Acta Neuropsychiatrica 2015

DOI: 10.1017/neu.2015.8

ACTA NEUROPSYCHIATRICA

Review Article

Combined use of clozapine and ECT: a review

Grover S, Hazari N, Kate N. Combined use of clozapine and ECT: a review.

Objective: This paper aims to review the available evidence for the use of clozapine and electroconvulsive therapy (ECT) in combination.
Methodology: Electronic searches were carried out to identify reports describing the combined use of clozapine and ECT.
Results: Forty reports including 208 patients were identified. The majority of reports were in the form of case reports and case series, with few retrospective and open-label studies. The majority of patients were aged between 18 and 65 years and diagnosed with schizophrenia or schizoaffective disorder. Most of the patients refractory to clozapine were started on ECT as an augmentation therapy; however, in some reports, both ECT and clozapine were started concurrently, and in few cases clozapine was started after ECT. In terms of effectiveness, 37.5–100% patients improved in short-term, and sustained long-term improvement (3 weeks to 24 months) was described in few studies. In terms of the side-effect profile, five patients each had delirium and tachycardia and only four patients were described to have prolonged seizures. Overall, the combination was considered effective and safe.
Conclusion: There is evidence for the effectiveness and safety of the clozapine–ECT combination and it should be used in patients with treatment-resistant schizophrenia who do not respond to clozapine.

Sandeep Grover[1], Nandita Hazari[2], Natasha Kate[2]

[1]Department of Psychiatry, Post Graduate Institute of Medical Education and Research, Chandigarh, India; and [2]Department of Psychiatry, KEM Hospital, Mumbai, India

Keywords: augmentation; clozapine; ECT

Dr. Sandeep Grover, Assistant Professor, Department of Psychiatry, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India.
Tel: +0091 172 2756807 (O);
Fax: +91 172 2744401; 2745078;
E-mail: drsandeepg2002@yahoo.com

Accepted for publication January 20, 2015

First published online February 20, 2015

Summations

- The existing data suggest that combination of clozapine and electroconvulsive therapy is useful in managing patients who have treatment-resistant schizophrenia or who are refractory to clozapine alone.
- In terms of side-effects, there is a need to monitor patients carefully for side-effects like tachycardia, prolonged seizures and delirium.

Consideration

- Most evidence stems from case reports and case studies.
- Limited data are available with regard to the combined use of clozapine and electroconvulsive therapy.

Introduction

Clozapine is an atypical antipsychotic, which is usually reserved for patients with schizophrenia who have treatment resistance, because of its side-effect profile. Available evidence suggests that compared with other antipsychotics, clozapine has superior efficacy/effectiveness among patients with treatment-resistant schizophrenia (TRS) (1,2). However, it is now increasingly becoming evident that significant proportions (40–70%) of TRS patients have sub-optimal response to clozapine (1,2). Owing to this,

many patients with TRS do require augmentation of clozapine with other antipsychotics (3), other medications (3), transcranial magnetic stimulation (4–8) and transcranial direct-current stimulation (9).

Electroconvulsive therapy (ECT) is possibly the oldest treatment modality in psychiatry, which has survived till today and is considered to be useful in patients with various severe mental disorders including schizophrenia. Many studies have shown that ECT is efficacious in patients with schizophrenia (10). Over the years, in western countries, its use has been limited to patients with mood disorder, especially unipolar and bipolar depression. However, it is still used quite commonly in developing countries for the management of schizophrenia (11–13). Studies that have evaluated the effectiveness of ECT in schizophrenia have used it in combination with various antipsychotic medications and suggest that it is very useful and safe in patients with treatment-refractory schizophrenia (10).

As expected, due to existing evidence of the usefulness of ECT in patients refractory to antipsychotics including clozapine, many authors have evaluated the efficacy of the combined use of clozapine and ECT in patients with schizophrenia. Infact, the combined use of clozapine and ECT was proposed about 25 years ago (14) and was first reported a year later (15,16). However, initial reports caused an alarm about the epileptogenic potential of clozapine, as some patients experienced prolonged seizures with the combined use of clozapine and ECT (17,18). However, later reports suggested that the risk for prolonged seizures with the combined used of clozapine and ECT is not seen universally. As a result, many authors have evaluated the efficacy of the combined use of clozapine and ECT.

Over the past two-and-half decades, reasonable amount of literature has accumulated, which suggests that this combination may be useful in a significant proportion of patients with schizophrenia who do not respond to clozapine alone or the two modalities individually. Many previous reviews have looked at the evidence for the combined use of clozapine and ECT (10,19–22). Some of these reviews have specifically focused on the available evidence among patients with schizophrenia (20). These reviews have mostly focused on data published before 2005, and recent reviews (22) have not considered data published after 2005. In view of this, the present review aimed to systematically evaluate the available evidence for the combined use of clozapine and ECT in various psychiatric disorders.

Search strategies

For this review, an electronic search was carried out using PubMed, Google Scholar and Science Direct, EMBASE and SCOPUS to find all the relevant published studies in English language. The search terms that were used in various combinations were clozapine, ECT, combination, concurrent use, augmentation, schizophrenia, schizoaffective, bipolar disorder, mania, depression, treatment-resistance, clozapine-refractory and clozapine-resistance. All the search results were reviewed in order to identify studies reporting the use of a combination of clozapine and ECT. The full-text articles retrieved from the electronic search were further reviewed manually to locate additional references. Studies in which both clozapine and ECT were not used concurrently (i.e. there was no overlap of both the treatments) were excluded. The electronic searches also yielded reviews on this topic (10,19–22), and these were reviewed by the authors to find additional references. We were able to locate 40 reports (208 patients), which were reviewed for short-term effectiveness, long-term outcome and side-effects. Of these, occasional reports have described only the side-effect profile and have not explicitly commented on the outcome with regard to the effectiveness of the combined treatment (18,23,24).

Type of available data

The majority of reports were in the form of case reports and case series, with only occasional studies including more than 10 patients receiving the combined treatment (25–29).

Patient profile

The majority of data on the combined use of clozapine and ECT were available for patients diagnosed with schizophrenia. However, there were a little data for the use of combination in patients with schizoaffective disorder, bipolar disorder, current episode mania and patients with major depression. Occasional reports have used the combination for patients with psychosis in Parkinson's disease (30). In terms of patient profile, the majority of studies have included adults (19–65 years), with occasional reports including patients aged 18 or less (18,27) or those above 65 years of age (30–32). In terms of gender profile, the majority of studies had higher number of male patients.

Short-term effectiveness

Reports that evaluated effectiveness in patients of schizophrenia have mostly included patients who are refractory to clozapine and were receiving clozapine for some time before being augmented with ECT

https://doi.org/10.1017/neu.2015.8 Published online by Cambridge University Press

(25–28,33). However, occasional reports have used the combination concurrently (27,34,35). Although some of the reports have used rating scales such as the Positive and Negative symptom scale (PANSS) and Brief Psychiatric Rating scale (BPRS) to evaluate the response of the combined treatment, many authors have not relied on the standardised rating scales and have reported the outcome on the basis of the subjective outcome (25,28,36–38). Some of the studies that have used the rating scales have used various cut-offs such as more than 20–40% reduction in the scores to consider the treatment response (26,27,29), whereas other studies have just described the improvement in terms of reduction in the scores on the scale, without reporting the percentage of patients who responded to the treatment. One small case series ($n = 2$) used the combined treatment in patients with psychosis in the presence of Parkinson's disease and reported marked clinical improvement (30).

As shown in Table 1, there are 16 case reports/series providing information about 25 patients with schizophrenia or schizoaffective disorder (15,16). In most of these reports, ECT was considered after the use of clozapine, with some of the reports specifying that the patients were considered clozapine non-responsive before being considered for augmentation with ECT (26,27,29,31,36,39–41). However, occasionally, some reports mentioned the use of clozapine following the use of ECT (18). The dose of clozapine used for these patients varied from 50 to 800 mg/day and the number of ECT sessions varied from 8 to 35, with use of continuation/maintenance ECT in some reports (39,42). In most of the reports, authors have suggested the use of bilateral ECT. In terms of response to the combined treatment, the evidence from case reports suggests that the combined treatment leads to reduction in psychopathology; however, in only occasional reports, standard rating scales have been used (31,40,43,44). Some case reports have included patients with

Table 1. Case reports on use of clozapine and ECT in patients with schizophrenia and schizoaffective disorders

Authors	Sample size	Gender distribution	Clozapine dose in mg/day	ECT details	Outcome
Masiar and Johns (17)	1	M = 1			No benefit
Klapheke*(15)	1	F = 1	600	14 bilateral ECT	Improved clinically
Safferman and Munne (54)	1	F = 1	400	Eight bilateral ECTs	Improved clinically
Klapheke*(47)	1				Improved
Benatov et al. (43)	4	M = 2 F = 2	400-800	9–20 ECTs [Bilateral (specified for only one patient)]	Reduction in BPRS and PANSS by 40% or more in three out of the four cases
Bloch et al. (18)	1		50		Efficacy not mentioned
Bhatia et al. (55)	1	M = 1	800	Bilateral ECT	Showed improvement with successive courses of ECT Maintained improvement up to 20 months post-discharge on clozapine
Husni et al. (44)	1	M = 1	500	20 Sessions	BPRS reduced from 42 to 24
Kales et al. (31)	5	M = 3 F = 2	200–900	Bilateral ECTs number: 5–12	Significant improvement in GAF and CGI scores Improvement sustained for less than 4 months in three of the five patients Long-term outcomes were not good for most the patients
Dean (46)	1			Bilateral ECT	Patient with self-injurious behaviour, non- responsive to treatment showed marked clinical improvement
Sienaert et al. (56)	1	M = 1	600	13 Bifrontal ECTs	Improved clinically
Kurian et al. (57)	3	M = 3	350–450	8–10 ECTs	40–50% reduction in BPRS No cognitive deficits
Keller et al. (45)	1	M = 1	1700	Bilateral ECT Number of sessions: 20, followed by maintenance ECT	BPRS reduced from 34 to 30 Violent behaviour reduced
Biedermann et al. (40)	1	M = 1	300	12 Unilateral ECTs	Improvement in clinical symptoms (PANSS total reduced from 78 to 67) and cognitive measures by week 10
Bannour et al. (39)	1	F+1	700	Bilateral ECT (initial course of 16 sessions followed by eight maintenance ECTs)	With the combination and maintenance ECT, showed improvement
Vowels et al. (42)	1	F = 1	500	Bitemporal ECT course followed by continuation ECT (total >35 sessions)	Improved clinically

BPRS, Brief Psychiatric Rating scale; CGI, Clinical Global Impression scale; ECT, electroconvulsive therapy; F, female; GAF, Global Assessment of Functioning scale; M, male; PANSS, Positive and Negative symptom scale.

* These patients were diagnosed with schizoaffective disorder.

https://doi.org/10.1017/neu.2015.8 Published online by Cambridge University Press

schizophrenia with intellectual disability, (42) and in terms of specific symptoms some of the reports suggest improvement in violent (45) and self-injurious behaviour (46).

In terms of studies including five or more patients receiving combined clozapine and ECT treatment, we could identify 15 studies that included patients with schizophrenia or schizoaffective disorder, with sample sizes varying from 7 to 39 and with a total sample of 167 (See Table 2). Of these 15 studies, exact details were not available for two studies (14,29), as the author of one of these reports provided some information about the improvement in an editorial, (14) and in the second case the authors of the recently published study (38) mentioned about the improvement in a previous cohort of 15 patients, but they did not provide any reference for the same. Among these studies, some studies also included few patients with bipolar disorder and major depression (25). All these reports have been either retrospective studies (25,27,28,33) or open-label studies (29,34–36,47), except for that of Petrides et al. (29), which was a prospective randomised single-blind cross-over design study. Occasionally, studies have included a comparator group such as patients on clozapine alone (29,34,35) and ECT alone (34), non-clozapine group (27,28). As with case reports, majority of these reports have included patients with TRS as well as clozapine-resistant. Most of these studies have used standard rating scales such as PANSS, BPRS and Clinical Global Impression (CGI) severity scale. As expected, in most of the studies, ECT was considered after using clozapine for variable period of time. However, in occasional studies, the use of clozapine followed the use of ECT in some of the patients (27,33) or both the treatments were started concurrently (34,35,41). The dose of clozapine used varied from 200 to 800 mg/day and the number of ECT treatments varied from 8 to 18.

In terms of the percentage of patients responding to the combined clozapine and ECT treatment, the range varied from 35.7% to 100%. However, it is important to note that this wide variation is possibly due to the difference in the criteria used to define 'response' across different studies using different scales. In terms of percentage reduction in symptoms across different scales, studies have reported a range varying from 26.9% to 71% reduction in the severity of symptoms. In studies where the authors have evaluated the response to different types of symptoms, evidence suggests that the combined treatment is beneficial in positive, negative and disorganised symptoms (27).

When the combined treatment was compared with other strategies, evidence from one study suggested that the combined treatment led to higher reduction in negative symptoms in the combination and clozapine group compared with the ECT-only group (34).

However, other studies have reported no difference in symptom reduction, when the combined treatment was compared with the clozapine-only group (35). Studies that have compared combination of clozapine and ECT with that of ECT and other psychotropics reported no difference in the response rate between the clozapine and non-clozapine groups (27). In one study, which compared clozapine and non-clozapine groups, authors did not specifically report the response rate for the combined use of clozapine and ECT; however, in terms of comparison, they reported a lack of difference in improvement between the clozapine and ECT group and the non-clozapine and ECT group (28).

In terms of other outcome measures, studies suggest that the combined use of clozapine and ECT is associated with significantly lower duration of hospital stay and lower increase in the dose of clozapine in the combination group (35).

In terms of the effectiveness of the combined treatment of clozapine and ECT in mood disorders, data are limited to only 12 cases, of which eight cases are of bipolar disorder and four of unipolar depression (see Table 3). In general, these patients did not respond to the conventional treatments used in various combinations before being considered for clozapine. In a particular report, the patient did not respond to the treatment with clozapine alone or with ECT alone (52). Overall, evidence suggests beneficial effect of the combined treatment. However, maintenance ECT was used in four out of the 10 patients.

Long-term outcome

Compared with other aspects of the combined use of clozapine and ECT, reports have been inconsistent regarding the long-term outcome of the patients who received the combined treatment. Further, the reports that have mentioned about the long-term outcome have varied significantly in the duration of follow-up after last ECT, varying from 3 weeks to 24 months (See Table 4). From the available evidence, it can be concluded that some patients maintain sustained improvement after the last ECT.

Mechanism of action

Fink (14) suggested that the positive treatment response with the combined use of clozapine and ECT could be due to the physiological changes that occur with two treatments. According to Fink, ECT leads to increase in the blood–brain barrier permeability and because of this, bigger molecules like clozapine are able to penetrate the brain better and

https://doi.org/10.1017/neu.2015.8 Published online by Cambridge University Press

Table 2. Studies evaluating the effectiveness of clozapine and ECT in patients with schizophrenia and schizoaffective disorder

Authors	Sample size	Gender distribution	Diagnosis	Study design	Rating scales used	Response criteria	Sequence	Clozapine dose in mg/day	ECT details	Outcome
Kristensen et al. (28)	21 (of 79)	Clozapine pts-NA M = 31 F = 48	Clozapine pts-NA Schizophrenia (n = 55) Schizoaffective disorder (n = 17) Persistent delusional disorder (n = 7)	Retrospective study	None	NA	CLZ → ECT	NA	Bilateral ECT Mean −7 ECTs	Specific outcome information not available for clozapine group Overall augmentation of antipsychotic with ECT lead to excellent to good improvement in 66 patients (83.5%), moderate level of improvement in eight (10.1%), and poor improvement in five (6.3%) patients Excellent-to-good response in 85.7% of patients with delusional disorder: 83.6% patients with schizophrenia and 70.6% in patients with schizoaffective disorder
Fink (14)	7	NA	Schizophrenia (CR)	NA	NA	NA	CLZ → ECT	NA	NA	Six (85.7%) out of seven patients were markedly better
Petrides et al. (38)	7	NA	Schizophrenia (n = 6), schizoaffective (n = 1)	NA	NA	NA	NA	NA	NA	All improved
Cardwell and Nakai (33)	7	NA	Schizophrenia (n = 4), Schizoaffective bipolar (n = 2), Schizoaffective depressed (n = 1)	Retrospective study	BPRS	Not defined	CLZ → ECT (n = 4) ECT → CLZ (n = 3)	NA	NA	BPRS scores reduced by 26.9%, positive symptoms reduced by 25.3%, and negative symptoms improved by 21.3%. In terms of specific symptoms, hallucinatory behaviour (41.7%) and disorganisation (45.5%) were markedly reduced
Frankenburg et al.*(25)	12	M = 8 F = 4	Schizophrenia (n = 2), Schizoaffective, depressed (n = 6), schizoaffective bipolar (n = 1), Bipolar mania (n = 1), major depression with psychosis (n = 2)	Retrospective	None	NA	CLZ → ECT	550	NA	Three patients had a marked clinical improvement, one had moderate level of improvement, four had minimal improvement, two had minimal to no response, and two had no response
James and Gray (41)	6	NA	Schizophrenia (TRS)	Open trial	BPRS, GAS	Not defined	Concurrent use of CLZ and ECT	NA	12 ECTs	32% reduction in BPRS over the 6 weeks
Kho et al. (26)	11	M = 6 F = 5	Schizophrenia (CR)	Open trial	PANSS	reduction >30% on PANSS)	CLZ → ECT	250-800	UL	72.7% responded
Masoudzadeh and Khalilian (34)	6	M = 3 F = 3	Schizophrenia (TRS)	Open-label	PANSS	Not defined	Concurrent use of CLZ and ECT	NA	12 UL ECT	71% reduction in PANSS in the combination group, compared with 46% and 41% in the clozapine and ECT groups, respectively Higher reduction in negative symptoms in the combination and clozapine group compared with ECT only group

Table 2. (*Continued*)

Authors	Sample size	Gender distribution	Diagnosis	Study design	Rating scales used	Response criteria	Sequence	Clozapine dose in mg/day	ECT details	Outcome
Flamarique et al. (27)	12	M = 6	10 = Schizo 2 = Schizoaffective	Retrospective	PANSS CGI	≥20% improvement in the PANSS	CLZ → ECT (n = 6) Concurrent use of CLZ and ECT (n = 6)	316 (SD 178)	BL frontotemporal Number of ECTs 13 (SD-3.95) sessions	66.7% of patients showed response (reduction >20% on PANSS) Total PANSS reduced from 82.17 to 58.5 (28.8% reduction) and CGI reduced from 6.92 to 3.75 No difference in the response rate between clozapine and non-clozapine group
Koen et al. (35)	10	M = 8 F = 2	Schizophrenia (CR) Schizoaffective disorder (n = 3)	Open-label	PANSS	Not defined	Concurrent use of CLZ and ECT	550–570	6	No difference in reduction in psychopathology between combination and only clozapine group (mean reduction in PANSS score 20.2 vs. 27.6)
Petrides et al. unpublished (cross ref) (29)	15	NA	Schizophrenia (CR)	Open-label	BPRS	Decrease in rating by 40%)	CLZ → ECT	NA	Bilateral ECT	Nine (60%) out of 1five patients met the response criteria
Petrides et al. (29)	39	M = 28 F = 11	Schizophrenia (CR)	Randomised single-blind cross-over design trial	BPRS CGI CGI-S Neuro-congitive battery	≥40% improvement in the psychotic symptom subscale of BPRS CGI-severity rating of mild or less (<3) CGI-improvement rating of much improved (≤2)	CLZ → ECT	Cloz + ECT group: 525.0 (SD-224.3) Cloz group: 511.1(SD-171.0)	BL ECT Mean number of ECTs: Cloz + ECT group: 15.8 (SD-.2) Cloz group: 14.3 (SD-5.3)	10 (50%) out of 20 patients in the ECT augmentation group and none (0%) of the patients in the clozapine group met the response criterion In the crossover phase, nine (47.4%) of 19 patients met the response criterion Overall, 19 (48.7%) patients who received clozapine plus ECT responded
Kales et al. (36)	14	M = 9 F = 5	Schizophrenia (CR)	Open-label	NA	NA	NA	200–800 mg/day	8–18 BL	Five (35.7%) patients showed marked and sustained clinical improvement Five (35.7%) patients showed transient improvement followed by relapse (no mention of follow-up period) One (7.1%) patient had transient improvement followed by relapses and received maintenance ECT but experienced relapsed on maintenance ECT

BL, Bilateral; BPRS, Brief Psychiatric Rating scale; CGI, Clinical Global Impression scale; CLZ, clozapine; CR, clozapine refractory; ECT, electroconvulsive therapy; F, female; M, male; NA, not available; PANSS, Positive and Negative symptom scale; TRS, treatment-resistant schizophrenia; UL, unilateral.

* These studies also included some of the patients with schizoaffective disorder.

Table 3. Case reports on the use of clozapine and ECT in patients with mood disorders

Authors	Sample size	Gender distribution	Diagnosis	Sequence	Clozapine dose in mg/day	ECT details	Outcome
Landy (48)	2	F	Major depression with psychosis	CLZ → ECT	400	11–14 BL ECT along with maintenance ECT	GAF improved from 25–28 to 50–55
Frankenburg et al. (25)	Three out of 12	M = 1 F = 2	Bipolar mania (n = 1), major depression with psychosis (n = 2)	CLZ → ECT	550	NA	Outcome specifically not available for patients with affective disorders Overall, three patients had a marked clinical improvement, one had moderate level of improvement, four had minimal improvement, two had minimal to no response and two had no response
Beale et al. (32)	1	F	RDD with psychosis	NA	NA	Nine BL ECT along with maintenance ECT	Improved
Lurie (49)	1	M	Bipolar disorder, mania	NA	>200	NA	Improved
Poyurovsky and Weizman (50)	2 (treatment resistant mania)	M = 1 F = 1	Bipolar disorder, mania	ECT → CLOZ	250–350	7–12 BL bitemporal ECTs	Significant improvement in both the cases
Godeman and Hellweg (51)	1		Treatment refractory bipolar	ECT → CLOZ	NA	NA	???
Chanpattana et al. (52)	1	M	Bipolar disorder, mania (not responding to conventional treatment, ECT alone, clozapine alone)	ECT → CLOZ	150	BL ECT course followed by maintenance ECT	Improved
Tsao et al. (53)	1	M	Bipolar disorder, manic episode	CLZ → ECT	200 mg	BL ECT	Improved with addition of ECT Required maintenance ECT and relapsed on discontinuation of maintenance ECT

BL, bilateral; CLZ, clozapine; ECT, electroconvulsive therapy; F, female; GAF, Global Assessment of Functioning scale; M, male; NA, not available; UL, unilateral.

Table 4. Studies reporting the long-term outcome of patients receiving clozapine and ECT

	Diagnosis	Sample size	Outcome
Landy (48)	Major depression with psychosis	2	One patient remained well for at least 6 weeks on clozapine after completion of ECT One patient remained weak with maintenance ECT and clozapine for 2 months
Klapheke (15)	Schizoaffective disorder, mania	1	Remained well for at least 3 weeks on clozapine after completion of ECT
Safferman and Munne (54)	Schizophrenia	1	Remained well for at least 3 weeks on clozapine after completion of ECT
Factor et al. (30)	Psychosis related to Parkinson's disease	2	One patient remained well on clozapine for 8 month and another for 22 months
Kales et al. (36)	Schizophrenia (significant symptoms despite being on clozapine)	14	Five (35.7%) patients showed marked and sustained clinical improvement Five (35.7%) patients showed transient improvement followed by relapse (no mention of follow-up period) One (7.1%) patient had transient improvement followed by relapses and received maintenance ECT but experienced relapse on maintenance ECT
Benatov et al. (43)	Schizophrenia	4	Patients who responded remained well for 6 to 24 months
Bhatia et al. (55)	Schizophrenia	1	Maintained improvement till 20 months post-discharge on clozapine
James and Gray (41)	Schizophrenia	6	Only one of the six patients became disturbed again after 6 months
Kales et al. (31)	Schizophrenia (four of the five patients were clozapine-resistant)	5	Improvement sustained for less than 4 months in three of the five patients Long-term outcome –not good for most patients
Chanpattana et al. (52)	Bipolar disorder, mania	1	Improved, maintained well for the 18-month period
Kho et al. (26)	Schizophrenia (clozapine non-responders)	11	During the mean follow-up duration of 16 (range 4–42) weeks, five patients had relapse of symptoms after the initial response. Relapse occurred between week 3 and 19 Of those who relapsed, three of the five patients received a second ECT course and remained well with maintenance ECT and clozapine

Table 5. Side-effects associated with ECT in patients receiving combination of clozapine and ECT

Authors	Sample size	Side-effect noted
Klapheke (15)	1	Tachycardia
Landy (48)	2	Tachycardia
Masiar and Johns (17)	1	Prolonged Seizure (123 s) followed by two GTCS on day 4 and 6 ($n = 1$) after ECT
Safferman and Munne (54)	1	Tachycardia, hypertension
Beale et al. (32)	1	Supraventricular tachycardia (died 3 weeks after last ECT)
Kales et al. (36)	15	Significant tachycardia ($n = 1$)
Bloch et al. (18)	1	Prolonged seizure (6-min long terminated by diazepam) ($n = 1$)
Poyurovsky and Weizman (50)	2	30% prolongation in seizure after start of ECT ($n = 1$)
Godeman and Hellweg (51)	1	Delirium while on maintenance ECT and clozapine 50 mg/day
Bhatia et al. (55)	1	Tachycardia, hypertension
Chanpattana et al. (52)	1	Post ECT delirium ($n = 1$)
Kho et al. (26)	11	Memory problems ($n = 2$) Confusion ($n = 1$)
Sienaert et al. (56)	1	Recurrent episodes of delirium
Koen et al. (35)	5	Prolonged seizure ($n = 1$)
Keller et al. (45)	1	Cognitive deficits ($n = 1$)
Manjunatha et al. (23)	2	Delirium ($n = 2$)
Petrides et al. (29)	39	Mild confusion leading to postponement of treatment ($n = 2$)
Grubisha et al. (24)	1	Takotsubo cardiomyopathy ($n = 1$)

are able to reach to more areas of the brain. Accordingly, ECT augments the effectiveness of clozapine. Another mechanism that could explain the augmentation of clozapine with ECT is the evidence in the form of an association between response to clozapine and the degree of electroencephalogram (EEG) slowing. Accordingly, when clozapine was augmented with ECT, it enhanced the EEG slowing and led to better response.

Side-effects

Since the beginning of the combined use of clozapine and ECT, reports have raised concerns about the side-effects like prolonged seizures (15) and tachycardia (15,17,54). However, over the years, the available data suggest that the incidence of prolonged seizures is not very high. Overall, existing literature showed prolongation of seizure/prolonged seizures only in four cases. There are occasional reports of delayed seizures (18) and development of grandmal epilepsy in patients while on clozapine (17), which cannot in the real sense be considered related to the combined use of clozapine and ECT. As it is evident from Table 5, the common ECT-related side-effects seen with the combined use of clozapine and ECT include tachycardia and delirium or post ECT confusion. In terms of fatality, only one case report described fatal outcome in a patient 3 weeks after the last ECT, who developed supraventricular tachycardia (32). Another report described development of Takotsubo cardiomyopathy few hours after the last ECT while on clozapine (24). Some of the recent studies have specifically assessed cognitive functions of patients receiving the combined treatment and

https://doi.org/10.1017/neu.2015.8 Published online by Cambridge University Press

have actually reported no change (29,40,57) or improvement in the same. Overall, from the available evidence, it can be concluded that the risk for prolonged seizure is possibly not very high. Studies that have compared the side-effects of clozapine alone with clozapine and ECT in combination also do not suggest that the combined use increases the risk of clozapine-related side-effects (34).

Discussion

This review provides an update on the combined use of clozapine and ECT. Although some of the recent reviews have discussed the issue regarding the use of ECT in patients with schizophrenia (58,59), the present review provides further update on the available data for the combined use of clozapine and ECT. Further, in contrast with recent reviews (3,22), which have focused on data from clinical trials or observation studies only, the present review included all the existing data to the extent of case reports and covered additional data published recently regarding the combined use of clozapine and ECT (24,28,29,39,42).

This review suggests that over the years data on the combined use of clozapine and ECT has expanded. When one looks at the literature, data has now expanded from the single case reports to small-sample retrospective studies and open-label trials. With the recent addition of a randomised single-blind cross-over trial, it can be said that the level of evidence has been further strengthened. Further, in contrast with earlier reports, most of the current reports have reported improvement in the form of reduction in psychopathology on standardised scales and some have reported the long-term outcomes of the patients treated by the combination.

Available evidence suggests that the combined use may be useful in patients with TRS and clozapine-refractory patients at least in the short-term. The recent randomised single-blind cross-over trial clearly shows that about half of the patients who initially did not respond to the clozapine trial responded to the clozapine and ECT combination. This study clearly shows the role of augmentation of clozapine with ECT. With regard to the long-term effectiveness, some of the data suggest that augmentation with a course of ECT with or without maintenance ECT leads to sustained improvement in some of the patients. In terms of the side-effects of the combined use of clozapine and ECT, available evidence suggests that incidence of worrisome side-effects is not very high (10,19–22,59).

In routine clinical practice, it is quite often seen that patients with schizophrenia who do not respond to one or two adequate trials of antipsychotics are treated with polypharmacy. Studies across the globe suggest that about one-third or more patients receive polypharmacy before starting with clozapine treatment (60,61). Use of polypharmacy often leads to delay in starting with the clozapine treatment in patients who deserve the same. Some research suggests that this is probably due to the negative attitude towards and poor knowledge about clozapine among the psychiatrists (62). However, evidence suggests that clozapine is possibly the most effective antipsychotic medication in patients with TRS (63–65).

Accordingly, based on the available evidence, it can be said that patients with schizophrenia who have TRS should be adequately treated with clozapine as soon as possible so as to improve their outcome. In addition, if a patient does not respond to an adequate trial of clozapine, then clozapine must be augmented with ECT.

Data on use of the combination of clozapine and ECT in patients with bipolar and unipolar disorder are preliminary. However, this suggests that the combined use of clozapine and ECT may be a viable option in patients who do not respond to other treatments.

When one looks at the available literature, data are scarce in terms of evidence-based strategies to be used in treating patients with schizophrenia who do not respond to clozapine. The commonly used strategies include augmentation with other antipsychotic medication. The augmenting agents that have been evaluated include risperidone, aripiprazole, amisulpiride, sertindole, pimozide, ziprasidone, antidepressants, omega-3 fatty acids and lamotrigine (22). In a review of various double-blind placebo-controlled studies, open-label studies and case reports/case series evaluating the efficacy of these agents concluded than in general double-blind placebo-controlled trials show lack of superiority in treating patients with risperidone (two out of the three studies showing no additional benefit), aripiprazole, sertindole and placebo over placebo (22). Data from open-label studies provide some evidence to support the usefulness of some of these agents. However, some of these combinations are associated with higher rates of side-effects (22). When one compares the findings of augmentation of clozapine with ECT, the results appear to be more robust. Accordingly, it can be concluded that ECT should be held back for long in patients who show suboptimal response to clozapine.

However, it can be said that, although the evidence for the combined use of clozapine and ECT has expanded, there is still limited data on the combined use of clozapine and ECT. Further, the existing data are mostly in the form of case reports, case series and small studies. In many of these reports, the ratings of improvement are either not standardised and/or not blind. Most of the published literature is based on the

https://doi.org/10.1017/neu.2015.8 Published online by Cambridge University Press

positive treatment outcomes with only few studies reporting only the negative treatment outcomes and side-effects. Thus, it is quite possible that there is a bias towards publishing the positive response about the combination treatment. Accordingly, the non-response or negative response is not reported in the literature. The available evidence also suggests marked heterogeneity in the dose of clozapine used before starting ECT. Similarly, there is inconsistency in terms of issues related to the ECT technique and other ECT-related matters. Although some of the studies have reported the clozapine plasma levels, many studies do not provide information about the same. Accordingly, it can be mentioned that many cases considered as being 'clozapine resistant' may not actually be cases of 'true clozapine resistance', as these patients may not have been treated with clozapine at the desired plasma levels. Data on the cognitive outcome are also limited and marked by heterogeneity in the assessment of the same. Understandably, because of the small sample size, none of the studies have evaluated the correlates of the treatment response. In addition none of the studies have looked at other outcome measures like socio-occupational functioning and quality of life.

Therefore, there is further need to expand the literature. Future studies should follow a prospective study design in which patients are allocated to the combination of clozapine and ECT and other comparator groups such as clozapine alone, ECT alone, any other antipsychotic drug group or any other combination group. The raters and patients should be blind to the ratings of psychopathology, and long-term outcomes must be consistently evaluated. Besides psychopathology, studies also must evaluate other outcome measures like quality of life and socio-occupational functioning. Considering the fact that it may be possible to have a large sample at one centre, there is a need to have a multicentric study spread across different nations, using the same study design to evaluate the actual efficacy of the combined use of clozapine and ECT.

Acknowledgements

None. Authors' Contributions: S.G., N.H. and N.K.: conception of idea; S.G. and N.H.: carrying out internet and manual searches; S.G., N.H. and N.K.: extraction of the data; S.G. and N.H.: writing the draft; S.G., N.H. and N.K.: final approval of the manuscript.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest

None.

References

1. Kane JM, Honigfeld G, Singer J, Meltzer H. Clozapine in treatment-resistant schizophrenics. Psychopharmacol Bull 1988;**24**:62–67.
2. Meltzer HY. Defining treatment refractoriness in schizophrenia. Schizophr Bull 1990;**16**:563–565.
3. Sinclair D, Adams CE. Treatment resistant schizophrenia: a comprehensive survey of randomised controlled trials. BMC Psychiatry 2014;**14**:253–260.
4. Aleman A, Sommer IE, Kahn RS. Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. J Clin Psychiatry 2007;**68**:416–421.
5. Thirthalli J, Bharadwaj B, Kulkarni S, Gangadhar BN, Kharawala S, Andrade C. Successful use of maintenance rTMS for 8 months in a patient with antipsychotic-refractory auditory hallucinations. Schizophr Res 2008; **100**:351–352.
6. Wang J, Xu Y. Should repetitive transcranial magnetic stimulation (rtms) be considered an effective adjunctive treatment for auditory hallucinations in patients with schizophrenia? Shanghai Arch Psychiatry 2013;**25**:254–255.
7. Aleman A. Use of repetitive transcranial magnetic stimulation for treatment in psychiatry. Clin Psychopharmacol Neurosci 2013;**11**:53–59.
8. Shi C, Yu X, Cheung EF, Shum DH, Chan RC. Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: a meta-analysis. Psychiatry Res 2014; **215**:505–513.
9. Andrade C. Once- to twice-daily, 3-year domiciliary maintenance transcranial direct current stimulation for severe, disabling, clozapine-refractory continuous auditory hallucinations in schizophrenia. J ECT 2013;**29**:239–242.
10. Braga RJ, Petrides G. The combined use of electroconvulsive therapy and antipsychotics in patients with schizophrenia. J ECT 2005;**21**:75–83.
11. Chanpattana W, Kunigiri G, Kramer BA, Gangadhar BN. Survey of the practice of electroconvulsive therapy in teaching hospitals in India. J ECT 2005;**21**:100–104.
12. Chanpattana W, Andrade C. ECT for treatment-resistant schizophrenia: a response from the far East to the UK. NICE report. J ECT 2006;**22**:4–12.
13. Chanpattana W, Kramer BA, Kunigiri G, Gangadhar BN, Kitphati R, Andrade C. A survey of the practice of electroconvulsive therapy in Asia. J ECT 2010;**26**:5–10.
14. Fink M. ECT and clozapine in schizophrenia. J ECT 1998;**14**:223–226.
15. Klapheke MM. Clozapine, ECT, and Schizoaffective disorder, bipolar type. Convuls Ther 1991;**7**:36–39.
16. Klapheke MM. Follow-up on clozapine and ECT. Convuls Ther 1991;**7**:303–305.
17. Masiar SJ, Johns CA. ECT following clozapine. Br J Psychiatry 1991;**158**:135–136.
18. Bloch Y, Pollack M, Mor I. Should the administration of ECT during clozapine therapy be contraindicated? Br J Psychiatry 1996;**169**:253–254.
19. Kupchik M, Spivak B, Mester R et al. Combined electroconvulsive-clozapine therapy. Clin Neuropharmacol 2000;**23**:14–16.

https://doi.org/10.1017/neu.2015.8 Published online by Cambridge University Press

20. Havaki-Kontaxaki BJ, Ferentinos PP, Kontaxakis VP, Paplos KG, Soldatos CR. Concurrent administration of clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia. Clin Neuropharmacol 2006;**29**:52–56.
21. Tranulis C, Mouaffak F, Chouchana L et al. Somatic augmentation strategies in clozapine resistance – what facts? Clin Neuropharmacol 2006;**29**:34–44.
22. Vayisoğlu S, Yağcioğlu AE. Augmentation strategies in patients with schizophrenia who show partial response to clozapine treatment. Turk Psikiyatri Derg 2014;**25**(3):201–211.
23. Manjunatha N, Ram Kumar GS, Vidyendaran R, Muralidharan K, John JP. Delayed onset, protracted delirium and aspiration pneumonitis associated with a combination of clozapine and electroconvulsive therapy. Indian J Psychol Med 2011;**33**:80–82.
24. Grubisha M, Gopalan P, Azzam PN. Takotsubo cardiomyopathy in a young man after maintenance electroconvulsive therapy and clozapine initiation: a case report. J ECT 2014;**30**:e40–41.
25. Frankenberg FR, Suppes T, Mclean PE. Combined clozapine and electroconvulsive therapy. Convulsive Ther 1993;**9**:176–180.
26. Kho KH, Blansjaar BA, De Vries S, Babuskova D, Zwinderman AH, Linszen DH. Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia: an open label study. Eur Arch Psychiatry Clin Neurosci 2004;**254**:372–379.
27. Flamarique I, Castro-Fornieles J, Garrido JM et al. Electroconvulsive therapy and clozapine in adolescents with schizophrenia spectrum disorders: is it a safe and effective combination? J Clin Psychopharmacol 2012;**32**:756–766.
28. Kristensen D, Hageman I, Bauer J, Jørgensen MB, Correll CU. Antipsychotic polypharmacy in a treatment-refractory schizophrenia population receiving adjunctive treatment with electroconvulsive therapy. J ECT 2013;**29**:271–276.
29. Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra AK. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am J Psychiatry 2015;**172**:52–58.
30. Factor SA, Molho ES, Brown DL. Combined clozapine and electroconvulsive therapy for the treatment of drug-induced psychosis in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1995;**7**:304–307.
31. Kales HC, Dequardo JR, Tandon R. Combined electroconvulsive therapy and clozapine in treatment-resistant schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 1999;**23**:547–556.
32. Beale MD, Pritchett JT, Kellner CH. Supraventricular tachycardia in a patient receiving ECT, clozapine, and caffeine. Convuls Ther 1994;**10**:228–231.
33. Cardwell BA, Nakai B. Seizure activity in combined clozapine and ECT: a retrospective view. Convuls Ther 1995;**11**:110–113.
34. Masoudzadeh A, Khalilian AR. Comparative study of clozapine, electroshock and the combination of ECT with clozapine in treatment-resistant schizophrenic patients. Pak J Biol Sci 2007;**10**:4287–4290.
35. Koen L, Van Den Berg CE, Niehaus DJH. Combining ECT and clozapine in the treatment of clozapine-refractory schizophrenia and schizoaffective disorder – a pilot study. S AfrJ Psychiatry 2008;**14**:131–135.
36. Kales HC, Tandon R, Dequardo JR, Maixner D, Jibson M, Becks L. Combined electroconvulsive therapy and clozapine in schizophrenia. J Clin Psychiatry 1995;**37**:678.
37. Fink M. Clozapine and electroconvulsive therapy. Arch Gen Psychiatry 1990;**47**:290–291.
38. Petrides G, Fink M, Abaza A, Francis A. Concurrent use of ECT and atypical antipsychotic medication. Convulsive Ther 1998;**14**:139–140.
39. Bannour S, Bouhlel S, Krir MW et al. Combination of maintenance electroconvulsive therapy and clozapine in treating a patient with refractory schizophrenia. J ECT 2014;**30**:e29–e30.
40. Biedermann F, Pfaffenberger N, Baumgartner S, Kemmler G, Fleischhacker WW, Hofer A. Combined clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia: clinical and cognitive outcomes. J ECT 2011;**27**:e61–e62.
41. James DV, Gray NS. Elective combined electroconvulsive and clozapine therapy. Int Clin Psychopharmacol 1999; **14**:69–72.
42. Vowels EC, Hitturlingappa S, Bastiampillai T. Combination clozapine and electroconvulsive therapy in a patient with schizophrenia and comorbid intellectual disability. Aust N Z J Psychiatry 2014;**48**:689–690.
43. Benatov R, Sirota P, Megged S. Neuroleptic-resistant schizophrenia treated with clozapine and ECT. Convuls Ther 1996;**12**:117–121.
44. Husni M, Haggarty J, Peat C. Clozapine does not increase ECT-seizure duration. Can J Psychiatry 1999;**44**:190–191.
45. Keller S, Drexler H, Lichtenberg P. Very high dose clozapine and electroconvulsive therapy combination treatment in a patient with schizophrenia. J ECT 2009;**25**:280–281.
46. Dean CE. Severe self-injurious behavior associated with treatment-resistant schizophrenia: treatment with maintenance electroconvulsive therapy. J ECT 2000; **16**:302–308.
47. Klapheke MM. Combining ECT and antipsychotic agents: benefits and risks. Convuls Ther 1993;**9**(4):241–255.
48. Landy DA. Combined use of clozapine and electroconvulsive therapy: case report. Convulsive Ther 1991;**7**:218–221.
49. Lurie SN. Combined use of ECT and clozapine. J Clin Psychiatry 1996;**57**:94–95.
50. Poyurovsky M, Weizman A. Safety and effectiveness of combined ECT and clozapine in treatment-resistant mania. Eur Psychiatry 1996;**11**:319–321.
51. Godemann F, Hellweg R. Twenty-year-long prophylactic treatment of a bipolar-affective psychosis unsuccessful. Nervenarzt 1997;**68**:582–585.
52. Chanpattana W. Combined ECT and clozapine in treatment-resistant mania. J ECT 2000;**16**:204–207.
53. Tsao CI, Jain S, Gibson RH, Guedet PJ, Lehrmann JA. Maintenance ECT for recurrent medication-refractory mania. J ECT 2004;**20**:118–119.
54. Safferman AZ, Munne R. Combining clozapine with ECT. Convuls Ther 1992;**8**:141–143.
55. Bhatia SC, Bhatia SK, Gupta S. Concurrent administration of clozapine and ECT: a successful therapeutic strategy for a patient with treatment-resistant schizophrenia. J ECT 1998;**14**:280–283.
56. Sienaert P, Bouckaert F, Fernandez I, Hagon A, Hagon B, Peuskens J. Propofol in the management of postictal delirium with clozapine-electroconvulsive therapy combination. J ECT 2004;**20**:254–257.
57. Kurian S, Tharyan P, Jacob KS. Combination of ECT and clozapine in drug-resistant schizophrenia. Indian J Psychiatry 2005;**47**:245.

https://doi.org/10.1017/neu.2015.8 Published online by Cambridge University Press

58. Zervas IM, Theleritis C, Soldatos CR. Using ECT in schizophrenia: a review from a clinical perspective. World J Biol Psychiatry 2012;**13**:96–105.
59. Trezise K. ECT with clozapine: efficacy and safety. Br J Psychiatry 1996;**169**:671.
60. Taylor DM, Young C, Paton C. Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. J Clin Psychiatry 2003;**64**:30–34.
61. Howes OD, Vergunst F, Gee S, Mcguire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry 2012;**201**:481–485.
62. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. J Psychopharmacol 2010;**24**:965–971.
63. Moore TA, Buchanan RW, Buckley PF et al. The Texas Medication Algorithm Project: antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry 2007;**14**:1751–1762.
64. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines, 10th edn. Informa Healthcare, 2010, London, United Kingdom.
65. Warnez S, Alessi-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry 2014;**14**:102–106.

https://doi.org/10.1017/neu.2015.8 Published online by Cambridge University Press