in English and published in a peer reviewed journal since 1980. We included both controlled and non-controlled studies (including open label trials), as well as retrospective chart reviews or case series/case reports.

**Exclusion criteria**

We excluded (1) articles relating to ECT as a clozapine augmentation strategy for bipolar affective disorder, mania or psychotic depression, (2) studies in which clozapine was added after ECT had been commenced and/or (3) in which clozapine and ECT were not used concurrently.

**Information sources and searches**


The following basic search terms were used, both alone and in combinations: “schizophrenia,”
“clozapine,” “resistant,” “refractory,” and “electroconvulsive therapy,” “ECT”. In addition, the reference lists of the retrieved articles and relevant review articles were examined for cross-references. When necessary, corresponding authors were contacted to clarify study eligibility and/or acquire additional data.

Study selection and exclusion

All applicable abstracts were obtained, and independently examined by two of the authors (JL & JT). The two appraisers applied the eligibility criteria and a list of full text articles was developed through consensus. There was no search for unpublished works, although authors were contacted for clarification where necessary. This selection process refined the number of relevant articles to 29 clinical reports. Two of the publications were controlled studies, and we further identified 4 open label studies, 2 retrospective chart reviews, 6 case series and 15 case reports. We distinguished the data from controlled versus non-controlled (uncontrolled) studies to achieve a workable summary of our findings.

Primary outcome

The primary outcome was the response rate to C+ECT in people with TRS and if available, to C+Sham ECT or no ECT. We used dichotomous data of clinical improvement, as defined by the individual
studies, as the primary outcome measure of efficacy. These included response rates to treatment as measured by a pre-defined reduction in total BPRS, PANSS or CGI scores.

**Data extraction**

Articles included were critically reviewed by two authors (JL and JT) and the following information extracted where possible: demographic and clinical characteristics of patients, dosage and duration of clozapine monotherapy (before ECT), plasma clozapine levels reported pre- and post-ECT, mean clozapine dosage during ECT, number of ECT sessions, application of electrodes (unilateral or bilateral), mean ECT stimulus dosage received, clinical outcome, outcome measures used, adverse effects reported, information on patients’ perspectives, duration of follow-up, use of maintenance ECT and pattern of maintenance ECT use, other medications concurrently used during the combined treatment or during follow-up, and relapses reported during follow-up.

**Meta-Analysis**

All extracted data from the studies included were entered into Comprehensive Meta-Analysis version 2.0 (CMA v2, Englewood, NJ, USA).

We defined our primary outcome, response to C+ECT, according to the included study investigators’ operational definitions of response as provided in the original reports. Where binary outcomes were
used, we calculated the pooled proportion of those that responded with clinical improvement across all included studies together with 95% confidence intervals (CI).

Due to the methodological variability in the included studies, we anticipated heterogeneity and a random effects meta-analysis was employed. We quantified any observed heterogeneity by computing the $I^2$ statistic (Higgins et al., 2003).

We assessed publication bias with a visual inspection of funnel plots and quantitative testing through the use of Begg–Mazumdar (Begg and Mazumdar, 1994) and Egger bias tests (Egger et al., 1997).

Results

Study selection, study and participant characteristics

The study selection process, search results, and reasons for exclusion are given in figure 1.

The initial search yielded 1148 references. After checking titles and abstracts, 56 full texts were screened and 29 of these were included for data extraction. Citations within a paper were included as an additional source of references. At the full text review stage we contacted 5 author groups and 3 provided additional data to enable inclusion (Garg R et al., 2012; Grover et al., 2015; Pawelczyk et al., 2014).

Meta-Analysis
It was possible to pool data on the proportion of responders across 71 trial participants who underwent ECT across 5 studies, which included 4 open label trials (n=32) and 1 RCT (n=39). Overall, the proportion of people that responded to treatment was 54% (95%: CI 21.8-83.6%) (figure 2). There was evidence of some heterogeneity ($I^2=69\%$). A subgroup analysis demonstrated that the proportion of those that responded was 56% (95% CI: 19.4-87.2%) in 4 open label studies and 48.7% (95% CI: 33.6-64.0%) in the RCT.

The funnel plot was broadly symmetrical (figure 3), and the Begg–Mazumdar (Kendall's tau=-0.11, $P=0.80$) and Egger bias tests (intercept =0.98, $p=0.26$) did not indicate any publication bias.

We were unable to use data from the second identified RCT in the meta-analysis, as this study did not report a clinical response using dichotomised data of clinical improvement (Masoudzadeh and Khalilian, 2007). Only one of the two controlled studies (Petrides et al., 2015) reported response rates in the treatment versus control groups, thus precluding a meta-analysis of comparisons between treatment groups and control groups.

**Included studies**

Table 1 gives an overview of included controlled (n=2) and open label trials (n=4) and retrospective chart reviews (n=2). Supplementary Table 1 gives an overview of case series included (n=6) (Benatov et al., 1996; Cardwell and Nakai, 1995; Frankenburg et al., 1993; Grover et al., 2015; Kales et al., 1999;
Kurian et al., 2005). Supplementary Table 2 provides an overview of included case reports (n=15) (Bannour et al., 2014; Bhatia et al., 1998; Biedermann et al., 2011; Gerretsen et al., 2011; Husni M, 1999; Keller et al., 2009; Klapheke, 1991; Lee et al., 2008; Manjunatha et al., 2011; Safferman and Munne, 1992; Sienaert et al., 2004; Sinha and Shah, 2013; Vowels et al., 2014; Yoshino et al., 2014) (Manjunatha et al., reported on two individual case reports). Overall, these studies and reports include a total of 192 patients with a diagnosis of treatment resistant schizophrenia or schizoaffective disorder treated with C+ECT.

**Controlled trials**

We identified two controlled trials. The study of Petrides et al., (Petrides et al., 2015), used a single blind randomised crossover design to compare clozapine use only (n=19) versus clozapine augmented with ECT (n=20) in patients with TRS. In this study 50% of the C+ECT group achieved treatment response (defined by a > 40% reduction in BPRS scores) by the end of 8 weeks compared with none of those in the clozapine-only group (F=5.38, df=8, 238, p<0.0001). During a subsequent crossover phase (unblinded), members of the clozapine-only arm who had failed to respond (which transpired to be all of them) were treated with C+ECT. 48% obtained a treatment response when ECT was added. A total of 19 of the 39 participants (48.7%) had at least a 40% reduction in psychotic symptoms after receiving C+ECT. There was no significant difference between pre- and post-treatment global neurocognition.
scores between the two treatment groups. Further, no significant differences were found between the groups in the executive functioning and episodic memory domains. However, reduced processing speed was associated with ECT administration (with a mean decrease in the Rey Auditory Verbal Learning Test score of 1.5 (0.5) in the C+ECT group compared to the clozapine-only group (p=0.0063) when measured within 1 week of the final 8-week ECT course). Two people in the C+ECT group each had ECT treatment delayed by one day on one occasion, due to confusion.

A second controlled study by Masoudzadeh et al., (total n=18) compared ECT alone (n=6), clozapine alone (n=6) and C+ECT (n=6)(Masoudzadeh and Khalilian, 2007). However, it should be noted that the two studies differed in their inclusion criteria: in the Petrides et al., study, the main inclusion criterion was resistance to clozapine, whereas in Masoudzadeh et al., the main inclusion criterion was resistance to non-clozapine antipsychotics. Masoudzadeh et al., did not provide a response definition; therefore response rates were not reported. Instead, mean changes in PANNS scores were given.

Compared to the pre-treatment baseline there was a significant decrease of 71% (from 99-29) in PANSS total scores in the C+ECT group, compared to a 40% decrease (from 99-60) with ECT treatment alone, and a 46% decrease (from 96-52) with clozapine monotherapy (F=189.15, df=4,63, p<0.0001) (Masoudzadeh and Khalilian, 2007). In addition, compared to pre-treatment baseline, patients treated with C+ECT had an 80% (from 26 to 5) decrease in mean PANSS positive symptom
subscale scores compared to the other groups (p<0.001). In the ECT alone group there was a mean
decrease in positive symptoms of 51 % (from 25 to 12); whilst in patients taking clozapine alone the
mean decrease was 31% (from 23 to 16). The C+ECT group had a 60% decrease in mean PANSS
negative symptom subscale score (from 33-13), with the clozapine monotherapy group having a 63%
decrease (from 32-12). The ECT alone group had a 29% decrease (from 31-22), though the differences
between the groups were not statistically significant. This study reported no serious adverse events in
the C+ECT group, with no difference between Mini Mental State examination (MMSE) scores between
the start and end of the study between the different treatment groups.

Taken together these two controlled studies administered a mean of 15.1 ECT treatments per patient
by pre-defined protocols. All patients had a diagnosis of TRS, but those in the Petrides et al., trial were
additionally resistant to clozapine(Petrides et al., 2015). Participants in the Petrides et al study were
treated with bilateral (BL) ECT and those in the Masoudzadeh et al., 2007 treated with unilateral (UL)
ECT(Masoudzadeh and Khalilian, 2007).

**Prospective open-label trials**

Four prospective open-label studies were found in the literature search (see table 1), with a total of 32
patients identified. The majority of patients (n=24 out of 32) were treated with BL ECT and the mean
number of ECT treatments was 11.6. None of the open label studies used a predetermined number of
ECT treatments. 73% responded to ECT augmentation of clozapine in one open label trial (Kho et al., 2004). In another study 8 out 11 patients showed significant improvements in BPRS scores (response defined as a BPRS decrease > 30%; with one patient showing a non-significant improvement in BPRS scores (an 8.2% decrease in BPRS scores) and n=2 patients showing no improvement) (Garg R et al., 2012). Only 25% of patients showed significant improvement in PANSS total scores in another open label trial, though 50% had a significant reduction in PANSS positive subscale scores (Pawelczyk et al., 2014). In a smaller study, two patients showed a significant improvement in clinical global impression (CGI) scores (Hustig and Onilov, 2009).

No adverse events were reported in two of the open label trials (n=13 patients in total (Garg R et al., 2012; Hustig and Onilov, 2009)). In one of the studies, prolonged seizures (≥90s) were observed in 3 patients (90, 100, and 200 seconds) (Pawelczyk et al., 2014). In the other open label study, two patients reported memory problems (not quantified), with one experiencing confusion following every ECT treatment. This patient was treated with clozapine 450 mg, lithium carbonate 1000mg and oxazepam 50mg concurrent to ECT (Kho et al., 2004). No other adverse events were reported.

Follow up data were provided in two of the trials (n=10 patients) (Hustig and Onilov, 2009; Kho et al., 2004), with 50% (n=5) of patients in total relapsing (all in kho et al., 2004 (Kho et al., 2004)) over a mean follow-up period of 16 weeks (range=4–52 weeks).
Retrospective chart reviews

Two retrospective chart reviews were identified, with a total of 63 patients included (Gazdag et al., 2006; Kristensen et al., 2011). All patients were treated with twice weekly BL ECT for a mean of 7.4 ECT treatments. In one of the studies, 18 out of 20 patients were recorded as having an 'excellent or good response to ECT augmentation', but with 7 out of 20 requiring maintenance ECT therapy, due to relapses following the initial ECT treatment (Kristensen et al., 2011). In the other retrospective study (n=43) the mean improvement in CGI score was 2.3 (Gazdag et al., 2006). This improvement was most marked in the schizoaffective disorder subgroup (n=16), where a mean decrease in CGI of 6.25 to 2.30 was recorded, compared to a mean decrease in CGI of 5.86 to 4.65 in those with a diagnosis of schizophrenia (n=26, hebephrenic and catatonic subtypes). Transient side effects of headache (n=2), confusion (n=2) and raised systolic blood pressure (n=2) were reported (Gazdag et al., 2006).

Quality of life

We identified one secondary analysis of an open label study which quantitatively assessed quality of life (QoL) scores (using the World Health Organization Quality of Life Scale) of those with TRS treated with C+ECT (n=11). This found significant improvement in three of out of four QoL domains: satisfaction with physical capacity, health and environment (Garg R et al., 2012; Garg et al., 2011).
Case series and case reports

The identified case series and case reports are described in supplementary tables 1 and 2. Fifty two patients were identified in total in the case series and case reports, and all, except one (Biedermann et al., 2011), were treated with BL ECT. The mean number of ECT treatments was 12.8, with a clinical response rate of 76% (n=28/37 patients with clinical response quantified). The mean dose of clozapine used concurrent to ECT was 588.5 mg daily (for a total n=26 patients with dose documented). One patient died of a pulmonary embolism following ECT; the role of ECT in this was unclear.

Results summary for all 192 patients, including case series and case reports

Taken together, the included studies and case reports, showed an overall response to clozapine augmented with ECT of 76% (83 out of 126 patients responded to C+ECT). The mean number of ECT treatments used for all included studies and case reports (for n=192 patients) was 11.3 (range 4-30).

The mean number of ECT treatments used in the controlled (n=2) and open label trials (n=4) was 13.0 (for total n=77). The mean clozapine dose used was 412.3 mg daily (for n=127 patients), with a mean serum clozapine level of 772.6ng/ml (recorded for n=52 patients treated with an average clozapine dose of 506.9 mg daily (Gerretsen et al., 2011; Keller et al., 2009; Kho et al., 2004; Petrides et al., 2015)). In those non-controlled studies, case series and case reports with follow up data, a relapse rate
of 32% (20 out of 62 patients), was identified following an initial response to clozapine augmentation with ECT. Adverse events were reported in 14% of identified cases (24 out of 166 patients) (n=1 death secondary to pulmonary embolism; n=6 with post-ictal confusion; n=5 with prolonged seizure; n=4 with transient memory problems; n=3 with delirium; n=1 with aspiration pneumonia; n=2 tachycardia; n=1 with high blood pressure; n=1 truncal dystonia (‘Pisa syndrome’)).

Discussion

We present the first systematic review and meta-analysis of C+ECT in TRS, demonstrating a pooled estimate response of 54% to C+ECT. This systematic review is the most comprehensive study to date, incorporating newly available data and collating the available literature regarding the response to clozapine augmented with ECT (C+ECT) in TRS. We identified two randomised controlled trials both of which both demonstrated favorable results for C+ECT, when compared to ECT or clozapine monotherapy (Masoudzadeh and Khalilian, 2007; Petrides et al., 2015). These results are from the best conducted trials in this area so far; however the literature in this area is sparse and the methodological designs not as robust as for most pharmaceutical trials, owing to the difficulty of blinding. The two controlled trials were very different in the robustness of design and in the clinical relevance of their study findings. The Petrides et al., (2015)
trial addressed the important clinical question of whether ECT is a useful next step after clozapine non-response in a treatment sequence, providing evidence that it is an effective augmentation strategy (Petrides et al., 2015). The smaller trial from Masoudzadeh et al., (2007) suggests that C+ECT is better than either ECT or clozapine alone in TRS. However, this study was limited by a small sample size, lack of data in relation to mean clozapine doses, dose changes during the study, and unknown serum clozapine levels within the different groups (Masoudzadeh and Khalilian, 2007). The direct clinical relevance of this study is therefore uncertain. The findings from controlled trials are supported by generally positive outcomes for C+ECT in open label trials, retrospective chart reviews, case series and the majority of case reports.

Our findings are broadly in line with earlier reviews that indicated that C+ECT was an efficacious and safe treatment for clozapine refractory psychosis (Havaki-Kontaxaki et al., 2006; Kupchik et al., 2000)). Our systematic review includes many more cases where C+ECT was employed as a treatment strategy, and this along with other findings are compared in Table 2 with the two previous systematic reviews of C+ECT (Havaki-Kontaxaki et al., 2006; Kupchik et al., 2000).

**Limitations of this review**

**Limited primary data**
There is a paucity of controlled studies in the literature, with only one single blinded randomised controlled study located (Petrides et al., 2015), and the findings of that study are limited by the numbers recruited and the lack of a sham control group. The overreliance on open label studies in the meta-analysis may have led to an overestimation of the identified response rate to C+ECT.

**Heterogeneity of response definitions**

Owing to the heterogeneity of response definitions, it was necessary to pool data from studies that used different definitions of response. We recognise that this limits the validity of the findings.

**Publication bias**

We included one RCT and four open label trials with individual participant data in our assessment for publication bias in the meta-analysis. Visually, our funnel plot showed only minor asymmetry and Egger’s test for asymmetry was not significant (P=0.25). While this shows no evidence of publication bias, it is not possible to exclude given the small number of studies.

**Lack of blinding**

The absence of any double blinded data on efficacy or adverse effects limits the conclusions that can be drawn. This is of particular concern with ECT given the potentially powerful placebo effect. It is, of course, very difficult to conduct single blind studies of ECT, let alone double blind studies. Sham ECT, where the participant is briefly anaesthetised but receives no ECT, could theoretically allow blinding,
although the post-ictal confusion that often occurs post-ECT may unblind treatment in some cases.

The use of sham ECT in a clinical trial requires careful ethical consideration, given that patients are exposed to the potential risk of anesthesia but without the potential benefits of treatment.

**English language and exclusion criteria**

We only included studies published in English. The use of ECT in schizophrenia appears to be more common in Asian countries, and clozapine is commonly prescribed in China, but we did not include Chinese databases in the systematic review. However, it is noteworthy, that the Cochrane review on ECT combined with antipsychotics in schizophrenia (Tharyan and Adams, 2005), as well at this review, found substantial numbers of studies and reports from India and Thailand which were reported in English. We were also able to recover important data from open label trials of ECT augmentation of antipsychotics (including clozapine) (Garg R et al., 2012; Pawelczyk et al., 2014), which allowed for additional C+ECT outcomes to be included.

We excluded studies in adolescent and children. This meant that a recent observational study of ECT augmentation of antipsychotic treatment (which included n=6 adolescents with C+ECT) was excluded (Flamarique et al., 2012).

**Lack of quality of life and service user perspective**
Only one of the identified studies assessed quality of life (Garg et al., 2011). The assessment of patient and carer perception of clozapine augmentation with ECT was not reported in any of the other identified studies or cases. This is an area which requires further study, and we recommend that service-user perspectives are included in all future controlled trials of C+ECT. The views of service users and carers is particularly important, given the ongoing stigma and controversy which surrounds ECT treatment. A well-constructed systematic review of patients’ perspectives on ECT, including a qualitative analysis of patient testimony, highlighted that service users perceived coercion and memory problems with ECT treatment in depression (Rose et al., 2003), but this has not been investigated in in treatment resistant schizophrenia populations, where the balance of risks and benefits may be different.

**Implications for clinical practice**

Despite the caveats discussed above, the results suggest that ECT may be an effective augmentation strategy in patients who fail to respond to clozapine monotherapy.

**Number and dose of treatment required**

A consistent finding across studies is the greater number of ECT treatments used in clozapine augmentation in TRS than the six ECT treatments used on average in depression (Charlson et al., 2012; Waite and Easton, 2013). We identified an average of 15.1 ECT treatments (pre-determined ECT
schedules) in the controlled studies, and 11 ECT treatments in all the included studies and case reports; the vast majority received bilateral ECT (BL-ECT) at a twice weekly frequency.

In the best designed controlled study an average of 16 ECT treatments was used, which achieved a response rate of 50%. (Petrides et al., 2015) However, this was a predetermined schedule aiming for 20 ECT treatments, and which was not based on randomised comparisons of short versus longer courses of treatment.

Taken together, these data suggest, but by no means prove, that a larger number of ECT treatments may be required in order to achieve a response in TRS than is the case in depression.(Charlson et al., 2012)

Adverse effects with C+ECT

There was a low rate of adverse events reported with ECT augmentation, but it is possible that adverse effects may have been under-reported, and only 4 out of 8 studies reported adverse effects in a systematic way. Clozapine lowers the seizure threshold, and it has been suggested that prolonged seizures with ECT therapy may be precipitated by combined ECT-clozapine treatment. (Bloch et al., 1996) Three patients in an open label trial had one individual episode each of prolonged seizure activity with no reported sequelae. (Pawelczyk et al., 2014) From a case series a further two patients were
documented to have developed prolonged seizures after an ECT treatment which required treatment with lorazepam. (Grover et al., 2015) There were no other reports of prolonged seizure activity.

ECT use is often limited due to concerns about cognitive side effects, including memory loss. This was not widely observed in our review. In the best designed controlled trial, there was no significant change in global neurocognition (as measured by Mental State Examination (MMSE) scores) between baseline and end of ECT (Petrides et al., 2014). Additional cognitive impairment tests for executive functioning and episodic memory failed to identify significant differences between the C+ECT and clozapine only groups, though processing speed was impaired in the C+ECT group one week following the treatment course.

Cognitive adverse events as determined by changes in MMSE scores, were not found in the other controlled study. (Masoudzadeh and Khalilian, 2007) There was a low rate of subjective reports of memory problems in the non-controlled studies (n=4/146 patients reported memory problems), although it is not clear to what extent this information was sought by the researchers and to what extent they relied on spontaneous reporting by the patients. There were no reports of significant cardiac arrhythmias, although mild cardiac adverse events of tachycardia (Bhatia et al., 1998; Safferman and Munne, 1992) and raised blood pressure (Safferman and Munne, 1992) were described in case reports.
In one case report, a patient died following a pulmonary embolus. (Sinha and Shah, 2013) He had been treated with an alternate day ECT schedule, though there is no detail given in respect to ECT dose used, seizure duration, and other ECT related side effects, nor is there any information given in relation to the dose of clozapine used at the time. There is no indication whether he was receiving treatment for catatonia or that a DVT was identified. While ECT was not clearly implicated, and it is likely that the death led to the publication of the case report, future studies should assess whether the risks of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) may be increased by treatment with ECT.

Clozapine itself has been identified as a potential risk factor for venous thromboembolism, though there has been no systematic assessment of the prevalence of DVT or PEs associated with ECT, with there been only one other case report of fatal PE associated with ECT use. (Kursawe and Schmikaly, 1988)

A handful of other case reports of PE occurring in the context of ECT exist, but again do not allow for definitive associations to be made.

**Follow-up data on C+ECT**

Follow-up data on patient response in the medium to longer term is lacking in the literature. This review noted the well-recognised problem of patients who relapse in the months following discontinuation of ECT. (Kho et al., 2004; Kristensen et al., 2011) We identified a high relapse rate of 32% in the weeks to months after ECT discontinuation, though this finding was limited by the paucity of follow up data.
There are little data to guide practice on discontinuation of ECT. Consideration for a stabilisation period of ECT post remission from C+ECT may be warranted, followed by a gradual reduction in frequency of ECT.

Despite the low rates of cognitive dysfunction reported in the reviewed literature, caveats regarding the need for monitoring for cognitive dysfunction with C+ECT use in practice remain.

**Implications for research**

We consider that double blind randomised controlled clinical trials are not only possible, but are essential to determine whether these encouraging findings are sustained. The main obstacle to conducting a properly blinded trial is the ethical question as to whether it is justifiable to administer sham ECT as part of a clinical trial, whereby the patient receives an anaesthetic but no treatment. This drawback may be mitigated by using crossover designs, whereby all patients receive the active treatment as well as the sham treatment, provided that participants have a full understanding that they will undergo sham ECT as part of the crossover design. Ratings of response must be blind to treatment arm.

Another barrier, which affects all studies in TRS, particularly those who have not attained a sufficient clinical response to clozapine, is that patients may lack capacity to consent to be recruited into clinical
trials. It may be appropriate in such instances to involve carers or other consultees in the decision as to whether to participate in the trial.

Furthermore it is important that patient and carers are involved in the design and conduct of any study of ECT. We hope that this may lead to research that allows the treatment to be tested with full acknowledgement and investigation of adverse effects, including memory problems, and perceptions of treatment with ECT in TRS both before and after the treatment.

Longer term studies are required to assess the impact of the combination therapy on longer term remission, functional outcomes and adverse effects.

Conclusions

It is clear from this review that the efficacy and adverse effects of a C+ECT in patients with clozapine refractory schizophrenia remains poorly researched, most probably due to the practical challenges in establishing double blind ECT augmentation of clozapine trials in TRS. However a growing body of research from controlled and open trials and from case reports indicates that ECT may be an efficacious and safe clozapine augmentation strategy in TRS.

We can conclude that ECT should not be dismissed as a potential clozapine augmentation strategy in TRS, and that further well controlled ECT trials are required to evaluate the efficacy of the combination both in the short and long term. Further research is needed to determine the place of ECT in TRS.
treatment algorithms, including greater evidence on predictors of response, adverse events, the costs and benefits of this treatment and the experiences of service users and carers.

References


<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Cases</th>
<th>Mean clozapine dose (+/- mean serum clozapine level) during ECT</th>
<th>ECT treatment details (including mean no. of treatments, (SDs))</th>
<th>Response</th>
<th>Adverse events (AEs)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>n=140</td>
<td>366.6mg (n=101) ; 477.3 mg/L</td>
<td>10.7 (n=140)</td>
<td>62% (n=55/89 cases)</td>
<td>7.1% (n=10/140)</td>
<td>40% relapsed (n=12/30)</td>
<td></td>
</tr>
<tr>
<td>Petrides et al. 2014</td>
<td>Single blind RCT</td>
<td>39 with TRS ECT plus clozapine group=20; clozapine-only group n=19</td>
<td>518.2 mg/day Serum clozapine level 842.2ng/ml</td>
<td>15.6 B/L ECT treatments Twice weekly</td>
<td>Response defined as decrease of ≥ 40% from baseline psychotic subscale score on BPRS ; 50% (n=10/20) in C+ECT group responded -0% in the clozapine-only group</td>
<td>No significant treatment related AEs.</td>
<td>Not yet reported (personal communication)</td>
</tr>
<tr>
<td>Masoudzadeh et al. 2007</td>
<td>RCT (unblinded)</td>
<td>18 with TRS 6&amp;6&amp;6= 3 groups</td>
<td>Not reported</td>
<td>All groups: 12 U/L ECT treatments Three times weekly</td>
<td>C+ECT group: Significant improvement – Total PANSS reduction of 71% (99-29) in C+ECT group Significantly &gt; greater than both</td>
<td>No serious AEs.</td>
<td>No follow-up</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patient Characteristics</td>
<td>Treatment Details</td>
<td>Response Criteria</td>
<td>Outcome</td>
<td>Adverse Events</td>
<td>Follow-up</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>--------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>---------</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Paweleczyk et al., 2014</td>
<td>Open label trial</td>
<td>8 with TRS</td>
<td>306.25mg/day</td>
<td>15.75 B/L (2.38) ECT treatments Three times weekly ECT only and clozapine only group ECT only-PANSS total reduction of 40% (99-60) &amp; Clozapine only - PANSS total reduction of 46% (96-52) in (F=189.15, df=4.63, p&lt;0.001)</td>
<td>Response defined as decrease of ≥ 25% in total PANSS: PANSS total 25% (n=2/8); PANSS positive 50% (n=4/8); PANSS negative 0% (0/8) Outcome: 25% responded</td>
<td>Prolonged seizures (&gt;30s) were observed in 3 patients (90, 100, and 200 secs)</td>
<td>No follow-up</td>
</tr>
<tr>
<td>Garg et al 2012</td>
<td>Open label trial</td>
<td>11 with TRS</td>
<td>331.8mg/day (100.7) Range: (150 – 500mg)</td>
<td>6.7 B/L ECT treatments (range 6-10 ECT treatments)</td>
<td>Response defined as decrease of ≥ 30% in BPRS: 72.7% (8/11) responded BPRS scores: pre ECT- 55.9 (7.2) decrease to Post ECT-37.5 (16.3) (p=0.005) PANSS scores significantly improved: Pre ECT- Total PANSS mean score-89.3 (18.5) decreased to mean score 67.7 (25.5) (p=0.008);</td>
<td>No serious AEs.</td>
<td>No follow-up</td>
</tr>
</tbody>
</table>
Hustig and Onilov, 2009

Open label trial
2 with TRS
Not reported
16 B/L ECT treatments
ECT improved CGI scores:
CGI decreased from 6-4
100% response rate
None reported
Clinical improvement maintained at 12 months.
0/2 relapsed

Kho et al. 2004

Open label trial
11 with TRS
454.5mg/day (range 250mg-800mg/day)
Serum clozapine level 440 ng/ml
8.1 ECT treatments twice weekly
U/L for n=10 and B/L for n=3
Response defined as decrease of ≥30% in baseline Total PANSS:
72.7% (n=8/11) responded
Mean improvement in total PANSS score of 21
Transient memory problems (n=2)
Mean follow up 14.6 weeks Range (3-42)
5/8 patients relapsed

Kristensen et al. 2011

Retrospective chart review
20 (TRS=15 and TR SA=5)
No dose reported
10 ECT treatments (range 2-24)
BL and twice weekly
90% (18/20) showed an "excellent or good response"*
13/15 for TRS and 5/5 for TR SA
7/20 cases required maintenance ECT

Gazdag et al. 2006

Retrospective chart review
43 with TRS (n=27) or TR SA (n=16)
250mg/day
4.7 ECT treatments
Twice weekly and B/L
Mean change in CGI of 2.3. Greatest improvement in TR SA group (n=16):
CGI decreased from 6.25 pre-ECT to 2.31 post-ECT.
No follow-up

Table 2. Update from previous systematic reviews C+ECT

<table>
<thead>
<tr>
<th>Kupchik, 2000</th>
<th>Havaki-Kontaxaki, 2006</th>
<th>Lally, 2015 (Current review)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included RCTs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Included open label trials and retrospective reviews</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Included case series and case reports</td>
<td>3 and 11</td>
<td>6 and 15</td>
</tr>
<tr>
<td>Sample size</td>
<td>35 (17 with ECT added to clozapine)</td>
<td>22</td>
</tr>
<tr>
<td>Response to C+ECT</td>
<td>67%</td>
<td>73%</td>
</tr>
<tr>
<td>Mean number ECT treatments</td>
<td>12</td>
<td>11.5</td>
</tr>
<tr>
<td>Adverse events</td>
<td>17%</td>
<td>23%</td>
</tr>
<tr>
<td>Follow up data: Sample size</td>
<td>None reported or found</td>
<td>22</td>
</tr>
<tr>
<td>Relapse rate</td>
<td>55%</td>
<td>32%</td>
</tr>
</tbody>
</table>
### Supplementary table 1. Case series of clozapine augmented with ECT in TRS

<table>
<thead>
<tr>
<th>Study</th>
<th>No. cases</th>
<th>Mean age and duration of illness (DOI)</th>
<th>Mean Clozapine dose during ECT (and serum clozapine levels if provided)</th>
<th>ECT treatment Details (including mean no. of treatments and stimulus and seizure duration)</th>
<th>Outcome and measures used</th>
<th>Adverse Events</th>
<th>Maintenance Treatment Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases:</td>
<td>37</td>
<td>Mean age: 32.9 years / DOI: 15.4 years</td>
<td>13.3</td>
<td>74% (n=20/27) with significant reduction in BPRS or PANNS scores</td>
<td>10.8% (4/37) of cases with adverse events reported</td>
<td>20% (n=4/20) relapsed. Range of follow up 1-108 months</td>
<td></td>
</tr>
<tr>
<td>Grover et al. 2015</td>
<td>11</td>
<td>Mean age: 32.7 years / DOI: 10.3 years</td>
<td>12.8 (range 6-30) BL Mean seizure duration: 39.9 seconds</td>
<td>100% (11/11 (as communicated by author) with significant reduction in PANSS total scores (&gt;20%) Mean reduction PANSS total =23.2</td>
<td>2 with 'prolonged' seizure (duration not stated); 2 with brief (approximately 2 hours) post ictal confusion</td>
<td>No relapse , 0/11 Duration of follow-up: 6 moths-108 month</td>
<td></td>
</tr>
<tr>
<td>Kurian at al. 2005</td>
<td>3 with TRS</td>
<td>Mean age: 26 years/</td>
<td>8-10 ECT treatments</td>
<td>All with a 40-50% reduction in BPRS scores</td>
<td>None.</td>
<td>No follow-up reported</td>
<td></td>
</tr>
<tr>
<td>Kales et al. 1999</td>
<td>5 with TRS</td>
<td>Mean age: 49.1 years / Mean DOI: 29.4 years</td>
<td>12.2 ECT treatments (range 5-12) BL</td>
<td>PANSS (n=2) Mean improvement of 48.5 (123.5-75) CGI (n=5) Mean improvement 1.8 (6-4); Mean GAF improvement: 22 (range-15-55)</td>
<td>None.</td>
<td>3/5 relapsed. Duration of follow-up 4-104 weeks One required additional ECT courses due to relapse within 1 month of discontinuation</td>
<td></td>
</tr>
<tr>
<td>Benatov et al. 1996</td>
<td>4 with TRS</td>
<td>Age N/A / Mean DOI: 18.25 years</td>
<td>14.25 ECT treatments</td>
<td>BPRS (n=3) One patient 'completely recovered' Decrease in BPRS scores &gt;50% in another. Other two BPRS</td>
<td>None.</td>
<td>¾ no relapse reported at follow up; duration of 6 to 24 months of follow -up Maintenance dose of clozapine average 400mg</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Mean Age</td>
<td>Total ECT treatments</td>
<td>Improvement in BPRS</td>
<td>Seizure duration</td>
<td>Response</td>
<td>Follow-up</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------</td>
<td>----------</td>
<td>----------------------</td>
<td>---------------------</td>
<td>------------------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Cardwell et al. 1995</td>
<td>5 (PS=4; SA=3)</td>
<td>41.25 years</td>
<td>21.6 ECT treatments (17-31)</td>
<td>26.9% improvement in total BPRS; 25.3% improvement in positive BPRS scores; 21.3% improvement in negative BPRS scores;</td>
<td>54.2 seconds</td>
<td>Pts: marked/moderate response =3; minimal response =3; minimal/no response=3</td>
<td>None</td>
</tr>
<tr>
<td>Frankenburger et al. 1993</td>
<td>9 (n=2 Schiz; n=7 SA)</td>
<td>36.3 years</td>
<td>11 ECT treatments Seizure duration: 54.2 seconds</td>
<td>3 Pts: marked/moderate response =3; minimal response =3 minimal/no response=3</td>
<td>54.2 seconds</td>
<td>Pts: marked/moderate response =3; minimal response =3 minimal/no response=3</td>
<td>None</td>
</tr>
</tbody>
</table>
Table 2. Case reports of clozapine augmented with ECT in TRS

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient age and gender</th>
<th>Diagnosis as reported and duration of illness</th>
<th>Clozapine dose when ECT commenced (and serum levels if provided)</th>
<th>Psychotropic medication during ECT (and serum levels if provided)</th>
<th>ECT treatment Details (including mean stimulus if provided)</th>
<th>Outcome and measures used</th>
<th>Adverse Events</th>
<th>Maintenance Treatment Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases (n=15)</td>
<td>31.5 years</td>
<td>14 with TRS and 1 with TRSAD</td>
<td>Mean dose: 626.7mg</td>
<td>11.6 (14/15 with BL ECT)</td>
<td>80% responded to C+ECT (n=8/10)</td>
<td>Outcome measures used</td>
<td>Adverse effects were reported in 11/15. n=4: mild and transient n=4: adverse effects led to discontinuation of ECT. N=1: death secondary to PE</td>
<td>44% (n=4/9) relapsed 33% (n=4/12) maintenance ECT for longer than 1 month</td>
</tr>
<tr>
<td>Bannour et al (2014)</td>
<td>32, Female</td>
<td>Undifferentiated Schizophrenia, 11 years</td>
<td>700mg bd</td>
<td>Clozapine 700mg bd</td>
<td>16 sessions of BL ECT (3 sessions per week)</td>
<td>BPRS score decreased from 95 to 29</td>
<td>None reported</td>
<td>ECT continued at the rate of 1 session per</td>
</tr>
</tbody>
</table>

BPRS: Brief Psychiatric Rating Scale
<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Duration</th>
<th>Medication Details</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatia et al (1998)</td>
<td>35</td>
<td>Male</td>
<td>Paranoid Schizophrenia</td>
<td>4 years</td>
<td>Pimozide (during ECT course 1 and 2), Clozapine (during ECT course 3, titrated during treatment to 800mg), Clonazepam 0.5mg tds</td>
<td>Discharged to community, Stable at 20 months.</td>
</tr>
<tr>
<td>Biederman et al (2011)</td>
<td>39</td>
<td>Male</td>
<td>Paranoid Schizophrenia</td>
<td>&gt;20 years</td>
<td>Clozapine 300mg daily, 12 right unilateral ECT sessions</td>
<td>None reported</td>
</tr>
</tbody>
</table>

After 24 sessions, patient was 'well stabilized', and functioning socially.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Initial Treatment</th>
<th>Final Treatment</th>
<th>ECT Details</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerretsen et al (2011)</td>
<td>39, Male</td>
<td>Paranoid Schizophrenia</td>
<td>Clozapine 450mg bd</td>
<td>15 bilateral ECT treatments</td>
<td>BPRS: 3 months before ECT = 64; during ECT 26</td>
<td>Cognitive dysfunction on days of treatment</td>
<td>Maintenance on clozapine and reduced to twice weekly bilateral ECT for 3 weeks.</td>
</tr>
<tr>
<td>Keller et al (2009)</td>
<td>19, Male</td>
<td>Schizophrenia</td>
<td>1600 mg daily; 917 ng/mL (previously up to 1800mg daily)</td>
<td>Increased to 1700mg during treatment; 1083ng/mL</td>
<td>8 weeks bilateral ECT (3/week for 4 weeks, 2/week for 4 weeks)</td>
<td>BPRS: From 34 pre-treatment to 30 post-treatment</td>
<td>Postictal confusion and mild difficulties with anterograde memory</td>
</tr>
<tr>
<td>Authors</td>
<td>Age, Gender</td>
<td>Diagnosis</td>
<td>Initial Treatment</td>
<td>Treatment Details</td>
<td>Outcomes</td>
<td>Side Effects</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
<td>----------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------------------------------</td>
<td>------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Klapeheke et al (1991)</td>
<td>26, Female</td>
<td>Schizoaffective Disorder, Bipolar type (duration not reported)</td>
<td>450mg daily</td>
<td>Titrated during ECT to 600mg daily</td>
<td>9 sessions bilateral, brief pulse ECT- 14 adequate seizures (Pulse freq 50/0Hz, Pulse width 0.75 or 1.5ms, Duration 1.25 or 1.5s)</td>
<td>'Dramatic clinical response with resolution of hallucination, delusions and thought disorder</td>
<td>Tachycardia only, Sustained improvement over 3 weeks with continued upward titration of Clozapine (to 400mg bd)</td>
</tr>
<tr>
<td>Lee WK et al (2008)</td>
<td>57, Female</td>
<td>Schizophrenia, 30 years</td>
<td>400mg daily</td>
<td>Clozapine 400mg daily</td>
<td>10 sessions bilateral ECT, then discontinued due to a/e*</td>
<td>-</td>
<td>*PISA SYNDROME, Clozapine reduced to 25mg due to s/e, then maintained at 300mg after</td>
</tr>
<tr>
<td>Manjunatha et al (2011)</td>
<td>39, Male</td>
<td>Paranoid Schizophrenia, (duration not reported)</td>
<td>400mg daily</td>
<td>Clozapine 400mg daily</td>
<td>Bitemporal, thrice-weekly, suprathreshold, modified ECT Stopped after 12th session due to a/e*</td>
<td>-</td>
<td>*DELIR-IUM, Complete recovery from delirium within 48 h without any further complications; Clozapine was restarted after 2 days; dose gradually increased to 150 mg</td>
</tr>
<tr>
<td>Manjunatha et al (2011)</td>
<td>40, Male</td>
<td>Paranoid Schizophrenia, (duration not reported)</td>
<td>300mg daily</td>
<td>Clozapine 300mg daily</td>
<td>Bitemporal, thrice-weekly, suprathreshold, modified ECT Stopped after 6th session due to a/e*</td>
<td>-</td>
<td>*DELIRIUM and ASPIRATION PNEUMONITIS, Following recovery, Clozapine monotherapy was restarted at a dose of 300 mg/day without re-emergence of delirium</td>
</tr>
<tr>
<td>Safferman et al (1992)</td>
<td>33, Female</td>
<td>Paranoid Schizophrenia, 10 years</td>
<td>400mg daily</td>
<td>Clozapine 400mg daily, Lorazepam tapered and stopped after 3rd ECT</td>
<td>8 bilateral ECT sessions (pulse freq 60-80hz, pulse width 1.4-1.6ms, stimulus duration 1.4-1.6s)</td>
<td>Positive symptoms ‘markedly reduced in intensity’, improved sociality</td>
<td>Mild hypertension and tachycardia</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>---------------------------------</td>
<td>-------------</td>
<td>------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Sieneart et al (2004)</td>
<td>37, Male</td>
<td>Paranoid Schizophrenia (duration not reported)</td>
<td>600mg daily</td>
<td>Clozapine 600mg daily Reduced to 450mg daily after 3rd treatment due to a/e*</td>
<td>Bilateral ECT, 11 treatments (Pulse width 0.5 milliseconds, frequency 30 Hz, duration 5 seconds, charge 120 mC, current 800 mA)</td>
<td>Hours and days after 1st treatment: ‘remarkable diminishment of anxiety, hostility, and agitation’</td>
<td>Motor agitation and confusion directly after 1st treatment</td>
</tr>
<tr>
<td>Sinha et al, 2013</td>
<td>22, Male</td>
<td>Paranoid Schizophrenia (duration not reported)</td>
<td>100mg daily</td>
<td>Clozapine 100mg daily 4 ECT treatments</td>
<td>-</td>
<td>Patient died from pulmonary embolism after 4th treatment</td>
<td>-</td>
</tr>
<tr>
<td>Study</td>
<td>Gender</td>
<td>Age (years)</td>
<td>Diagnosis</td>
<td>Treatment Details</td>
<td>Side Effects</td>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------</td>
<td>-------------</td>
<td>----------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Vowels et al (2014)</td>
<td>Female</td>
<td>18</td>
<td>Schizophrenia and Moderate Intellectual Disability, (duration not reported)</td>
<td>1st Treatment: 8 ECT sessions</td>
<td>500mg daily Clozapine 500mg daily 2nd Treatment: 12 ECT sessions 1st Treatment: significant improvement was observed with no evidence of ongoing auditory hallucinations or physical aggression. 2nd Treatment: 'again result[ed] in improvement' Relapse after 1-2 weeks after both treatments</td>
<td>None reported</td>
<td>'With continuation ECT (currently at a total of more than 35 sessions), continues to show behavioural stability, is able to attend school, and has been discharged to supported community accommodatio n following a 16 month admission’</td>
</tr>
<tr>
<td>Yoshino et al (2014)</td>
<td>Female</td>
<td>37</td>
<td>Schizophrenia, 11 years</td>
<td>BPRS Before Clozapine: 81; on Clozapine: reduced to 67; after one course of ECT reduced to 40 Bilateral ECT-10 treatments (2 or 3 per week)</td>
<td>Anterograde amnesia resolved after a few hours</td>
<td>Continuation (maintenance) ECT was then done twice every 4 weeks and there were no significant ill effects. Maintenance ECT</td>
<td></td>
</tr>
</tbody>
</table>