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ELECTROCONVULSIVE THERAPY AS A LAST RESORT IN TREATING SEVERE DEPRESSION AND BIPOLAR DISORDER

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Abstract

Treatment of bipolar depression (BD-D) continues to represent a significant unmet need. On average, patients with bipolar disorder (both bipolar I (BD-I), defined by the presence of mania, and bipolar II (BD-II), defined by presence of hypomania) who are treated according to established guidelines are euthymic only about 50% of the time. Further, patients with bipolar disorder spend three times more days depressed than manic or hypomanic. Depression, therefore, represents a quite common mood state among patients with bipolar disorder. This is particularly worrisome as BD-D significantly impacts an individual's psychosocial functioning, with impairments in work, social and family life. Suicides, which are disproportionately high in bipolar disorder, predominantly occur in the depressive state. Furthermore, BD-D is the major contributor to disability associated with the illness. Despite these serious adverse impacts of bipolar disorder, over 50% of patients with bipolar disorder are at least partially non-adherent to medications. Many factors contribute to non-adherence, including lack of psychoeducation and insight into the chronic and episodic nature of the disease. Additionally, a significant number of patients experience intolerable side effects of medications.

INTRODUCTION

Depression is an illness characterized by a constellation of symptoms such as low mood, lack of motivation, sleep disturbances, physical symptoms, and in more severe cases, thoughts of death or dying. The most common method for diagnosing depression uses the diagnostic criteria laid out by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (1), which requires an individual must have at least five of the following nine symptom criteria: depressed mood, amotivation, sleep disturbances, increased guilt, decreased energy, difficulty concentrating, changes in appetite, feelings of restlessness or being slowed down, or thoughts of death or dying (suicidal thoughts) (1). At least one symptom must be depressed mood or amotivation, and these symptoms must last ≥2 weeks causing significant distress or impairment in an individual's functioning (2).

In addition to its significant impact on an individual's functioning, depression is also extremely common, with a lifetime and 12-month prevalence of 16.2% and 6.6%, respectively (3). As a result of this high prevalence, the World Health Organization ranks depression as the single largest contributor to disability across the worldwide population (4). The majority of the burden from depression is due to its impact on an individual's functioning and resulting disability (5).

However depression also confers an increased risk of mortality compared to the general population through a combination of adverse behavioural/lifestyle factors (e.g., poor diet or increased substance use), reduced access to health care and negative social determinants of health (e.g., low socioeconomic status, fewer social supports) (6, 7). Reducing the burden of depression therefore requires effective treatments for patients experiencing this illness.

Treatment Resistant Depression

TRD is commonly defined as non-response to ≥2 medication trials of adequate dose and duration from different classes (12). This is a distressingly common phenomena impacting up to 40% of individuals with depression (13). Despite numerous trials and attempts to develop effective treatments for TRD, there has been no universally accepted medication or psychotherapy treatment with proven efficacy in TRD, which is likely related to the clinical heterogeneity of TRD (8).

Initial assessment of TRD typically involves careful diagnostic consideration. The first step is to determine the type of depressive episode. Most individuals presenting with a major depressive episode according to the DSM-5 criteria will have a major depressive episode

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without psychotic features, as part of major depressive disorder, which comprises a single episode of depression or recurrent episodes (called "unipolar" depression). However, it is also possible for major depressive episodes to occur with psychotic features, or as part of a bipolar disorder where a history of mania or hypomania is present. The first-line treatment considerations may differ depending on whether psychotic symptoms are present, and whether the disorder is of a unipolar or bipolar nature. Undiagnosed psychotic or bipolar depression is prevalent amongst individuals with TRD, and an appropriate diagnosis can lead to more optimal management (14). Once the diagnosis of TRD is established, the second step is to verify the adequacy of previous treatment trials. This is due to the fact that many individuals may have had inadequate medication trials as assessed by their dose or duration, which is not TRD but instead pseudo treatment-resistance (15). These individuals do not yet have TRD, but rather undertreated depression and the first step is to ensure an adequate trial of an evidence-based antidepressant medication (8). The third step is assessing for general medical conditions that may cause an individual to be presenting with symptoms of depression, such as multiple sclerosis, stroke or hypothyroidism (1). In these cases, the primary treatment is that of the underlying medical condition. The fourth step is to assess for comorbid psychiatric disorders contributing to treatment resistance, which may not have been previously recognized or adequately treated (15). Two particularly common psychiatric comorbidities that portend a poorer prognosis in depression – especially when not treated – are anxiety disorders, and personality disorders (16, 17).

Electroconvulsive Therapy (ECT)

Electroconvulsive therapy (ECT) is a medical treatment most commonly used in patients with severe major depression or bipolar disorder that has not responded to other treatments. ECT involves a brief electrical stimulation of the brain while the patient is under anesthesia. It is typically administered by a team of trained medical professionals that includes a psychiatrist, an anesthesiologist, and a nurse or physician assistant.

History of ECT

Electroconvulsive therapy (ECT) was originally developed by two Italian physicians Ugo Cerletti and Lucio Bini at the Clinic for Nervous and Mental Disorders in Rome in 1938 (24). The basis of the procedure was Dr. Ladislas Meduna's theory of a negative correlation between

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schizophrenia and epilepsy (25). This was based on neuropathological evidence that nerve fibres were thinner in schizophrenia than in epilepsy (26). This led to the hypothesis that inducing artificial seizures in subjects with schizophrenia might cause nerve hypertrophy and alleviate their mental illness (26). Prior to the development of ECT, this theory of the antagonism between epilepsy and schizophrenia had led to the development of convulsive therapies where medication, rather than electricity, was used to elicit generalized seizures, most commonly using cardiazol (25). However, the difficulty using cardiazol was that patients often did not have a therapeutic seizure, had a delayed therapeutic seizure or had a seizure that was too long (27). In contrast, the use of electricity to elicit therapeutic seizures allowed for significantly improved control over the elicitation of generalized seizures, and as a result ECT gradually replaced pharmacotherapy for induction of seizures (27).

Modern Use and Delivery of ECT

Modern ECT is typically delivered 2 to 3 times per week over the course of several weeks in a setting where close physiological monitoring, resuscitation equipment and healthcare providers adept at managing general anesthesia are available. For the procedure, an individual first receives a short acting intravenous general anesthetic agent followed by a short-acting paralytic agent (typically succinylcholine). After an individual has received these medications they will then receive the electrical stimulus that causes widespread, synchronous recruitment of neurons resulting in a generalized tonic-clonic seizure (31). After the seizure has terminated there is a post-ictal period lasting 30-45 minutes after which an individual then returns home or back to the inpatient unit. An acute course of treatment is typically delivered in 6-15 treatment sessions over the course of several weeks (22). While the mechanism of action for ECT is not known (34), previous studies have found that both an electrical stimulus and a resulting seizure are required to achieve efficacy (31).

CT for Depression

There are two primary reasons clinical practice guidelines recommend ECT for the treatment of depression: efficacy and speed of response (22). With respect to efficacy, while medications in TRD achieve remission in 10-15% of individuals (11), ECT has demonstrated the ability to achieve remission in 60% or more of individuals with TRD (38). In some studies, this remission rate increases to nearly 90% when considering individuals experiencing depression with

psychotic features (39). In a meta-analysis of all sham-controlled clinical trials conducted between 1960 and 1983 comparing active ECT vs sham ECT (i.e., individuals received anesthesia but no electrical stimulus), active ECT was found to have a standardized effect size of approximately 0.90 on depression psychometric rating scales (40). In contrast, the standardized effect size for antidepressant medications vs placebo in a recent network meta-analysis was only 0.30 (19).

The second reason why ECT is recommended is the speed of response with treatment. As a result, aside from treatment-resistance, ECT is also indicated in situations where rapid response is required such as acute suicidality or refusal to maintain oral intake (22). Previous work has found that ECT achieves response in more than 50% of individuals (53.8%) after three treatments (i.e., 1 week) that increases to 83.4% after six treatments (i.e., 2 weeks), and plateaus at 94.1% after ≥11 treatments (i.e., approximately 4 weeks) (41). In contrast, medication treatment typically requires at least two weeks to demonstrate any appreciable benefit and 4-6 weeks for the full therapeutic effect (8).

DOES ECT WORK?

Extensive research has found ECT to be highly effective for the relief of major depression. Clinical evidence indicates that for individuals with uncomplicated, but severe major depression, ECT will produce substantial improvement in approximately 80 percent of patients. It is also used for other severe mental illnesses, such as bipolar disorder and schizophrenia. ECT is sometimes used in treating individuals with catatonia, a condition in which a person can become increasingly agitated and unresponsive. A person with catatonia can seriously injure themselves or develop severe dehydration from not eating or drinking.

What are the Steps Involved When Getting ECT?

Before beginning a series of ECT treatments, a patient should receive a thorough psychiatric assessment, a medical examination and sometimes a basic blood test and an electrocardiogram (ECG) to check heart health.

Informed consent is another important part of the process. A patient must provide written informed consent before ECT is administered. In situations where a person is too ill to make decisions for him or herself, the consent process is governed by state law (for example, a court-

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appointed guardian).

Patients and their families should discuss all options for treatment with the psychiatrist before making a specific treatment decision. They should be provided with sufficient information to fully understand the procedure and the potential benefits, risks, and side effects of each treatment option before providing written consent.

BIPOLAR DISORDER

Bipolar disorder (BD) is a serious and extremely recurrent illness frequently associated with cognitive and functional deterioration that poses many treatment challenges. Despite a growing armamentarium of psychotropic medications, many patients with BD remain refractory to pharmacological treatment, relapses are common and morbidity and mortality remain elevated. Because of the high rate of treatment nonresponse, the use of complex polypharmacy has increased dramatically over the years. Although there are several examples of "rational polypharmacy" and anecdotal evidence that some BD patients may benefit from certain complex regimens, the increased reliance on polypharmacy occurred in the absence

of any controlled evidence. Indeed, the efficacy of combined treatment consisting of three or more medications is not demonstrated . Whether "rational" or "irrational", the medication burden associated with increased use of complex polypharmacy raises several concerns including increased switches rate, rapid cycling, treatment resistance, apart from adverse side effects due to drug interactions and patient nonadherence. Concern about the efficacy of current treatments for BD has been particularly marked for bipolar depression: adjunctive second-generation anti-depressants over monotherapy with mood stabilizers do not seem to bring any benefit. Moreover, a recent prospective naturalistic longitudinal study reported a significantly lower likelihood of recovery in BD inpatients with depressive compared to those with manic episodes.

BIPOLAR DEPRESSION

The studies supporting the effectiveness of ECT in severe and refractory depression have been conducted mostly in patients with major depressive disorder (MDD). ECT in BD depression is less extensively studied . This is rather unexpected, because literature data showed significant

differences in antidepressants' efficacy between MDD and BD depression. Not only depression in BD patients resulted less responsive than in MDD, but also the use of antidepressants may induce manic switching, mixed states (MS) and cycle acceleration . A better response to ECT was also observed in patients suffering from MDD compared with BD depression. In a large sample of 130 patients (17 unipolar, 67 BP II and 46 BP I), unipolar depressive patients showed rates of remission (HAM-D <8) significantly higher (70.6%) compared to BD II (43.3%) and BD I (34.8%). In another report unipolar patients showed response rates higher than BP patients, using measures of subjective evaluation. On the other hand, other Authors did not show a different outcome in MDD and bipolar depression. In all these studies the rate of manic switch was not increased in BD depressive patients in comparison with MDD. As regard the rapidity of response to ECT, some Authors have observed a more rapid improvement in symptoms and a faster response in BD than in MDD patients, regardless of the final outcome.

OBJECTIVE OF THE STUDY

1. To assess the neurocognitive profiles in treatment-resistant, acutely admitted BD-depression patients, to compare the neurocognitive function in patients with BD I and II, and to identify the demographic and clinical illness characteristics associated with cognitive function (Paper I).

2. To compare the effects of ECT and APT on general neurocognitive function and autobiographical memory shortly after treatment (Paper III).

REVIEW OF LITERATURE

Depression may be considered as a normal human emotion, a symptom of a somatic illness, a neuropsychiatric illness or one of the main symptoms of mood disorders. Depression often recurs (Angst et al., 1996), it is associated with an increased risk of suicide (Harris and Barraclough, 1997), and causes much disability (Wells et al., 1989). The risk of suicide in follow-up studies of affective disorder has decreased compared to that reported in previous reviews (O'Leary et al., 2001). The availability of ECT and antidepressants (ADs) may have contributed to this decrease, but it cannot be assumed that ECT can be prescribed for all patients. Depressive illness has been the fourth leading global cause of disability -adjusted life years (DALYs) in 1990 and it has been predicted it will be the second leading cause of DALYs in 2020 (Murray and Lopez, 1997).

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Different criteria for mood disorders have been used over the last decades. The criteria according to Feighner et al. (1972), and the Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) have included criteria for both primary and secondary depression. Secondary major depression occurs in a person who has a preexisting non-affective psychiatric disorder (which may or may not still be present), or a serious or life-threatening medical illness, which precedes and parallels the symptoms of depression contrary to primary depression. In Finland, the criteria according to the International Classification of Diseases (ICD, version 10, World Health Organization, 1992) are officially used for mood disorder diagnostic. On the other hand, depression studies have widely used the criteria for mood disorders of the Diagnostic and Statistical Manual of Mental Disorders (DSM) □American Psychiatric Association (APA)□. The latest version (DSM-IV) (APA, 1994) has been used in the studies which make up this thesis.

DSM-IV defines a mood disorder as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important area of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom.

The DSM-IV mood disorders are as follows: 1) mood disorder due to a general medical condition, 2) substance induced mood disorder, 3) bipolar I disorder, 4) bipolar II disorder, schizoaffective disorder, 6) cyclothymic disorder, 7) major depressive disorder, 8) dysthymic disorder, 9) adjustment disorder with a depressed mood and 10) depressive disorder not otherwise specified. The term major depression indicates that the depressive disorder is severe.

MATERIAL AND METHODS

The Bipolar Research and Innovation Network

This thesis is based on the Norwegian Randomized Controlled Trial of ECT in BD, a study conducted within the Bipolar Research and Innovation Network (BRAIN) in Norway. The BRAIN is a clinical network of outpatient clinics and hospital departments in different parts of Norway. Clinicians with a special interest in affective disorders have joined forces to assess several aspects of BD, such as age at onset [16], suicidality [23], and treatment of insomnia [25]. The BRAIN study is thus a multicenter study describing BD patients in Norway. All

patients in the current study were also included in the BRAIN study.

Study population

Treatment-resistant BD-depression patients with clinical indications for ECT were included in this study.

Diagnostic process

Patients who were acutely admitted to one of the study centers with severe depressive symptoms and a possible indication for ECT were asked if they were willing to be screened for the study. During the screening the recruiting clinician determined whether the patient fulfilled all of the inclusion criteria and none of the exclusion criteria. The HCL-32 [18] was applied when it was necessary to increase the awareness of hypomanic symptoms. The diagnosis was made primarily on the basis of a clinical interview supported by information from significant others and hospital records, and subsequently verified by the Mini International Neuropsychiatric Interview (MINI; specifically the MINI-Plus) [236] or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [237]. The assessing psychiatrists had participated in structured SCID-I or MINI-Plus training programs.

STATISTICAL ANALYSIS

The power analysis in the current study was performed for the primary outcome variable (i.e., the change in MADRS scores). The initial rather conservative power calculation was based on a power of 0.90 and an SD of 7, which estimated that 132 patients would need to be included in the study. However, a power of 0.90 is very conservative, and so we repeated the power analyses and found that based on an MADRS difference of 4 and with a power of 0.80 and a SD of 6, a sample of 72 patients would be sufficient. Based on the new power estimates, the study was terminated after the inclusion of 73 patients. A formal power analysis was not performed for changes in cognitive measures since there were no published results about cognitive changes and variances after ECT for treatment-resistant BD depression.

The characteristics of the patients in the two groups were compared using t- tests for normally distributed continuous variables, Mann-Whitney tests for nonnormally distributed continuous variables, and exact chi-square tests for categorical variables (Papers I–III). Correlation and multiple linear regression analyses were performed between neuropsychological measures and

demographic variables (gender, age, length of education, and premorbid IQ), course of illness (BD subtype, number of hospitalizations due to depressive episodes, number of psychotic episodes, comorbid substance abuse, and comorbid anxiety), and current symptoms (MADRS, PANSS pos, and GAF-S scores). Due to the small number of patients relative to the large number of independent variables, analyses were conducted unadjusted, and adjusted for age and length of education only (Paper I).

The efficacy analyses were performed on an intention-to-treat sample comprising all randomized patients who had at least one postbaseline assessment. In analyses of the continuous efficacy outcome, the longitudinal trajectories of the MADRS scores over the treatment course were compared for the ECT and APT groups using linear mixed-effects (LME) modeling [59] (Paper II). The data were registered as missing in the continuous outcome variables (i.e., MADRS, IDS-C30, and CGI-BP scores) if the patients did not return for the final assessment within eight days of finishing the six-week acute treatment phase. This occurred in 14 patients, who are included in the 23 indicated as dropouts in the flow chart for the study shown in Figure 1. However, analyses involving the full longitudinal profile of MADRS, IDS-C30, and CGI-BP scores did not require imputation of missing values since LME modeling accommodates missing data (Paper II). Response and remission rates were compared using t-tests. Times to response and remission with the MADRS score as the outcome measure were quantified in Cox regression analyses. A frailty model was used to handle the multicenter structure, without producing changes in the results. Missing values were in the survival analyses handled through censoring.

The effects of the two treatment alternatives on neurocognitive function were compared by performing mixed between–within repeated-measures analyses of variance (ANOVAs) for each of the domain scores as well as for the composite score, with treatment group (APT vs ECT) as the between-group variable and assessment time (pre- vs posttreatment) as the within-group variable. Effect sizes (partial $\eta 2$ values) for the effects of time and group and the interaction effect between time and group were computed (Paper III). The AMI-SF pre- and posttreatment scores were analyzed by mixed between–within ANOVAs, whereas the AMI-SF consistency scores in the two groups were compared using t-tests. Correlational analyses were performed between neurocognitive measures and depressive symptoms (using the MADRS) (Paper III).

The cutoff for statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using SPSS (version 18 or 20.0) and R [60].

ETHICAL CONSIDERATIONS

The study was approved by the Regional Committee for Medical Research Ethics, Central Norway, the Norwegian Data Inspectorate, and the Norwegian Medicines Agency. All subjects were evaluated by the treating clinician as being capable of giving informed consent, and they provided informed written consent to participate after both the treatment options and the possible side effects had been fully explained to them. The study is registered at ClinicalTrials.gov (no. NCT00664976).

RESULTS

In the study described in Paper I we assessed the neurocognitive functioning in treatment-resistant, acutely admitted BD-depression inpatients. We found that neurocognitive impairments were evident in the BD I and BD II depression inpatients within all assessed cognitive domains. The MCCB profiles indicate neurocognitive functioning at a level between 1 and 1.5 SDs below normal means across domains.

The scores for all MCCB measures were numerically lower in the BD I group than the BD II group, with a significant difference for one of the measures: category fluency. BD I patients had higher rates of global deficits: 68.4% of the BD I patients had clinically significant impairment (>1.5 SDs below the normal mean) in two or more domains, compared to 37.5% of the BD II patients ($p=0.045$). Higher age was associated with greater neurocognitive deficits compared to age-adjusted published norms. The estimated premorbid IQ did not differ between the groups, both of which performed in the "above normal" range. The performance on the WASI was significantly worse for the BD I patients than for the BD II patients. This indicates a decline in IQ in the BD I patients from the premorbid to the current level.

In Paper II we report data on the efficacy of ECT compared to APT in treatment-resistant BD depression. LME analysis revealed that treatment with ECT was significantly more effective than APT: the mean MADRS score at 6 weeks was 6.6 points lower in the ECT group [standard error=2.05; 95% confidence interval (CI)=2.5–10.6, $p=0.001$]. The IDS-C30 and CGI-BP secondary outcome measures showed similarly significant results, with the mean IDS-C30 and

CGI-BP scores being 9.4 and 0.7 points lower, respectively, in the ECT group. The response rate was higher in the ECT group than in the APT group (73.9% vs 33.3%, p=0.014), but there was no significant group difference in the remission rate (34.8% vs 28.6%, p=0.75). The times to response and remission did not differ significantly between the ECT and APT group, however there was a nonsignificant tendency for both times to be shorter in the ECT group.

In the study described in Paper III we compared the effects of ECT and APT on neurocognitive function in treatment-resistant BD depression. In both treatment groups we found a significant improvement of cognitive function from pre- to posttreatment toward a normalization of MCCB scores, with no significant group differences. Improvements in neurocognitive performance were significantly correlated with reductions in the posttreatment depression ratings. We found a reduced autobiographical memory consistency in both groups from pre- to posttreatment, and an additional reduction in autobiographical memory consistency in the ECT group compared to the APT group.

DISCUSSION OF THE MAIN RESULTS

The treatment options for BD depression are poor, and for treatment-resistant depression the treating clinician needs to decide whether to start ECT or to continue with pharmacological treatment. The current study represents the first RCT to compare the effects of ECT and APT on treatment-resistant BD depression. The main finding is that ECT is more effective than APT in the acute treatment phase (Paper II), and hence the current study supports the superiority of ECT in the acute treatment of treatment-resistant BD depression.

The dose titration schedules for RUL and BF ECT

	RUL stimulus					BF stimulus				
	Dose	**Current**	**Pulse width**	**Frequency**	**Duration**	**Dose**	**Current**	**Pulse width**	**Frequency**	**Duration**
	mC	A	ms	Hz	s	mC	A	ms	Hz	s
First level	25.2	0.9	1.0	30	0.47	50.4	0.9	1.0	30	0.93
Second level	50.4	0.9	1.0	30	0.93	100.8	0.9	1.0	30	1.87
Third level	75.6	0.9	1.0	30	1.4	151.2	0.9	1.0	50	1.68
Fourth level	100.8	0.9	1.0	30	1.87	201.6	0.9	1.0	50	2.24

The patient is stimulated using an increased stimulus dose with an interval about 30 s between the stimuli until she or he has a generalized ECT-induced epileptic discharge.
The seizure threshold is defined as the ECT stimulus which elicits a generalized convulsive activity lasting for at least 25 s.

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All the clinical evaluations and the pre-ECT EEG recordings, pre-ECT MRI recordings and MEG recordings prior, during and after ECT were done blinded to ECT treatments. The attending physicians completed a structured questionnaire formulated for the pre-ECT evaluation according to the recommendations of the APA (1990). This questionnaire was used during the whole study period as a referral (N = 140) to the ECT-T-U. Fifty-eight patients were not recruited to the study. Twenty-three patients did not receive ECT: twelve patients refused to have ECT, four patients had present alcohol abuse, one patient had present abuse with BZDs, and six patients were in partial remission. Thirty-five patients were excluded: two patients did not give their consent to the study, five patients received outpatient ECT, one patient received BT ECT for schizophrenia, three patients were treated because of severe catatonia at the Meilahti hospital with BT ECT, one patient could not have methohexital anesthesia due to methohexital allergy, fourteen patients were not 36 stimulated with the standard RUL and BF ECT schedule (in five cases due to technical problems, in two cases due to a higher than the standard initial RUL dose and in seven cases due to a higher initial BF dose), six patients were treated with age based dosing, and three patients continued with their AD medication. Thus, 82 patients entered the study. DSM-IV diagnoses are based on the semi-structured clinical interviews made either by E.S. or P.H, always prior to ECT. The collection of psychiatric history included a symptom checklist for criteria of major depressive episode.

PATIENTS

All the 82 patients who entered the study fulfilled the inclusion and exclusion criteria for studies II and III as shown in Table 4.2

Inclusion and exclusion criteria to the Studies I – V

	Study I	Studies II and III	Study IV	Study V	
Time period used for inclusion the patients to Studies I-V (month/year)	6/95-6/96	11/94-2/97	10/95-2/97	10/95 -2/97	
Number of included patients	7	82	24	Group 1 16	Group 2 24
Inclusion criteria					
Age (years)	20-50	> 20	> 20	> 20	> 20
Major depressive episode	yes	not necessary	yes	yes	yes
Unipolar (U) / bipolar (B) depression	U	U and B	U and B	U and B	U and B
Severity of depression on MADRS or HDRS scale	MADRS >25	no limit	HDRS > 16	HDRS > 16	no limit
AD wash out at leat 5 days prior to ECT	No	not necessary[a]	yes	yes	yes
Exclusion criteria					
Previous ECT during a 6 or 3 months' period	6 months	3 months	3 months	3 months	3 months
Pre-ECT EEG recording (abnormal/normal)	abnormal	No criteria	no criteria	no criteria	no criteria
Pre-ECT MRI imaging (abnormal/no criteria)	abnormal	No criteria	no criteria	no criteria	no criteria
Lithium medication	yes	no	no	no	no
History of rapid-cycling bipolar illness[b]	yes	no	yes	yes	no
History of alcohol abuse during previous year	yes	no	yes	yes	no
History of schizophrenia	yes	no	yes	yes	no
History of schizoaffective disorder	yes	no	yes	yes	no
History of any other concurrent psychosis	yes	no	yes	yes	no
History of a severe medical illness	yes	no	yes	yes	no
History of a neurological illness	yes	no	yes	yes	no

[a] The AD medication was either stable or reduced by the attending physician.
[b] At least four mood episodes occur during the previous 12 months' period.

The selection criteria for studies I, IV and V are also shown in Table 4.2. In Group 2 of Study V, four patients had had a mild major depressive episode, eight patients had a history of alcohol abuse during the previous year, six patients had a history of schizophrenia, schizoaffective disorder or another psychotic disorder which was not part of the mood disorder (four patients had psychotic disorder not otherwise specified, and two schizoaffective disorders), two patients had a history of a neurological illness (one patient had cerebellar ataxia, and the other ischemic cerebrovascular disease) and four patients had a history of a severe medical illness (three patients had hypertensive cardiovascular disease with concomitant risk factors: one had an aortic homograft, one a history of epilepsy, and one a risk for esophageal reflux, and one patient had coronary artery disease with coronary artery bypass grafting).

CONCLUSIONS

In conclusion, this first RCT of ECT in BD depression has produced the following findings. Patients with treatment-resistant BD depression show global neurocognitive impairments. The severity of neurocognitive impairment increases with age. ECT is more effective than APT in treating treatment-resistant BD depression. The response rate is higher in the ECT than in the APT group. The remission rates are modest, with no differences between the treatment groups.

Autobiographical memory consistency is reduced in patients treated with ECT compared to those receiving APT. General neurocognitive function is unaffected shortly after RUL ECT. From the present study three future research questions arise. First, the low remission rates reflect the need for research focusing on more efficient treatment options for the challenging condition of BD depression. Other stimulation techniques, such as DBS, might be worth investigating, as well as the combination of multiple treatment strategies. The ECT patients included in this study received no pharmacological treatment other than concomitant medication, which is contrary to clinical practice.

The use of ECT as an add-on to pharmacological treatment might have enhanced the remission rate. Controlled studies of the impact of pharmacological treatment on the efficacy and side effects of ECT on BD depression are needed.

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