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ORIGINAL PAPER

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Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia

An open label study

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Abstract *Objective* This open label study describes the efficacy of electroconvulsive therapy (ECT) as adjunctive treatment in clozapine nonresponders suffering from schizophrenia. *Method* The results of clozapine and ECT treatment in 11 clozapine nonresponders suffering from schizophrenia are reported in terms of remission and relapse. *Results* Eight patients had a remission with this combination treatment. After remission of symptoms five patients had a relapse. Three of the five patients who relapsed had a second successful ECT course and remained well with maintenance ECT and clozapine. No evidence for adverse effects was found. *Conclusion* Adjunctive ECT can be efficacious in clozapine nonresponders suffering from schizophrenia.

Key words electroconvulsive therapy · clozapine nonresponders · schizophrenia · open label study

Introduction

Treatment with conventional antipsychotic medication is usually efficacious in 50 % of patients suffering from schizophrenia (Van Putten et al. 1990). Kane et al. (1988) showed that clozapine could be efficacious in 50 % of patients who still suffer from schizophrenia after unsuccessful treatment with two different antipsychotics at adequate doses including a depot medication. Although the superior efficacy of clozapine compared to conventional antipsychotics has been shown in a meta-analysis by Wahlbeck et al. (1999), in theory 25 % of all patients suffering from schizophrenia cannot be treated adequately with either conventional antipsychotics or with clozapine. Adjunctive treatment with electroconvulsive therapy (ECT) is one of the treatment options used for clozapine nonresponders. To the authors' knowledge no controlled trials on the efficacy of adjunctive ECT treatment in patients suffering from clozapine resistant schizophrenia have been published. The evidence for its efficacy is mainly based on case reports and case series.

A Medline search using the keywords ECT and clozapine identified 21 case reports and case series published between 1991 and 2000 describing 60 patients who have been treated with clozapine and ECT (see Table 1).

Patients suffering from schizophrenia nonresponsive to clozapine were described in nine case reports and case series (Safferman and Munne 1992; Frankenburg et al. 1993; Cardwell and Nakai 1995; Benatov et al. 1996; Petrides et al. 1998; Bhatia et al. 1998; James and Gray 1999; Kales et al. 1999; Husni et al. 1999) comprising 23 patients. Of these patients, 21 were reported to have responded well to the clozapine and ECT combination treatment, whereas two did not improve. Patients who responded well to this combination treatment remained well for three weeks to two years. Except for two reports (Bhatia et al. 1998; Kales et al. 1999) no information was given on relapse rates. The patient described by Bhatia et al. (1998) had a relapse within two weeks after a successful ECT course. This patient however was clozapine noncompliant following ECT. The case series by Kales et al. (1999) reported relapses occurring after one to four months in four out of five patients who responded well to adjunctive ECT treatment. The only patient who did

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Table 1 Published articles on ECT and clozapine

Study	No. of pat. & gender	Age (years)	Diagnosis	Cloz. blood level	Results	Adverse effects	Follow-up results	Comments
Masiar and Johns 1991	1 m	26	Chronic paranoid schizophrenia	n. a.	No improvement after 1 ECT session	2 grand mal seizures 4 and 6 days after ECT		14 days prior to ECT clozapine 800 mg daily was tapered and stopped 4 days prior to ECT. 14 days prior to ECT diazepam 20 mg daily was tapered to 5 mg daily 3 days prior to ECT.
Landy 1991	1 f	34	Major depression with psychosis	n. a.	Improvement of depression GAF25 to 55	Tachycardia	Remained well for at least 6 weeks with clozapine	Psychosis improved with clozapine, but depression remained. ECT was given for depression.
	1 f	26	Major depression with psychosis	n. a.	Improvement of depression and psychosis GAF28 to 50	Tachycardia	Remained well with maintenance ECT and clozapine for at least 2 months	Tachycardia probably due to clozapine.
Klapheke 1991	1 f	26	Schizoaffective disorder bipolar type, mania	n. a.	Improvement	Tachycardia during several ECT sessions	Remained free of psychosis for at least 3 weeks with clozapine	
*Safferman and Munne 1992	1 f	33	Chronic paranoid schizophrenia	> 662 ng/ml for 12 months	Improvement of auditory hallucinations and delusions	None	Remained well for at least 3 weeks with clozapine	
*Frankenburg et al. 1993	2 m	32, 39	Schizophrenia	n. a.	1 minimal improvement 1 moderate improvement	None		Retrospective review of medical records.
	4 m:2 f	28–50	Schizoaffective depressed	n. a.	Improvement: 4 none 3 minimal 3 marked	None		Retrospective review of medical records.
	1 m	32	Schizoaffective bipolar					
	1 m	48	Bipolar manic					
	2 f	30, 47	Major depression with psychosis					
Klapheke 1993	1 ?		Schizoaffective disorder	n. a.	Improvement	None?		
Dassa et al. 1993	1 f	40	Major depression with psychosis	n. a.	Improvement: 88% reduction of BPRS	None	Remained well for more than a year	ECT was inefficacious, afterwards good response to clozapine.
Green et al. 1994	1 f	38	Schizoaffective disorder, disruptive behavior	n. a.	Improvement	None	Remained well for more than 3 years	In both patients ECT was completed before clozapine was started.
	1 f	53	Schizoaffective disorder, mute and catatonic	n. a.	Improvement	None	Remained well for more than 2 years	
Beale et al. 1994	1 f	66	Recurrent depression with psychosis	n. a.	Improvement	Supraventricular tachycardia	Died 3 weeks after her last ECT session	Caffeine used to counteract a decrease in seizure duration could have caused tachycardia.
*Cardwell and Nakai 1995	3 m:4 f	Mean: 41.25 (36–45)	3 par. schizophrenia 1 des. schizophrenia 2 schizoaff. bip. 1 schizoaff. depr.	n. a.	Improvement on BPRS: • 26.9 % total • 25.3 % positive • 21.3 % negative	Absence of: • Prolonged seizure. • Tachycardia. • Tardive seizure within 1 year following ECT.		All patients received ECT and clozapine. In 4 ECT preceded clozapine. In 3 clozapine preceded ECT

Table 1 *Continued*

Study	No. of pat. & gender	Age (years)	Diagnosis	Cloz. blood level	Results	Adverse effects	Follow-up results	Comments
Factor et al. 1995	1 f	69	Parkinson psychosis	n. a.	Improvement of psychosis, mobility and depression	None	Remained well for 8 months with clozapine	ECT was started after clozapine treatment was stopped.
	1 m	70	Parkinson psychosis	n. a.	Improvement of psychosis	None	Remained well for 22 months with clozapine	
Lurie 1996	1 m	47	Bipolar disorder	n. a.	Improvement	None		ECT was efficacious but caused memory problems. Titration of clozapine started during ECT treatment.
Bloch 1996	1?	18	Refractory psychosis	n. a.	Improvement of psychosis	Prolonged seizure		ECT was inefficacious. Improvement after addition of clozapine.
*Benatov et al. 1996	2 f:1 m	35, 45, 47	Disorganized schizophrenia	n. a.	2 improved: > 40 % BPRS reduction 1 no improvement	None	Improvement was maintained for 6 and 24 months	Clozapine was inefficacious. Improvement after adjunctive ECT.
	1 m	24	Disorganized schizophrenia	n. a.	Improvement: > 50 % BPRS reduction	None	Remained well for 24 months	ECT was inefficacious. Improvement after adjunctive clozapine (not medication refractory) .
Poyurovsky and Weizman 1996	1 m:1 f	24, 41	Acute Mania	n. a.	Improvement	Prolonged seizure		Clozapine was started to augment ECT.
*Petrides et al. 1998	7	23–45	6 schizophrenia 1 schizoaffective dis.	n. a.	All improved	None		
*Bhatia et al. 1998	1 m	35	Paranoid schizophrenia	> 266 ng/ml	Improvement: 46% reduction in BPRS score	None	Remained well for 20 months	Clozapine was inefficacious. Improvement after adjunctive ECT.
*James and Gray 1999	2 f:4 m	Mean: 30 (22–42)	Schizophrenia	n. a.	All patients were less disturbed. Mean BPRS score dropped by 32 % (23–37 %) at 6 weeks.	None	Only 1 patient became disturbed again after 6 months	ECT was used to achieve a rapid response. Clozapine was started after 2 ECT sessions.
*Kales et al. 1999	2 f:3 m	Mean: 49 (36–66)	Schizophrenia: 4 clozapine refractory 1 intolerant to therapeutic clozapine dose	n. a.	3 markedly effective 2 modestly effective	None	Remained well for several weeks to 2 years	Clozapine refractory patients were given adjunctive ECT. Following ECT maintenance therapy with clozapine was given.
*Husni et al. 1999	1 m	25	Schizophrenia	n. a.	Improved	None		
Chanpattana 2000	1 m	26	Mania	n. a.	Improved	Post seizure delirium	Remained well for 18 months	The patient remained well with maintenance ECT and low dose clozapine

*Case reports/series describing adjunctive ECT for clozapine nonresponders suffering from schizophrenia.
n. a. not available

not have a relapse remained well during two years of follow-up.

Despite concerns raised by several authors there were only a few reports of adverse effects. Masiar and Johns (1991) reported the occurrence of grand mal seizures several days after one ECT session in a patient who was tapered off diazepam and clozapine prior to ECT. Although these seizures could be precipitated by the single ECT session the tapering of diazepam and clozapine could also be the cause. A prolonged seizure, which seemed to be benign, was reported in two case studies (Bloch et al. 1996; Poyurovsky and Weizman 1996). Cardwell and Nakai (1995) specifically reported the absence of prolonged seizures with this combination treatment. Several reports described tachycardia as an adverse effect (Landy 1991; Klapheke 1991; Beale et al. 1994). This side effect seemed to be benign although Beale et al. (1994) reported that a patient treated with clozapine, ECT, and caffeine for a psychotic depression, died three weeks after her last ECT session. The authors considered it unlikely that ECT precipitated her death. Chanpattana described post seizure delirium, which occurs in 10 % of ECT treatments (Poyurovsky and Weizman 1996).

These reports support the use of ECT as adjunctive treatment for clozapine resistant schizophrenia. To add to the literature on this combination treatment we describe the results of an open label study of clozapine plus ECT treatment for 11 clozapine nonresponders suffering from schizophrenia.

Materials and methods

From January 2001 to May 2003, 13 clozapine nonresponders suffering from schizophrenia were given adjunctive ECT treatment in GGZ Delfland, a general psychiatric hospital in the Netherlands. Clozapine nonresponse was defined as persistence of psychotic symptoms (hallucination or delusion) despite treatment with clozapine. All patients had to be admitted due to the severity of their psychotic symptoms except for case 2. This patient was treated at the outpatient department but requested to have ECT because of persistence of psychotic symptoms. His PANSS score was the lowest (see Table 2). All patients who gave informed consent were included in the analysis even if the treatment course was terminated prematurely.

The diagnosis of schizophrenia according to DSM IV criteria was made using the Mini International Neuropsychiatric Interview (MINI, Overbeek et al. 1999). When the MINI pointed to the presence of an affective disorder the 17-item Hamilton Rating Scale of Depression (HRSD, Hamilton 1967) or the Mania Scale (Young et al. 1978) was applied. As affective symptoms frequently occur in the course of schizophrenia (Johns and Thompson 1995) and ECT is an effective treatment of affective disorders, the monitoring of affective symptoms is necessary to allow discrimination between the effects of ECT on affective and psychotic or negative symptoms of schizophrenia. Information on patient and illness characteristics and clozapine treatment was obtained from the medical files. Once weekly the symptoms of schizophrenia were monitored using the Positive and Negative Scale of Schizophrenia (PANSS, Kay et al. 1987) by KK, SdV and DB. Two raters assessed several patients, in order to achieve good inter-rater reliability. Good inter-rater reliability was defined as a difference in total PANSS score less than ten points achieved on several simultaneous assessments. Thereafter each patient was followed by one rater throughout the course or replaced by the second rater if necessary. At follow-up the PANSS was applied once weekly to once every four weeks.

Prior to the ECT course the PANSS was applied at least three times to ensure that a reduction in PANSS scores was not due to spontaneous remission of schizophrenic symptoms. The ECT course was only started when the baseline PANSS scores remained stable or increased. Remission was defined as a drop of at least 30 % from the mean baseline total and positive PANSS scores. Relapse after a successful ECT course was defined as an increase of the total and positive PANSS scores to at least the mean baseline scores. Clozapine blood levels were assessed before and after the ECT course, which allowed the comparison of changes in blood levels and PANSS scores.

Analyses were conducted using the Statistical Package for Social Science software version 10 (SPSS, Chicago, IL). With paired t-tests the mean baseline total PANSS score and clozapine blood level were compared to the mean score and blood level post-ECT; tests were two-tailed.

ECT was given twice weekly. Prior to and during the ECT course clozapine and other psychotropic medication were continued (see Table 2). Anesthesia was induced with intravenous thiopentone sodium (4–5 mg/kg) and succinylcholine (0.5–1 mg/kg). The blood oxygen level was kept above 95 %. Seizures were induced with the Thymatron DGx twice weekly. Treatment was started with unilateral electrode placement, which was changed to bilateral placement if there was an insufficient response after six sessions. The stimulus settings were initially based on the age (Abrams 1997) but raised in following sessions when the length of the seizures measured by the EEG fell below the required minimum of 20 seconds. The adequacy of the treatment was discussed weekly with the patients by KK. Patients were weekly asked to report any adverse events which may be related to ECT. A decision to stop the treatment was made by the patient and KK taking into account the change in total and positive PANSS scores, adverse effects of ECT and the preference of the patient. If the total and positive PANSS scores remained above 70 % of the mean baseline scores after six bilateral treatments the ECT course was stopped. After such a failed course, treatment with clozapine was continued. If the total and positive PANSS scores fell below 70 % of the mean baseline scores, the course was continued until no further improvement was seen. After such a successful course, the patient was followed up for signs of relapse, in which case a second ECT course was recommended. Patients could decide to end the ECT course prematurely because of adverse effects or without giving any reason.

Results

Using the MINI the diagnosis of schizophrenia was confirmed in all patients. Out of the 13 patients one did not give informed consent and was therefore excluded from analysis. Another patient was excluded because she was monitored using the Brief Psychiatric Rating Scale (BPRS) instead of the PANSS. The analysis was performed on 11 patients, which included two patients (cases 3 and 4), who stopped the ECT course prematurely. Case 3 stopped the course prematurely because of lack of efficacy after six unilateral sessions and case 4 because he experienced a reduction of auditory hallucinations, which he enjoyed hearing. The patient characteristics are given in Table 2.

Six male and five female patients were treated with ECT. At the start of ECT the mean age was 43 years (s. d. = 14, range = 23–67), with a mean duration of total illness of 194 months (s. d. = 157, range = 30–528) and mean duration of current psychotic episode of 24 months (s. d. = 35, range = 2–120). Except for case 11, who previously responded well to a combination of risperidon 6 mg daily, lithium 600 mg daily and ECT but

Table 2 Eleven patients suffering from schizophrenia treated with ECT and clozapine

Case no.	Gender	Age (years)	Dur. of illness (months)	No. of previous adm.	[c]No. of adequate trials prior to cloz.	Dur. of current psychotic episode (months)	Cloz. dose prior to ECT (mg)	Dur. of cloz. treatment prior to ECT (weeks)	Concurrent medication (except clozapine)	Cloz. blood level prior to ECT (ng/ml)	Mean baseline PANSS score	Uni/bil ECT	Mean charge during course (mC)	Cloz. blood level post ECT (ng/ml)	Post ECT total PANSS score	Adverse effects	[d]Follow-up dur. (weeks)	Relapse
1	M	23	30	1	4	5	600	14	Sodium valproate 1000 mg	0.47	63	9/0	176	0.48	40		18	No
2	M	25	48	1	2	48	400	> 8	None	> 0.30	47	6/2	158	n. a.	38	Memory problems		
3	M[a]	33	96	7	5	39	600	14	Paroxetine 40 mg	0.49	67	6/0	160	0.36	70			
4	M[a]	36	192	4	6	120	700	10	Pipamperon 160 mg	0.26	63	2/0	202	0.26	74			
5	F	38	72	1	3	2	200	8	Oxazepam 50 mg	0.48	86	7/0	202	0.35	56		20	No
6	F[b]	39	96	3	2	3	300	10	Oxazepam 50 mg Zucl. 200 mg/2 wk	0.06	76	6/0	227	n. a.	40		42	No
7	M	43	144	3	2	16	800	16	Clonazepam 6 mg	0.33	101	12/0	208	0.29	44		4	Yes
8	F	52	300	4	5	5	450	12	Lithium 1000 mg Oxazepam 50 mg	0.87	77	3/0	218	0.42	31	Memory problems and confusion	7	No according to criteria, yes clinically
9	F	56	240	10	5	3	300	10	None	0.66	67	11/0	252	0.5	39		4	yes
10	M	58	384	3	5	18	400	20	None	0.71	92	7/10	273	0.47	62		19	yes
11	F	66	528	8	4	10	250	2	Lithium 600 mg	0.26	81	0/15	302	0.18	47		3	Yes

[a] Patient stopped ECT course prematurely
[b] This patient stopped clozapine treatment 2 months prior to ECT. ECT was started with zuclopenthixol decanoate. During the ECT course zuclopenthixol decanoate was replaced by clozapine
[c] An adequate trial was defined as treatment with an antipsychotic from one group for at least four weeks with a dose within the recommended range
[d] Patients were followed up until the end of the study or until relapse occurred
n. a. not available

relapsed when ECT was stopped, none of the patients had previously received ECT.

Fig. 1 shows the changes in mean total, positive, negative and global PANSS scores at baseline, during and after ECT. Three baseline scores are shown: the first, the lowest and the last score. At the baseline a 10 point difference between the mean highest and lowest scores was seen. During the ECT course two scores are shown: the first and the last score. During the course a drop in mean PANSS scores was seen. The criteria for remission (a drop of at least 30% from baseline total and positive PANSS scores) applied to eight patients who had a successful course after a mean number of 10 sessions (s. d. = 5, range = 3–17).

There were significant differences between the mean baseline and post-ECT PANSS scores for the total (n = 11, $t = 4.14$, $P = 0.002$), positive (n = 11, $t = 4.03$, $P = 0.002$), negative (n = 11, $t = 3.16$, $P = 0.01$) and global scores (n = 11, $t = 4.50$, $P = 0.001$). Case 6 remained psychotic despite clozapine treatment prior to the ECT course. Clozapine was stopped prior to the course so she did not have adjunctive ECT treatment. During the course clozapine was restarted. Analysis excluding this patient did not affect the significant differences between mean baseline and post-ECT total (n = 10, $t = 3.64$, $P = 0.005$), positive (n = 10, $t = 3.55$, $P = 0.006$), negative (n = 10, $t = 2.73$, $P = 0.02$) and global scores (n = 10, $t = 3.99$, $P = 0.003$). Excluding patients who had clozapine treatment for less than eight weeks or clozapine blood levels below 0.30 ng/ml (n = 8) did not affect the significant drops during the ECT course with P-values remaining < 0.05 for all comparisons. Of the eight pa-

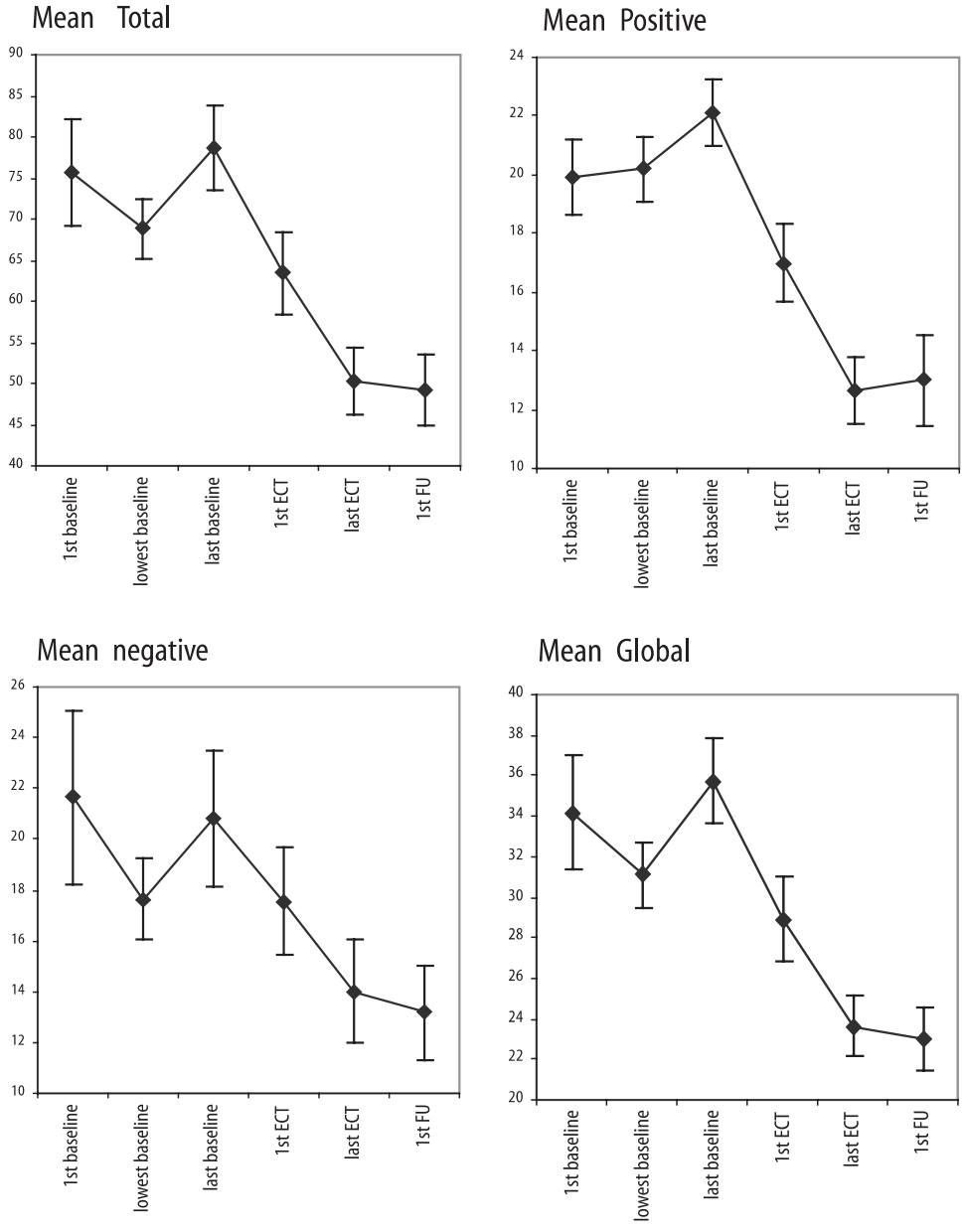

Fig. 1 Total, positive, negative, and global PANSS scores prior to, during, and after ECT

tients who responded well to ECT six had received clozapine treatment for at least eight weeks with blood levels of at least 0.30 ng/ml prior to ECT. On average, blood levels even dropped (n = 6, $t = 2.52$, $P = 0.053$) during the ECT course. The MINI showed that only case 5 suffered from an affective disorder, depression, as well as schizophrenia. In this patient the HRSD score fell from 13 pre-ECT to 8 post-ECT.

The eight patients who responded well to ECT were followed up for signs of relapse for a mean period of 16 weeks (s. d. = 12, range = 4–42). Relapses occurred in four patients after 3–19 weeks (cases 7, 9, 10, and 11). Case 8 did not have a relapse according to the definition but did so clinically. Cases 7, 8 and 10 received a second successful ECT course followed by adjunctive maintenance ECT in a frequency of once weekly for a period of 6, 12, and 8 weeks respectively. These patients have not had a relapse since.

No evidence was found for prolonged seizures or for cardiac arrhythmia. Two patients (cases 2 and 8) reported memory problems during the course. Case 8 also complained of confusion for several hours after each session. This patient was treated with a combination of lithium carbonate, clozapine, and ECT.

Discussion

Our open label study describes the results of adjunctive ECT treatment in 11 clozapine nonresponders suffering from schizophrenia. All patients except one had never received ECT before. These patients had suffered from psychosis for two months to ten years prior to ECT despite treatment with clozapine monitored by blood levels. The graphs in Fig. 1 show that the changes in mean total, positive, negative and global PANSS scores follow a similar pattern. Previous reviews (Christison et al. 1991, Fink & Sackeim 1996) concluded that ECT is more efficacious for the treatment of positive than negative symptoms of schizophrenia. In this case series however comparable efficacy for positive and negative symptoms of schizophrenia was found as shown by significant results from paired *t*-test comparing mean baseline and post-ECT scores. A possible explanation is the causal relationship between positive, negative and global symptoms. Patients who suffer from positive symptoms tend to withdraw increasing the negative PANSS score. Equally, patients with positive symptoms are likely to show more global symptoms of schizophrenia (anxiety etc.). Still the possibility that ECT is effective for alleviating negative symptoms separate from its antipsychotic properties cannot be excluded as some antipsychotic medication may be specifically efficacious for negative symptoms (Möller 1999, 2001).

The monitoring of schizophrenic symptoms with the PANSS and of affective symptoms with the HRSD was not done blind to the treatment condition. Another source of bias, which may exaggerate treatment results, is the inclusion of patients who despite the persistence of psychotic symptoms agreed to have ECT. Despite these possible sources of bias the efficacy of ECT in this group of patients is remarkable as eight out of 11 patients achieved remission defined by a 30 % decrease in total and positive PANSS scores compared to the mean baseline PANSS scores. Two of the three patients who did not have a remission ended the ECT course prematurely.

The criteria for clozapine resistance in schizophrenia are still under debate. Two variables, clozapine blood levels and duration of clozapine treatment, can be used to define these criteria. Studies by Miller et al. (1994), Kronig et al. (1995), VanderZwaag et al. (1996), and Spina et al. (2000) showed that remission rates increase significantly with clozapine blood levels exceeding 350 ng/ml. Meltzer et al. (1989) described the possibility of late response to clozapine even after nine months of treatment and Lieberman et al. (1994) estimated that it can take 12 to 24 weeks before optimal efficacy of clozapine is reached. Conley et al. (1997) however showed in a well-designed study that patients who responded to clozapine showed a significant remission within eight weeks after reaching an effective dose. Group analyses excluding patients with less adequate clozapine treatment (less than 8 weeks clozapine or clozapine blood levels below 0.30 ng/ml) showed significant drops in PANSS scores after adjunctive ECT treatment. Most patients had a remission of their symptoms after 3 to 17 ECT sessions. Remissions cannot be explained by a more adequate clozapine treatment, as blood levels dropped (non-significantly) during the ECT course. Nor can it be explained by successful treatment of affective symptoms, as only one patient had symptoms of depression prior to ECT.

In the search for new and improved antipsychotics the interactions between different neurotransmitters are studied (Carlsson et al. 1999). ECT as well as antipsychotics influence different neurotransmitters. The interaction between ECT and clozapine on neurotransmitters may yield interesting avenues for further research and aid in gaining insight into the efficacy of antipsychotic medication.

Patients who had a remission were followed for variable periods of time. Although after a successful ECT course five out of eight patients relapsed despite continuation of clozapine, some patients remained well for a long period of time. This suggests that ECT followed by maintenance clozapine treatment can have a prolonged effect in some patients. Three patients received a second successful ECT course followed by maintenance adjunctive ECT treatment and have not relapsed since. The follow-up period with maintenance ECT is too short and the number of patients too small to allow conclusions on the beneficial effect of adjunctive maintenance ECT.

In this case series no evidence for serious adverse effects was found. Prolonged seizures were not observed contrary to findings from previous reports (Miller et al. 1994; Bloch et al. 1996). One patient was confused for several hours after each session, which could be due to the combination of lithium, clozapine, and ECT. The

combination of ECT and lithium has been reported to cause prolonged periods of confusion (Abrams 1997). This study serves as a pilot to the design of a randomized, controlled study into the efficacy of this combination treatment. The results of this study justify and demand such a randomized controlled trial in patients suffering from clozapine resistant schizophrenia.

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