Predictors of ECT Efficacy in Severe Depression

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PhD thesis, Erasmus University Rotterdam, The Netherlands

ISBN / EAN: 978-94-6375-867-3
Cover photo: Willemijn Heijnen, Rotterdam 2020
Editing: Willemijn Heijnen and Daan van Dam
Layout and design: Rutger van Aken | persoonlijkproefschrift.nl
Printing: Ridderprint | www.ridderprint.nl

Predictors of ECT Efficacy in Severe Depression

Voorspellers van de eff ectiviteit van ECT bij patiënten met een ernstige depressieve stoornis

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnifi cus
Prof.dr. R.C.M.E. Engels
en volgens het besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op:

vrijdag 30 oktober 2020 om 11.30 uur

door

Wilhelmina Theodora Catherina Johannes Heijnen

geboren te Maasbree

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotor:	Prof. dr. W.J.G. Hoogendijk
Overige leden:	Prof. dr. A.H.J. Danser Prof. dr. B. Sabbe Prof. dr. M.L. Stek
Copromotor:	Dr. T.K. Birkenhäger

ELECTROCONVULSIVE THERAPY

This motor won't start

My mate takes me to the hospital, again
Why? Drugs don't work.
My mouth is a dry, bowel clogged,
brain slow, singed heart falters.
Life is shot.

I wish I could fade into a junkyard,
with other carcasses of colonels and cars.

Electricity, doctors insist.
They want to jumpstart me.
They should give up, hang up their
cables, like the noose I dream of.

How can a seizure help?
Again wife and daughters plead.
We are destined to failure;
I finally yield.

They wheel me down,
put a mask on my face,
drugs in weakened veins.
I smell apples.

Four more times:
dreams of stockcars and winning,
and, they say, convulsions.
The scent of fruit and
the buzz of honeybees return to me.

My brain begins to rev,
the starter motor works;
we used to neck in my t-bird.
I feel my sex jumping.

My angels surprises me
in the golden courtyard
as I argue merits of politics, ECT,
and John Deere tractors.

She wonders at my smile.
Why shouldn't I? It is harvest time,
and I love to reap god's bounty.

I always wanted a flaming red sportscar.
Together we stroll, discuss prices,
engines,
and admire the orange mums.

Elspeth Cameron Ritchie, M.D, 1993

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Chapter 1

General introduction

GENERAL INTRODUCTION

Major depressive disorder

Major depressive disorder (MDD) is one of the oldest well-recognized medical disorders (1). MDD is a seriously health problem with a high impact on disability and morbidity. Its lifetime prevalence is 16-20% worldwide and it has been projected to become the second most common cause of disability by 2020 (2, 3). MDD is characterized by a depressed mood and/or markedly diminished interest or pleasure in almost all activities for at least two weeks. Further, patients have other symptoms like:

- significant weight loss, weight gain or decrease or increase in appetite
- insomnia or hypersomnia
- psychomotor agitation or retardation
- fatigue or loss of energy
- feelings of worthlessness or excessive or inappropriate guilt
- diminished ability to think or concentrate, or indecisiveness
- recurrent thoughts of death or suicide or suicide plans

In total, patients must have five or more of the above described symptoms according to the standard classification of mental disorders (DSM-5) to meet the criteria for MDD.

The DSM-5 assumes that MDD is a single category and that clinical presentations only vary in severity (4). This results in MDD being a heterogeneous disorder with no established etiology and an inconsistent response to treatment (5). Therefore, in this thesis we focused on patients with severe MDD, especially those with melancholic and/or psychotic features. In melancholic depression, episodes are characterized by psychomotor retardation or agitation, weight loss, inappropriate guilt, lack of reactivity and/or diurnal variation of mood (6). A depression with psychotic features is a severe form of MDD. Psychotic features are generally with mood congruent delusions, such as delusions of guilt, nihilism and poverty and infrequently with (acoustic) hallucinations. These subtypes of depression have a low placebo response (7). Their response to biological treatments such as antidepressants and ECT is superior to response to psychotherapy (8).”

Electroconvulsive therapy in major depression

Electroconvulsive therapy (ECT) is the oldest somatic treatment in psychiatry still in use. It was introduced in 1938 by the Italian clinicians Ugo Cerletti and Lucio Bini and soon after ECT spread quickly in popularity. It started as a treatment for schizophrenia, but greater effectiveness for depression was shown soon after its discovery (9). The

success of ECT was clear, especially after advances in anesthesia techniques in the 1950s allowed for the use of general anesthesia and muscle relaxation (10). It was the most effective treatment for MDD before the introduction of antidepressants (11) with an 80-90% response rate in early studies. After the introduction of antidepressants in the 1960's and especially because of the 'antipsychiatry movement' in the 1970s and 1980s there was a substantial decline of ECT use at least in the Netherlands.

From the 1990's the use of ECT revived again. However, the widespread use of antidepressants changed the patient population that currently receives ECT. In the 1940s it was a first line treatment of depression and from the 1990s until now it is mainly used for patients who are resistant to all pharmacologic treatments.

ECT involves deliberately inducing generalized seizures by administering an electrical stimulus of 0.8 to 0.9 Ampere for several seconds to a patient's brain via electrodes applied to scalp (12). Today, brief pulse wave ECT rather than sine-wave ECT with a constant voltage and energy is recommended (13). A generalized seizure is necessary for ECT to be effective. Seizure threshold is the minimum stimulus dose at which a generalized seizure is elicited, therefore it is necessary to exceed the seizure threshold.

In the Netherlands, ECT is usually administered twice weekly under general anesthesia. Anesthesia is achieved after premedication with glycopyrrolate, with propofol (an anaestheticum), alfentanil (an analgesic) and succinylcholine (a muscle relaxant). Physiological monitoring includes pulse oximetry, non-invasive blood pressure, electrocardiogram and electroencephalogram. ECT is considered as a safe treatment with few side effects: post-ECT confusion, headache and some patients suffer from anterograde and/or retrograde amnesia after ECT (14). However, amnesia is mostly temporary and related to the period of impairment immediately following ECT (15).

Several hypothesis have been studied, but underlying cerebral mechanisms of ECT still remain unclear (16).

A meta-analysis carried out in 2003 (17) found that ECT was significantly more effective when compared to sham (simulated) ECT in adult patients with depressive disorder with a mean difference in decrease of HAM-D score of 9.7 points in favor of real ECT. Furthermore, they found ECT to be significantly more effective than pharmacotherapy. This meta-analysis also found bilateral ECT to be more effective than unilateral ECT. Altogether, ECT is a highly effective treatment for patients with

severe depression, especially those with psychotic features (18). Regardless of the substantial proof of efficacy, ECT still continues to be one of the most controversial, stigmatized and misunderstood treatments in medicine.

Predictors of ECT efficacy in severely depressed patients

Despite the high response rates of ECT in severe depression, up to 30-45% of the patients do not achieve full remission (19). Only few clinical predictors of efficacy of ECT in major depression are known: previous successful ECT treatment (20), shorter duration of the index episode (21, 22) and the presence of delusions (23-25). Therefore, reliable predictors of ECT efficacy would be useful for patient selection.

Medication resistance as a predictor for ECT efficacy

In the Netherlands, ECT is mainly used for patients who do not respond to adequate trials of antidepressants (medication resistance) (26). A substantial number of patients suffering from severe depressive disorder fail to respond to adequately performed treatment with antidepressants.

The literature seems to be divided as to whether medication resistance has a negative influence on efficacy of ECT.

Recent (American) studies found that depressed patients who did not respond to adequate treatment with antidepressants had lower remission rates to ECT compared to patients who did not receive adequate treatment with antidepressants (27-30). Other (predominantly European) studies found no difference (31-34) in efficacy between patients who did or did not receive adequate treatment with antidepressants.

If antidepressant refractory patients show a decreased efficacy of ECT it should be considered earlier in the treatment algorithm in severely depressed patients instead of being a ‘last resort’ treatment.

Polarity as a predictor of ECT efficacy

ECT is widely used for the treatment of severe and treatment resistant unipolar and bipolar depression. However, it remains unclear whether differences in ECT efficacy between unipolar and bipolar depression are present. This is mostly due to the fact that the efficacy of ECT (and antidepressants) in bipolar depression is not well studied, since bipolarity often is an exclusion criterion in randomized clinical trials (35). This is unfortunate, since bipolar disorder is mainly a ‘depressive’ disorder with limited

treatment options, and there is a risk for a switch to hypomania or mania caused by treatment with antidepressants (36). Also, the efficacy of antidepressant treatment in bipolar depression is questionable (37). Therefore, assessing the efficacy of ECT in bipolar depression is clinically relevant.

Older age as a predictor of ECT efficacy

The literature on whether elderly depressed patients show higher ECT efficacy compared to younger depressed patients is inconclusive. Higher efficacy of ECT in older patients with major depression was found in several studies (38-40), but not in all (41-43). However, in two of the latter three studies the population was a mixture of patients with major depression, schizophrenia and schizoaffective disorder (42, 43). Two meta-analyses found an association between older age and higher efficacy of ECT (18, 21). Nonetheless, this association was weak and heterogeneity between studies was substantial.

ECT often is the treatment of choice in elderly severely depressed patients due to poor tolerance of psychotropic medication and comorbid medical illness. Therefore, it is important to investigate whether older age is a predictor of higher efficacy of ECT.

Psychomotor disturbance and psychotic features as predictors of ECT efficacy

Psychomotor disturbance, especially psychomotor retardation, is a central feature of severe major depression and includes motor and cognitive impairments affecting motility, speech and ideation (44). Psychomotor retardation is one of the strongest indicators of melancholic depression (45). Melancholic features are associated with biological dysregulation, like shorter REM latency and dexamethasone non suppression (46). Therefore, it is possible that psychomotor disturbance is a predictor for higher efficacy of ECT, since ECT is a biological treatment, which may correct such dysregulation. Hickie et al. (1996)(47) found marked psychomotor disturbance to be associated with superior response to ECT in depressed patients.

Further, as mentioned, the presence of psychotic features in depression is a convincing predictor for ECT efficacy.

Since psychomotor retardation and psychotic features might be more common in elderly patients (38, 48), it is possible that psychomotor disturbance and psychotic features partly explain the finding that older age predicts higher ECT efficacy.

Predictors for early relapse after successful ECT

High rates of relapse after successful ECT treatment remain a major problem (49). A recent meta-analysis found a relapse rate of 51% in the first 12 months following ECT, with the majority of patients (38%) relapsing within the first 6 months (50). Therefore, in order to prevent relapse, identifying predictors of relapse after ECT may be useful.

Only few clinical predictors of post-ECT relapse are known. The risk of relapse appears to be reduced by continuation treatment with a tricyclic antidepressant (TCA), the combination of a TCA and lithium or continuation ECT (51). Moreover, medication resistant patients may be prone to early relapse after successful ECT (30, 52). Little is known about possible biological predictors for relapse after successful ECT and other potential clinical predictors.

HPA axis hyperactivity as predictor of relapse after successful ECT

Major depression is associated with both hypocortisolemia and hypercortisolemia, with hypocortisolemia being more prevalent in patients with chronic major depression (53). MDD occurs frequently in patients with endocrine disorders affecting the hypothalamic-pituitary-adrenal (HPA) axis, such as Cushing disease and Addison disease, a primary adrenocortical insufficiency which leads to glucocorticoid- and/or mineralocorticoid deficiency (54). Studies have reported hyperactivity of the HPA axis in MDD leading to elevated cortisol levels and less suppression of cortisol on the dexamethasone suppression test (DST) (55-57). Furthermore, it is reported that an imbalance of mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) may contribute to HPA axis hyperactivity (58).

A meta-analysis found that post treatment persistent non-suppression on the DST after clinical treatment response (ECT and/or antidepressants) in MDD was strongly associated with poor long-term outcome (59). When focusing on ECT treatment alone, inconclusive results have been reported. Several studies found no association (60-62). One study found a poorer outcome in patients with persistent non-suppression on the DST (63) whereas another study found better outcome in persistent non-suppressors after successful ECT (64).

Therefore, it is important to investigate whether persistent HPA axis hyperactivity after successful ECT predicts early relapse. If such a relation would exist it might be useful to continue ECT treatment in clinically improved patients with persistent HPA-axis hyperactivity until normalization of the HPA axis is attained.

Aims of this thesis

Only few convincing predictors of ECT efficacy in MDD and even fewer predictors of relapse after successful ECT are known. Further, high relapse rates after successful ECT remain a major cause for concern. For these reasons, it is of value to investigate potential predictors for ECT efficacy and for relapse after successful ECT.

The aims of this thesis are:

A. To assess the possible influence of medication resistance on the efficacy of subsequent ECT (**chapter 2, 3**)
B. To compare the efficacy of ECT in bipolar depression to the efficacy of ECT in unipolar depression (**chapter 4)**
C. To test the hypothesis that older age predicts higher ECT efficacy in MDD (**chapter 5**)
D. To explore the hypothesis that persistent HPA axis hyperactivity after successful bilateral ECT course, predicts early relapse of MDD (**chapter 7**)

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Chapter 2

Treatment failure with a tricyclic antidepressant followed by lithium addition and response to subsequent electroconvulsive therapy

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Journal of Clinical Psychiatry, 2008;69:1887-1891

ABSTRACT

Objective: To examine the predictive value of resistance to a tricyclic antidepressant (TCA) and lithium with respect to the efficacy of subsequent electroconvulsive therapy (ECT).

Method: This open prospective study was conducted in the inpatient depression unit of a university hospital in The Netherlands. Patients were enrolled in the study from October 1996 to June 2002 and had to meet DSM-IV criteria for major depressive disorder. Eighty-six patients were treated twice weekly with ECT until recovery or no progress during at least 10 bilateral treatments. Patients were maintained drug free during the ECT treatment. Clinical evaluation of depressive symptoms was performed each week; scores on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) were obtained 1 to 3 days prior to ECT and 1 to 3 days after treatment termination. The primary outcome criterion was defined as the mean difference in HAM-D score before and after ECT for patients who had received adequate treatment with a TCA and lithium compared with patients who had not received adequate treatment with a TCA and lithium. Adequate treatment was defined as 4 weeks taking a predefined plasma level of a TCA; nonresponders had lithium added to the medication, and the minimal duration of the lithium addition was 3 weeks with a plasma level of at least 0.6 mmol/L. Independent samples t test was used to analyze this primary outcome criterion.

Results: According to the primary outcome criterion, patients who had received adequate treatment with a TCA and lithium (N = 56) had a mean difference in HAM-D score pre-ECT and post-ECT of 16.4 compared to a HAM-D score difference of 19.5 in the patient group who had received inadequate treatment with a TCA and lithium (N = 30). This inequality in differences in mean HAM-D scores is not significant (p = .2).

Conclusion: In the present study sample, treatment failure with adequate pharmacotherapy with a TCA and lithium addition appears to be unrelated to outcome following subsequent ECT.

INTRODUCTION

Electroconvulsive therapy (ECT) was recognized as the most effective treatment for major depression before the introduction of antidepressants (1). Early studies reported that 80% to 90% of depressed patients showed substantial clinical response to ECT (2). The widespread use of antidepressant pharmacotherapy as a treatment for depression has changed the population that currently receives ECT. In The Netherlands, ECT is mainly used for patients who do not respond to adequate trials of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), TCAs with lithium addition, and monoamine oxidase inhibitors (3). Thus, failure to respond to antidepressants is the most common indication for ECT. Despite this change in the indication for ECT, there is little consensus about the impact of medication treatment failure on the efficacy of subsequent ECT.

Several uncontrolled studies have suggested that clinical outcome of ECT is independent of previous failure to respond to antidepressant pharmacotherapy (4-7). These studies were uncontrolled, because response to ECT was only examined among patients who were thought to be medication treatment failures. A comparison patient sample that had not received adequate antidepressant pharmacotherapy prior to ECT was not included. Other methodological concerns included weak or inappropriate criteria for medication resistance and nonuniform outcome criteria.

Two studies used a prospective design to investigate this subject (8,9). The first study examined a sample of 53 depressed patients (8). Only patients randomly assigned to bilateral ECT were included. Patients who failed to respond to adequate antidepressant pharmacotherapy had lower response rates to ECT (50%) than patients who had received inadequate antidepressant pharmacotherapy (86%) (8).

The second study examined a sample of 100 nonpsychotic depressed patients (9). The patients in this study were treated predominantly with low-dose right unilateral ECT. This form of ECT is considered to be inadequate. Patients who failed to respond to adequate antidepressant therapy again had lower response rates to ECT (63%) compared to patients who had received inadequate antidepressant pharmacotherapy (91%) (9).

The influence of medication resistance on response to ECT has been investigated in The Netherlands in 2 studies (10,11); neither of these studies found an influence of medication treatment failure on the outcome of subsequent ECT. The first study examined 41 depressed inpatients (10). No significant difference in response rate

was found in patients who had received adequate antidepressant treatment prior to ECT (72%) compared to patients who had received inadequate antidepressant pharmacotherapy (67%) (10).

The second study examined 104 patients who met DSM-IV criteria for major depressive disorder (11). Again, no significant difference in response rate was found between patients who received adequate antidepressant treatment prior to ECT (62.5%) and patients who received inadequate antidepressant treatment (81.1%) (11).

In the United Kingdom, medication-refractory and medication-nonrefractory patients are also reported to have the same antidepressant response with ECT (12). Apart from European studies casting doubt on the influence of antidepressant treatment failure on ECT response, a recent study from the United States found that treatment failure with antidepressant medication as assessed by the Antidepressant Treatment History Form (ATHF) was not predictive of remission status after ECT (13). The ATHF has been the reference in the reported instances of treatment resistance. Thus, the results of the above-mentioned studies regarding the influence of medication treatment failure are somewhat conflicting.

Newer antidepressants have more tolerability and safety benefits than older TCAs. Similar efficacy in unselected depressed samples is suggested by some authors (14). However, the TCAs demonstrated greater efficacy in severely depressed patients and in depressed inpatients. Other studies have shown TCAs to be more efficacious than SSRIs and other newer antidepressants in depressed inpatients (15-18).

A substantial number of patients suffering from depressive disorder fail to respond to adequately performed treatment with antidepressants. Several treatment strategies have been proposed to treat such refractory depression, of which the best studied is lithium addition (19); this latter meta-analysis is quite convincing and confirms the efficacy of this strategy. Two other studies have confirmed the efficacy of the treatment strategy of a TCA followed by lithium addition (20,21).

It is possible that resistance to a “stronger” antidepressant trial (i.e., adequate treatment with a TCA and lithium) results in a significantly poorer response to ECT. No study has examined the predictive value of treatment failure of a TCA and lithium with respect to the efficacy of ECT; the present study attempts to address this issue.

METHOD

This open prospective study was carried out in the inpatient depression unit of the Department of Psychiatry at the University Hospital-Erasmus Medical Center, Rotterdam, The Netherlands. Patients were enrolled in the study from October 1996 to June 2002. Informed consent was obtained, and written informed consent was also required.

Patients had to meet the DSM-IV criteria for major depressive disorder to be enrolled in the study. Patients with organic brain syndrome, schizophrenia, or bipolar or schizoaffective disorder were excluded. Patients treated with ECT in an earlier episode were excluded from evaluation and analysis. Diagnosis was based on clinical observation during a routinely drug-free period. If patients received more than 1 course of ECT, only the first course was reviewed.

The ECT was administered with a brief-pulse, constant-current apparatus (Thymatron DGx, Somatics, Lake Bluff, Ill.). Seizure threshold was determined during the first session with stimulus titration. If the starting stimulus dose failed to elicit a seizure of at least 25 seconds' duration measured with the cuff method, stimulus charge was increased according to the titration schedule, and the patient was restimulated after 30 seconds.

Seizure threshold was defined as the stimulus dosage that elicited a seizure for at least 25 seconds according to the cuff method. For the second treatment, the stimulus dosage was set at 1.5 times the initial seizure threshold for bilateral treatment. For unilateral treatment, the stimulus dosage was set at 2.5 times the seizure threshold. During the course of ECT, stimulus dosage settings were adjusted upward to maintain a seizure duration of at least 25 seconds as measured with the cuff method.

Patients were initially treated with right unilateral ECT. Patients were crossed over to bilateral ECT if response was inadequate after 6 treatments. Patients in a critical condition started with bilateral ECT.

Patients were treated twice weekly until recovery or no progress during at least 10 bilateral treatments. Clinical evaluation of depressive symptoms was performed each week using the Montgomery-Asberg Depression Rating Scale, and scores on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) were obtained 1 to 3 days prior to ECT and 1 to 3 days after treatment termination.

Patients were withdrawn from all psychotropic medication before ECT and were maintained medication free during the course of ECT. In case of severe agitation, incidental use of haloperidol was allowed.

Patients were classified as responders when their HAM-D score showed a reduction of at least 50% posttreatment compared to pretreatment. Patients were classified as being in full remission when their posttreatment HAM-D scores were 7 or less.

Prior to ECT, resistance to treatment with a TCA and lithium during a depressive episode was evaluated. Adequate treatment was defined as 4 weeks taking a predefined plasma level of a TCA; nonresponders had lithium added to the medication, and the minimal duration of the lithium addition was 3 weeks with a plasma level of at least 0.6 mmol/L.

Statistical Analysis

Primary outcome criterion was defined as the mean difference in HAM-D score before and after ECT treatment for patients who received adequate treatment with a TCA and lithium compared with patients who did not receive adequate treatment with a TCA and lithium. Independent samples t test was used to analyze this primary outcome criterion.

Fisher exact test was used to analyze the differences in response rate to ECT and remission rate between patients who received adequate treatment with a TCA and lithium and patients who did not receive adequate treatment with a TCA and lithium. Statistical significance was defined as $p < 0.05$. All analyses were carried out using SPSS version 13.0 (SPSS Inc., Chicago, Ill.).

RESULTS

The patient sample consisted of 104 inpatients meeting DSM-IV criteria for depressive disorder. Eight patients were excluded because it was not known if they received a TCA and lithium prior to ECT. Three patients were excluded because they had been previously treated with ECT, and 7 patients were excluded because their HAM-D score before ECT was not known. The remaining 86 patients were included for analysis.

Table 1 presents the demographic and clinical characteristics for the total patient sample and as a function of inadequate and adequate treatment with a TCA and lithium prior to ECT. Thirty patients received inadequate treatment with a TCA and lithium, whereas 56 patients received adequate treatment with a TCA and

lithium and were classified as medication treatment failures to a TCA and lithium. A comparison of both groups revealed no significant differences with regard to age and psychotic depression. Patients with adequate treatment with a TCA and lithium had a significantly longer duration of current depressive episode (p=0.03) compared with the inadequately pretreated patients.

Table 1. Demographic and clinical characteristics for the total patient sample and as a function of inadequate and adequate treatment with a TCA and lithium prior to ECT

Characteristic	Total Sample (N = 86)	Adequate Treatment With a TCA and Lithium (N = 56)	Inadequate treatment With a TCA and Lithium (N = 30)
Age, mean (SD), y	54.9 (12.7)	54.6 (11.9)	55.5 (14.3)
Female, N (%) (SD)	60 (71) (5)	19 (66) (5)	24 (80) (4)
Psychotic, N (%) (SD)	37 (43) (5)	25 (45) (5)	12 (40) (5)
Length of index episode, mean (SD), mo	18.6 (12.6)	20.8 (11.9)	14.5 (12.9)
Pre-ECT HAM-D score, mean (SD)	28.1 (8.1)	27.7 (7.6)	28.9 (9.0)
Post-ECT HAM-D score, mean (SD)	10.7 (7.8)	11.4 (8.1)	9.3 (7.3)

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, TCA = tricyclic antidepressant.

Treatment Effects

According to the primary outcome criterion, patients with adequate treatment with a TCA and lithium had a mean difference in HAM-D score pre-ECT and post-ECT of 16.4 compared to a mean difference in HAM-D score of 19.5 in the patient group with inadequate treatment with a TCA and lithium. This inequality in difference in mean HAM-D scores was not significant (p =0.2).

Again, neither response nor remission was influenced by adequate pretreatment with a TCA and lithium (p=0.3 and p=0.3, respectively). Response to ECT after adequate treatment with a TCA and lithium addition was 67% and remission was 39% compared to inadequate treatment with a response to ECT of 77% and remission of 50%. Only 16 patients were treated with right unilateral ECT; the remaining 70 patients were treated with or switched to bilateral ECT.

DISCUSSION

In the present study sample, resistance to adequate pharmacotherapy with a TCA and lithium addition appears to be unrelated to both the primary outcome criterion

(mean difference in HAM-D score pre-ECT and post-ECT treatment) and the secondary outcome criterion (response and remission to subsequent ECT). This is in accordance with several previous studies (11-13) but in contrast with others (8,9,22).

Different staging methods can be used to assess levels of treatment resistance in depression (23). We used a rigorous definition of medication resistance. All of our patients were inpatients. Diagnosis was ascertained during a routinely psychopharmacologic drug-free observation period of at least 1 week. Those patients belonging to the medication-resistant group all had at least 4 weeks of adequate plasma levels with a TCA. Doses of TCAs were routinely adjusted to obtain adequate plasma levels, which were monitored weekly. With lithium addition, the dose was adjusted in order to achieve a lithium level of 0.6 to 1.0 mmol/L for at least 3 weeks.

Baseline psychotropic medication use is mostly quantified with the ATHF (9,24). This is a clinician-rated instrument to assess treatment resistance. The cut-off point for treatment resistance is a score 3 or more. This score is already achieved when treated with an adequate dosage of a single SSRI for 4 weeks, which would probably not be considered as a “strong” antidepressant trial by many clinicians. No criterion for treatment adherence or accuracy of the diagnosis is required. Moreover, the strategy of a TCA with lithium addition is considered to be very efficacious (19-21).

The accuracy of diagnosis in our sample was greatly enhanced by our routine drug-free observation period before ECT. This procedure benefits the selection of patients suitable for ECT. This is in contrast with previous reports in which details about patient selection were not disclosed (8,9).

Psychotically depressed patients have a significantly higher difference in HAM-D score (22) pre-ECT and post-ECT compared to nonpsychotic depressed patients (13, $p < 0.001$); this is in accordance with the consideration that psychotically depressed patients have a superior response rate with ECT relative to nonpsychotic patients (25,26).

It seems reasonable that patients with more difficult-to-treat illness will respond less well to all subsequent treatments, ECT included; however, the greater efficacy of ECT in psychotic depression (generally viewed as the more severe form of depression) argues against this.

In the present study, comparison of the group with adequate treatment with a TCA and lithium and the group with inadequate treatment revealed no significant differences regarding age, sex, psychotic depression, and pre-ECT HAM-D score. Patients adequately treated with a TCA and lithium had a significantly longer duration of index episode (p=0.03) compared to patients who were treated inadequately with a TCA and lithium; this difference has also been reported in previous trials (9,10,12). A reason for this difference could be the fact that some time is needed to adjust a TCA and lithium to an adequate dosage for each individual.

A previous study used predominantly unilateral ECT (8), whereas in the present study only 16 patients were solely treated with unilateral ECT, and the remaining 70 patients were started directly with bilateral ECT or started with unilateral ECT but were switched to bilateral ECT. Bilateral ECT is considered to be the most effective electrode placement of ECT; the unilateral placement and dosing used in the present trial are considered to be less effective (22,27). Our patients were not randomly assigned to electrode placement for this trial, and conclusions about electrode placement and efficacy are therefore not permitted. Nevertheless, the large percentage of patients treated with bilateral ECT in this trial can also contribute to the efficacy of ECT since bilateral ECT is considered to be the most efficacious electrode placement.

Limitations

While the criteria used in the ATHF to rate medication resistance are based on data from efficacy trials and expert judgment, these criteria are arbitrary. It is not known to what extent imposing more stringent cut-offs (such as requiring a minimum treatment duration of 6–8 weeks to define an adequate trial) would have altered the findings of this study. Furthermore, the 2 groups had an unequal sample size, and both had a relatively small sample size, which also could have influenced the results.

CONCLUSION

In the present study, sample resistance to adequate pharmacotherapy with a TCA and lithium appears to be unrelated to the primary outcome criterion (mean difference in HAM-D score pre-ECT and post-ECT treatment for patients who received adequate treatment with a TCA and lithium compared to patients who did not receive adequate treatment with a TCA and lithium) and response or remission to subsequent ECT. Moreover, the concept of “medication resistance” as defined by arbitrary (ATHF) criteria is irrelevant in the decision for a trial of ECT in patients with severe depressive illness, whether psychotic or nonpsychotic.

It is encouraging that even in severely depressed inpatients who have failed to respond to a TCA and lithium, ECT can be an effective treatment. Patients with a depressive disorder not responding to a strong antidepressant trial (adequate treatment with a TCA and lithium) can still largely benefit from subsequent ECT.

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Chapter 3

Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis

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Journal of Clinical Psychopharmacology 2010; 30(5):616-619

ABSTRACT

Failure to respond to antidepressants probably is the most common indication for electroconvulsive therapy (ECT). The literature seems to be divided as to whether medication resistance has a negative influence on the efficacy of subsequent ECT. Therefore, we performed a systematic review to investigate the effect of previous pharmacotherapy failure on the efficacy of ECT. Relevant cohort studies were identified from systematic search of the PubMed electronic database. Seven studies were included in this meta-analysis: the overall remission rate amounts to 48.0% (281/585) for patients with and 64.9% (242/373) for patients without previous pharmacotherapy failure. An exact analysis with the Mantel-Haenszel method (fixed effect model) shows a reduced efficacy of ECT in patients that received previous pharmacotherapy (OR, 0.52; 95% confidence interval [CI], 0.39-0.69). In conclusion, the efficacy of ECT is significantly superior in patients without previous pharmacotherapy failure as compared with medication-resistant patients. Because this finding is based on observational studies, it might be caused by a confounding factor, for example, the presence of psychotic features or the duration of the index episode. Electroconvulsive therapy seems to be an effective treatment for severely depressed patients as well as for patients with previous pharmacotherapy failure.

INTRODUCTION

Before the introduction of antidepressants, electroconvulsive therapy (ECT) was recognized as the most effective treatment for major depression (1). Early studies report that 80% to 90% of depressed patients responded to ECT. Widespread use of antidepressant pharmacotherapy has changed the population of patients that currently receive ECT for major depression. Nowadays, failure to respond to antidepressants is probably the most common indication for ECT. More recent studies found that depressed patients who did not respond to antidepressants have lower remission rates with ECT compared with patients who did not receive adequate treatment with antidepressants (2-4). Other studies found no difference in response to ECT between patients with and without previous pharmacotherapy failure (5-9).

If antidepressant-refractory patients indeed show a decreased efficacy of ECT, this may have consequences for the administration of ECT in these patients. However, the opinions seem to be inconclusive as to whether medication resistance has a negative influence on the efficacy of subsequent ECT. Therefore, we performed a systematic review to investigate the influence of previous pharmacotherapy failure on the response to subsequent ECT.

METHODS

Inclusion and Exclusion Criteria

Prospective cohort studies including subjects who were treated with ECT for major depressive disorder were included. The studies had to use accepted diagnostic criteria for major depression, that is, Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) (R), DSM-IV, or Research Diagnostic Criteria, and had to report the outcome according to a valid depression rating scale, that is, the Hamilton Rating Scale for Depression (HAM-D) (10) or the Montgomery-Asberg Depression Rating Scale (11). All patients had discontinued antidepressant drugs at least 3 days before and during the ECT course. Patients in the selected studies were diagnosed with major depression with or without psychotic features. Medication resistance was defined according to the Antidepressant Treatment History Form (ATHF) developed in 1990 by the Columbia University Group (2,3). For patients with psychotic depression, the adequacy of both antidepressant and antipsychotics were assessed. The criteria involved separate standards for patients with psychotic depression relative to nonpsychotic depression.

Literature Search

The search was conducted in June 2009.

Relevant cohort studies were identified from systematic searches of the PubMed electronic database. The search terms were ECT[All Fields] AND ("depressive disorder"; [MeSH Terms] OR ("depressive" [All Fields] AND "disorder" [All Fields]) OR "depressive disorder" [All Fields]) AND ("antidepressive agents" [MeSH Terms] OR ("antidepressive" [All Fields] AND "agents" [All Fields]) OR "antidepressive agents" [All Fields] OR "antidepressant" [All Fields] OR "antidepressive agents" [Pharmacological Action]) AND (("pharmaceutical preparations" [MeSH Terms] OR ("pharmaceutical" [All Fields] AND "preparations" [All Fields]) OR "pharmaceutical preparations" [All Fields] OR "medication" [All Fields]) AND resistance [All Fields]) AND (remission [All Fields] OR response [All Fields]) AND ("humans" [MeSH Terms] AND English[lang]).

A manual search of the references of the included studies was also performed. A total of 21 studies were identified using this search strategy.

Clinical Outcomes

Because most of the patients with severe major depression will show some response to ECT, the response criterion (≥50% reduction on the HAM-D) may not be the most appropriate measure of the efficacy of ECT, and remission may be more suitable (5).

In the current review, the primary outcome criterion was the remission rate. Remission is defined as either a score 7 or less on the 17-item HAM-D, a score of 10 or less on the 24-item HAM-D, or a score of 8 or less on the Montgomery-Asberg Depression Rating Scale, with preference given in that order if more than 1 scale was reported. In 1 study, a score of 9 or less on the 24-item HAM-D was used as a remission criterion (2).

Quality Assessment of the Studies

Each article was assessed by 3 of the authors (W.T.H., T.K.B., and W.W.vdB.) with the use of an assessment form compiled by the Dutch Institute for Healthcare Improvement (CBO). This form was designed to evaluate cohort studies for the development of evidence-based guidelines. The form abstracts data on the adequacy of the definition of the cohort, selection bias, blinded outcome assessment, confounders, prognostic factors, and clinical outcomes.

Statistical Analysis

Differences in remission rates between patients with previous pharmacotherapy failure versus patients without previous pharmacotherapy failure are expressed as odds ratios (ORs). Exact P values and confidence intervals (CIs) were calculated with the Mantel-Haenszel method (fixed effect model). Heterogeneity across studies

was assessed using the Cochran Q test and I2 statistic. Pooled ORs were calculated using fixed effects meta-analysis. Statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS Inc, Chicago, Ill).

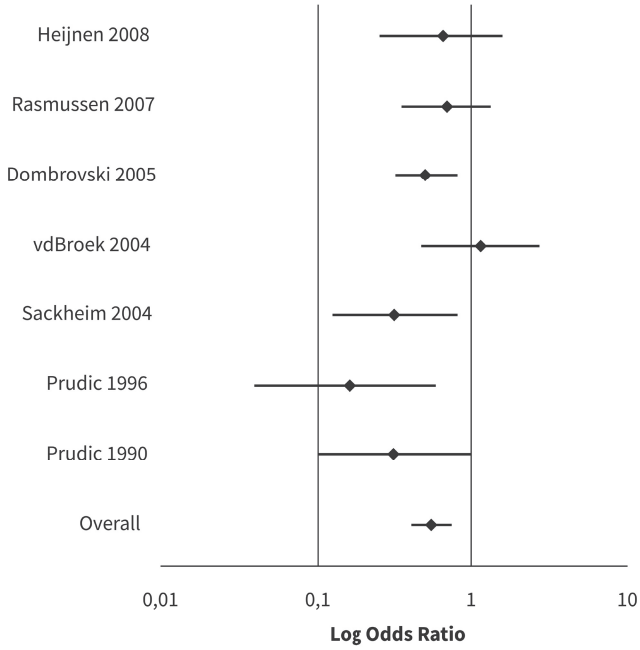
RESULTS

A total of 21 studies were identified by our search strategy. Seven of these did not address the issue of this meta-analysis and were excluded. Another 4 studies were not included because they focused on relapse (12-15) or continuation therapy after successful ECT (16,17). The remaining 8 studies were assessed using the Dutch Institute for Healthcare Improvement form: of these, 1 study was excluded because it was a retrospective study (5). and another was excluded because the remission rate was lacking (7). One of the reviewers suggested assessing 5 other prospective trials that were left out in the initial search strategy (18-22). However, because only Sackeim et al (18) provided remission percentages both for medication-resistant and non-medication-resistant patients, this study was added to the meta-analysis. Thus, finally, 7 studies (2-4,6,8,9,18) were included in this meta-analysis. The included studies comprise a total of 585 patients with previous pharmacotherapy failure and 373 patients without medication resistance. The overall remission rate amounts to 48.0% (281/585) for patients with previous pharmacotherapy failure and 64.9% (242/373) for patients without previous pharmacotherapy failure. The Cochran Q test ($\chi 2 = 9.10$, df = 6, p= 0.17) and I2 statistic (34.1% CI, 0%-72%) suggest nonsignificant heterogeneity. Table 1 gives the description of the included studies and estimated ORs of remission of the sample with previous pharmacotherapy relative to the sample without medication resistance. An exact analysis shows a reduced efficacy of ECT in patients that received previous pharmacotherapy (OR, 0.58; 95% CI, 0.44-0.75). A second analysis calculating a weighted OR showed a similar result (OR, 0.52; 95% CI, 0.39-0.69). Figure 1 shows the plots of the ORs after natural logarithmic transformation.

Table 1. Description of the included studies and estimated ORs of remission in medication-resistant versus non medication-resistant patients

	No. Patients With Adequate Pretreatment	Remission Rate With Adequate Pretreatment (%)	No. Patients With Inadequate Pretreatment	Remission Rate With Inadequate Pretreatment (%)	OR	95% CI
Prudic 1990[2]	24	42	29	69	0.32	0.1-1.00
Prudic 1996[3]	65	63	35	91	0.16	0.04-0.58
Sackeim 2000[18]	46	37	34	65	0.32	0.13-0.81
van den Broek 2004[6]	48	44	37	41	1.14	0.48-2.72
Dombrovski 2005[4]	178	48	150	65	0.51	0.33-0.80
Rasmussen 2007[8]	168	63	58	71	0.69	0.36-1.32
Heijnen 2008[9]	56	39	30	50	0.65	0.26-1.58
Overall, adjusted					0.52	0.39-0.69
Overall, unadjusted					0.58	0.44-0.75

Figure 1. Plot of the ORs of response to ECT in patients with previous pharmacotherapy failure relative to patients without pretreatment per study, with 95% CI, after natural logarithmic transformation



DISCUSSION

This meta-analysis provides evidence that the efficacy of ECT is significantly superior in patients without previous pharmacotherapy failure as compared with medication-resistant patients. However, 3 of the 7 studies did not individually show a significant difference between the 2 patient samples: this requires some discussion. All studies that did show a difference were conducted by the same group (Columbia University, New York); these 4 studies had a similar methodology, albeit that in two of these studies (2,18) bipolar depressives were included, and in another study (3) only patients with non-psychotic depression were selected.

In these studies, a substantial proportion of the patients were treated with right unilateral ECT, which is nowadays considered a less effective form of ECT unless an electrical stimulus of 6x seizure threshold is used. However, these studies did not use high-dose right unilateral ECT. This may have influenced the results, but it is not possible to adjust for this difference. Furthermore, patients were allowed to use lorazepam during the ECT course. Both latter factors could have contributed to the less favorable results, especially in the adequately pretreated group. In 2 studies (6,9) incidental use of haloperidol as concurrent medication during the ECT course was allowed; however, haloperidol probably does not interfere with the efficacy of ECT. The study of van den Broek et al (6) is the only one to report a (nonsignificant) higher efficacy of ECT in the sample with previous pharmacotherapy failure (Fig.1) (6). Differences between study results may be due to chance; however, with heterogeneity, the difference between the results of the various studies is larger than one would expect by chance. A possible explanation for the heterogeneity could be that some studies (2-4,18) used the research diagnostic criteria for major depression, whereas others used the DSM-IV criteria (6,8,9). Furthermore, 2 different versions of the HAM-D (and 2 different definitions of remission) were used: in most studies, the 24-item version of the HAM-D was used (2-4,8,18) whereas 2 studies used the 17-item version (6,9). Another relevant issue is the proportion of patients with psychotic depression in the selected studies. Two studies excluded patients with psychotic depression (3,8), whereas in the studies of Dombrovski et al (4) and Sackeim et al (18), a minority (resp 28% and 36%) of patients showed psychotic features, whereas in the remaining 3 studies, almost 50% of the sample had psychotic depression (2,6,9). Because patients with psychotic depression show a substantially higher response rate to ECT (23,24), the proportion of patients with psychotic depression is likely to influence study results. The impact of treatment failure on the outcome of psychotic depression has not been studied previously.

Limitations of this meta-analysis

Meta-analysis, a systematic approach for combining the results of relevant studies to draw conclusions about a body of research, has been frequently applied to randomized controlled trials (RCTs). However, in some situations, a randomized controlled trial is not feasible, and only data from observational studies are available (25). This applies to medication resistance. Several clinical features determine whether a depressed patient is treated with pharmacotherapy or receives ECT directly. This choice depends on a patients' age, somatic condition, the severity of the depressive episode, the presence of psychotic features, and fluid and food intake. However, a meta-analysis of observational studies has inherent biases and differences in study designs. Several of these differences have been mentioned above. The staging method of treatment resistance in depression forms an additional limitation. Baseline psychotropic medication use is mostly quantified with the Antidepressant Treatment History Form (2,3).This is a physician-rated instrument to assess treatment resistance. The cutoff point for treatment resistance is a score 3 or less. This score is already attained when treated with an adequate dosage of a selective serotonin reuptake inhibitor for 4 weeks, which would probably not be considered a strong antidepressant trial by many physicians.

CONCLUSIONS

The efficacy of ECT seems to be superior in patients without previous pharmacotherapy failure compared with adequately pretreated patients. Because this finding is based on observational studies, it might be caused by a confounding factor, for example, the presence of psychotic features or the duration of the index episode.

Furthermore, the overall remission rate for patients with previous pharmacotherapy failure is encouraging (48%). Therefore, ECT seems to be an effective treatment for severely depressed patients as well as for patients with previous pharmacotherapy failure.

Optimal administration of ECT is very important especially in medication-resistant patients to consider bilateral ECT, to refrain from benzodiazepines as concomitant medication, and to continue the ECT course as long as the patient improves.

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Chapter 4

Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: a meta-analysis

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Bipolar disorders 2012;14:146-150

ABSTRACT

Objective: Bipolar major depression differs considerably from unipolar major depression with regard to the efficacy of treatment with antidepressants. In bipolar depression, response to treatment with antidepressants is disappointing. Whether response to electroconvulsive therapy (ECT) differs between bipolar and unipolar depression remains unclear. Therefore, this systematic review investigates the relative efficacy of ECT in both forms of depression.

Methods: Relevant cohort studies were identified from a systematic search of the PubMed electronic database. Six studies were included in this meta-analysis.

Results: In this meta-analysis, the overall remission rate was 50.9% (n=402/790) for patients with unipolar depression and 53.2% (n=168/316) for patients with bipolar major depression. A pooled odds ratio (OR) and confidence interval (CI) were calculated using random-effects meta-analysis with the Mantel–Haenzel method. This analysis shows similar efficacy of ECT in patients with unipolar and bipolar depression (OR = 1.08, 95% CI: 0.75–1.57).

Conclusion: ECT appears to be equally effective for both bipolar and unipolar depression and the remission rates are encouraging, especially for bipolar depression.

INTRODUCTION

Although electroconvulsive therapy (ECT) is widely used for the management of severe and refractory depression (1), its utility in bipolar depression has not been well studied. This is surprising since there are indications that major differences exist in treatment response between unipolar and bipolar depression (2, 3). For example, in a study comparing the addition of paroxetine or imipramine to lithium therapy with placebo in bipolar depression, neither the paroxetine-treated nor the imipramine-treated group showed any significant benefit over the placebo group (4). More recently, antidepressant add-on in bipolar depression was again shown to be no more efficacious than optimized mood stabilizer monotherapy (5). Moreover, treatment with antidepressants in bipolar depression carries the risk of manic switches (6).

ECT is routinely employed for the treatment of severe and treatment-resistant major depression. However, ECT treatment response differences between unipolar and bipolar depression remain unclear. One study reported that ECT had equivalent efficacy in both types of depressive patients (7) and similar results were reported by others (8-10). However, another retrospective study reported that patients with unipolar depression were more likely to show marked improvement than patients with bipolar depression (11). Similar results were reported in a study investigating 137 patients with unipolar depression and 113 with either bipolar I or II disorder; unipolar patients had higher remission rates than both bipolar I and II disorder patients (3).

Since major differences exist in antidepressant treatment response between bipolar and unipolar depression, assessing the efficacy of ECT in bipolar depression is clinically relevant.

It remains unclear whether the efficacy of ECT in bipolar depression is comparable to its efficacy in unipolar depression. Therefore, this systematic review investigates the relative efficacy of ECT in both forms of depression.

METHODS

Inclusion and exclusion criteria

We included prospective and retrospective cohort studies comparing the efficacy of ECT in patients suffering from unipolar major depressive disorder to patients with bipolar major depression. Studies had to use accepted diagnostic criteria for major depression [i.e., the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III), DSM-IV, or Research Diagnostic Criteria] and had to report the

outcome according to a valid depression rating scale [i.e., the Hamilton Rating Scale for Depression (HAM-D) (12) or the Montgomery–Åsberg Depression Rating Scale (13)].

Literature search

The search was conducted in June 2010. Relevant studies were identified from systematic searches of the PubMed electronic database. The search terms used were [*ECT* (all fields) or *electroconvulsive therapy* (all fields)] and *unipolar* (all fields), *bipolar* (all fields), and *depression* (all fields). Studies prior to 1980 were omitted, thereby allowing the selection of studies using the DSM-III or DSM-IV criteria.

Since ECT techniques have changed considerably in the last few decades with regard to stimulus form (brief-pulse instead of sine wave), stimulus dosing, and choice of anaesthetic agent, a manual search of the reference lists of the included studies was also performed. This search strategy identified a total of 105 studies.

Clinical outcomes

Since most patients with severe depression will show some response to ECT, the response criterion (≥ 50% reduction on the HAM-D score) may lack the sensitivity needed to detect differences in treatment efficacy between unipolar and bipolar depression; therefore, we opted to use the remission criterion instead.

In the current review, the primary outcome criterion was the remission rate. Remission was defined as either a score ≤ 7 on the 17-item HAM-D or a score ≤ 10 on the 24-item HAM-D, with preference given in that order if more than one scale was reported. In one study, a score ≤ 11 on the 24-item HAM-D was used as remission criterion (8).

Quality assessment of the studies

Each article was independently assessed by two of the authors (BD and TKB) with the use of an assessment form compiled by the Dutch Institute for Healthcare Improvement (CBO). The form retrieves data on the adequacy of the definition of the cohort, selection bias, blinded outcome assessment, confounders, prognostic factors, and clinical outcomes. Study validity is assessed with regard to definition of the study samples, the adequacy of the intervention studied, and the use of clearly defined outcome criteria, resulting in a general judgement of the studies (14).

Statistical analysis

Differences in remission rates between patients with bipolar or unipolar depression disorder are given as odds ratios (ORs) and confidence intervals (CIs). One study

reported outcomes for bipolar I and II disorder patients separately (3); therefore, to be consistent with the other studies, these two outcomes were merged into one bipolar major depression group.

A pooled OR and CI were calculated using both fixed-effects meta-analysis and random-effects meta-analysis with the Mantel–Haenzel method. Heterogeneity across studies was assessed using Cochran's *Q*-test. Statistical analyses were performed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 105 studies were identified by our search strategy; of these, 94 did not address the study topic and were excluded. Another four studies (7, 14-16) were excluded because they did not use the HAM-D as an endpoint measure, and one additional study (17) was excluded due to lack of information on the remission rate. As a result, six studies were included in the meta-analysis (3, 8, 9, 19-21): five studies were prospective and one consisted of a chart review (8). The included studies comprised a total of 1106 patients, of whom 790 were diagnosed with unipolar depression and 316 were diagnosed with bipolar depression.

The overall remission rate was 51.5%; for patients with unipolar depression it was 50.9% (n=402/790) and for patients with bipolar depression it was 53.2% (n=168/316). In all six studies, severity of depression at baseline (as measured by the HAM-D) was similar when comparing unipolar and bipolar disorder patients (3, 8, 9, 18-20). No differences were reported in the occurrence of psychotic symptoms. In four studies, bipolar disorder patients presented with a more severe course of illness than unipolar patients, as evidenced by an increased number of episodes prior to the current episode (3, 18, 19) or by a higher number of hospital admissions (9). In three studies (9, 18, 19), antidepressant drugs were discontinued at least three days before and during the ECT course, two studies (8, 20) did not provide information on concurrent use of antidepressants, and in the remaining study (3), concurrent use of antidepressants was permitted.

Cochran's *Q*-test (χ^2=8.8, p=0.1) is indicative of heterogeneity between the studies using the more stringent p-level of 10%. Hence, only the results of the random-effects model meta-analysis are displayed because it was able to handle the heterogeneity between the studies. Table 1 describes the six studies and gives the estimated ORs of remission, which show similar efficacy of ECT in patients with unipolar and bipolar depression (OR = 1.08, 95% CI: 0.75–1.57). When we omitted the single retrospective

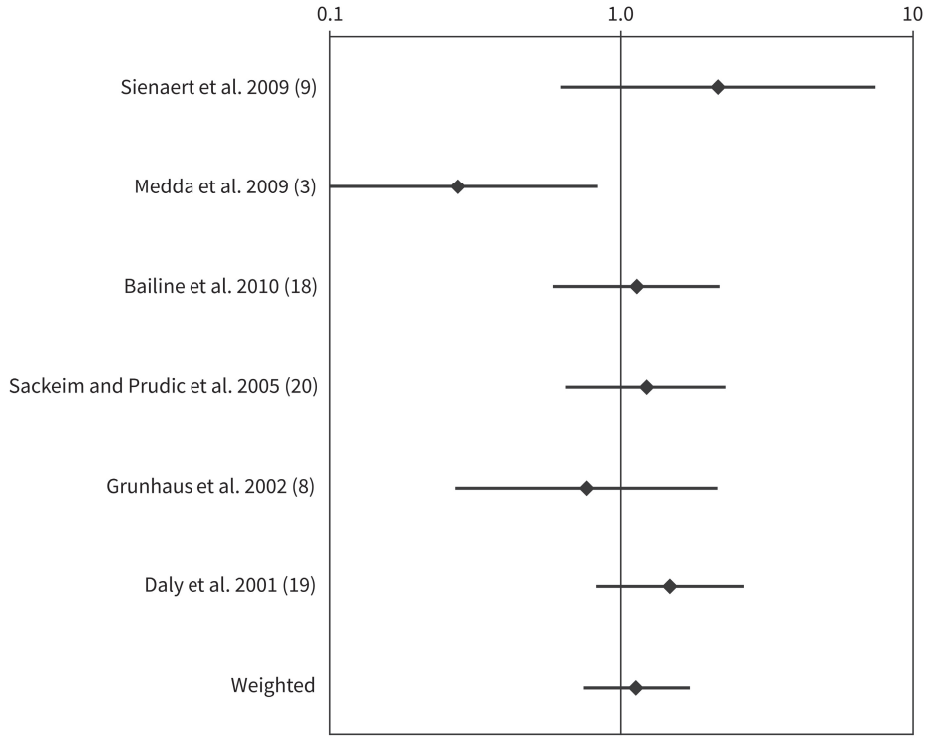
study (8) from the analysis, heterogeneity remained present (χ^2=8.56, p=0.09). In addition, results from the random-effects model were similar (OR = 1.12, 95% CI: 0.74–1.71). Figure 1 shows the plots of the ORs after natural logarithmic transformation.

Table 1. Description of the included studies and estimated odds ratios (ORs) of remission in unipolar versus bipolar depression

Study	Study type	Unipolar (n)	Bipolar (n)	OR[a] (95% CI)
Bailine et al. 2010 (18)	Prospective	170	50	1.13 (0.6–2.2)
Sienaert et al. 2009 (9)	Prospective	51	13	2.14 (0.6–7.3)
Medda et al. 2009 (3)	Prospective	17	BD-I= 46 BD-II = 67	0.28 (0.09–0.80)
Sackeim and Prudic 2005 (20)	Prospective	279	54	1.22 (0.7–2.3)
Grunhaus et al. 2002 (8)	Chart review	111	20	0.76 (0.3–2.1)
Daly et al. 2001 (19)	Prospective	162	66	1.47 (0.8–2.6)

Abbreviations: BD-I = bipolar I disorder; BD-II = bipolar II disorder; CI = confidence interval.
[a]Reference category: remission in unipolar depression

Figure 1. Plot of the odds ratios of response to electroconvulsive therapy in patients with unipolar versus bipolar depression per study, with 95% confidence interval, after natural logarithmic transformation



DISCUSSION

This meta-analysis provides evidence for the equal efficacy of ECT in unipolar and bipolar depression, despite bipolar disorder patients presenting with a more severe history of illness in most of the studies (3, 9, 18, 19).

This equal efficacy of ECT in unipolar and bipolar depression is important, since bipolar depression is hard to treat due to the limited effects of antidepressant add-on therapy and the additional risk of manic switches.

In addition, some clinicians report that patients with bipolar depression need (on average) fewer ECT sessions during their ECT course than patients with unipolar depression (18, 19). One study (20) showed that, among responders, bipolar disorder patients received fewer sessions of ECT (6.2±2.3) than unipolar patients (7.2±2.5). This was partially corroborated by another study (9) reporting that patients with bipolar depression needed fewer ECT sessions to reach response status. However, there was no significant difference in the number of ECT sessions needed to reach the most stringent remission criterion (17-item HAM-D score ≤ 7) (9). Although there were too few studies to perform a meta-analysis on speed of response, these findings further underscore the efficacy of ECT in bipolar depression. This is in addition to the efficacy of ECT in treating manic episodes in bipolar disorder, where it ranks as one of the most effective therapies for the treatment of severe mania and may be the treatment of choice for patients with treatment-resistant mania (21).

One study included in this meta-analysis (3) showed a greater efficacy of ECT in unipolar depressed patients, despite the fact that both patient groups had similar levels of depressive symptoms at baseline, a similar number of mood episodes in their history, and a similar duration of the current episode. In addition, unipolar and bipolar disorder patients received a comparable number of ECT sessions and the study protocol allowed the use of concomitant psychotropic medication (except anticonvulsant mood stabilizers) (3). Although all patients were non-responders to at least two regimens of pharmacological therapy, the concomitant pharmacological treatment may have slanted the results towards patients with unipolar depression (3).

One study (18) reported remission rates (61% for unipolar depression and 64% for bipolar depression) that were superior to the remaining studies. Several details of the administration of ECT and patient selection were examined in order to try to explain this difference in the efficacy of ECT. In all of the studies, with the exception of the study by Medda et al. (3), a substantial proportion of the patients were treated with

right unilateral ECT, and only two studies (9, 18) used an electrical stimulus of 6× the seizure threshold as standard procedure. Furthermore, Bailine et al. (18) employed a minimum duration of ten ECT sessions before concluding non-remission in a patient, whereas another study (8) required a minimum duration of six sessions, and the remaining studies did not report minimum requirements with regard to the ECT course. Therefore, the administration of ECT may have been less optimal in several of the other studies, as compared with the study of Bailine et al. (18). The applied criteria for remission did not explain the superior remission rate in the study of Bailine et al. (18); three studies (18-20) defined remission as a score ≤ 10 on the 24-item HAM-D, while two studies (3, 9) used a score ≤ 7 on the 17-item HAM-D. The remaining study (8) used a less strict remission criterion of a score ≤ 11 on the 21-item HAM-D.

Study limitations

Meta-analysis is a systematic approach for combining the results of relevant studies to draw conclusions about a body of research and is usually applied to randomized controlled trials (RCT); however, in some situations a RCT is not feasible (22). Due to the nature of the study subject, this is a meta-analysis of observational studies and is in contrast to a meta-analysis based on data from RCTs which may result in an increased vulnerability towards some form of bias. In the present study, there are inherent differences because, in effect, we are comparing two different patient groups. Several of these differences have been mentioned above; however, none of these are indicative of the bipolar disorder patients in these studies having a less severe course of illness or a less severe current episode.

The proportion of patients with psychotic depression is a potential confounding factor with regard to the efficacy of ECT, since ECT is particularly effective in patients with psychotic depression (23, 24). However, this factor does not appear to have influenced the results of this meta-analysis, since in four studies a similar proportion of patients in both samples suffered from psychotic depression, and a fifth study controlled for this variable in its analysis.

It should also be mentioned that the studies used different methods to ascertain the levels of treatment resistance in the participating patients, together with the additional problem of defining inclusion criteria that lead to comparable levels of treatment resistance being selected for both unipolar and bipolar disorder patients. This may be a relevant confounding factor, since previous pharmacotherapy failure is reported to reduce remission to subsequent ECT (25). This may have contributed to the statistical heterogeneity we observed across the studies.

CONCLUSIONS

ECT appears to be equally effective for bipolar depression as compared with unipolar depression. The remission rates of 50.9% in bipolar depression and 53.3% in unipolar depression show that the remission rate to ECT is very similar in both samples. These remission rates are encouraging, especially for bipolar depression, since this type of major depression often proves to be relatively treatment resistant.

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Chapter 5

Influence of age on ECT efficacy in depression and the mediating role of psychomotor retardation and psychotic features

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Journal of Psychiatric Research 2019;109:41-47.

ABSTRACT

Objective: To investigate whether older age predicts a higher efficacy of electroconvulsive therapy (ECT) in severely depressed patients. Also, to analyze whether psychomotor disturbance and/or psychotic features might explain the potential higher efficacy of ECT in older age.

Method: A total of 96 patients with major depressive disorder treated with bilateral ECT were evaluated. The 17-item HAM-D and the MADRS were used to evaluate the efficacy of ECT and time to remission, respectively. Psychomotor disturbance was defined according the HAM-D.

Results: Middle-aged (MA; 50 to 70 years) and older-aged (OA; ≥70 years) patients had a non-significant larger symptom reduction compared with young-aged (YA; <50 years) patients. Medium effect size was found in favor of MA (d=0.44) and small effect size in favor of OA (d=0.30), when compared to YA. Patients with psychotic features and patients with psychomotor retardation had a significantly larger symptom reduction ($p<0.001$ and $p=0.005$, respectively; d=0.88 and d=0.66, respectively). The association between age and ECT efficacy is mediated by psychomotor retardation ($p=.049$) and in lesser extent by psychotic features ($p=.071$).

Conclusion: The results show that psychomotor retardation and psychotic features are strong predictors of ECT efficacy and explain the association between age and ECT efficacy. Instead of focusing on the age of a patient, clinicians should focus on the presence of psychomotor disturbances and psychotic features of depression, when considering ECT treatment.

INTRODUCTION

Electroconvulsive therapy (ECT) is a highly effective treatment in severe major depression (UK ECT ReviewGroup, 2003). However, up to 30% of patients fail to achieve response (UK ECT ReviewGroup, 2003) and up to 45% of the patients do not achieve full remission (Kellner et al., 2010).

Few convincing clinical predictors of efficacy of ECT in major depression are known: The absence of medication resistance, the presence of delusions, previous ECT treatment and a shorter duration of the index episode (Birkenhager et al., 2003; Loo et al., 2011; Petrides et al., 2001). Further, marked psychomotor disturbance (agitation and/or retardation) might be a predictor for better ECT efficacy (Buchan et al., 1992; Hickie et al., 1996). Another relevant predictor of ECT efficacy might be older age as it is reported that ECT is more likely to be effective in older patients (Nordenskjold et al., 2012; O'Connor et al., 2001; Spashett et al., 2014; Tew et al., 1999). Apart from one study (Nordenskjold et al., 2012), all of the studies included patients with major depression exclusively. On the other hand, others failed to find an influence of older age on ECT efficacy (Birkenhager et al., 2010; Bloch et al., 2001; Damm et al., 2010). However, in two of these studies the population was a mixture of patients with major depression, schizophrenia and/or schizoaffective disorder (Bloch et al., 2001; Damm et al., 2010). Birkenhäger et al. (2010) found no linear relationship between age and ECT efficacy. Two meta-analyses of clinical predictors found an association between older age and higher ECT response rates (van Diermen et al., 2018; Haq et al., 2015). However, this association was weak and heterogeneity between studies was substantial.

Therefore, it is important to investigate whether older age is a predictor of efficacy of ECT. Specific symptoms such as the presence of psychotic features and marked psychomotor disturbance might be more common in elderly patients (Brodaty et al., 1997; O'Connor et al., 2001). Psychotic features in major depression are a convincing predictor for higher ECT efficacy (Birkenhager et al., 2003; Loo et al., 2011; Petrides et al., 2001) and the same might apply to marked psychomotor disturbance (Buchan et al., 1992; Hickie et al., 1996). Therefore, the hypothesized higher efficacy of ECT in older depressed patients might be partly explained by the presence of one or both of these symptoms.

Aims of the study

The primary aim of the present study is to test the hypothesis that older age predicts higher ECT efficacy and a shorter time to remission in severely depressed patients.

Next, it is important to identify possible underlying mechanisms, like specific depressive symptoms. Therefore, the secondary aim is to analyze whether psychomotor disturbance and/or psychotic features mediate the relationship between age and ECT efficacy.

METHODS

Patients

The PROSPECT cohort is a prospective study of depressed patients treated with ECT at the Department of Psychiatry of the Erasmus Medical Center from January 2006 up to date. Patients are included in the PROSPECT cohort if they meet the DSM-IV criteria (American Psychiatric Association, 1994) for major depressive disorder (MDD) with or without psychotic features and have a score of ≥ 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D) (Bech et al., 1986). Diagnoses are based on clinical observations during a routine drug-free period. A diagnosis of mood congruent psychotic depression is made solely when the patient shows definite mood-congruent delusions.

A subset of adult PROSPECT patients (18 years and older) was selected for the current analyses. We excluded all patients with alcohol or drug dependence, a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, psychotic disorder not otherwise specified, obsessive-compulsive disorder, dementia, and other neurological disorders. To avoid electrode placement acting as a confounding factor, only patients treated with bilateral ECT were selected. Although a recent randomized trial found no difference in efficacy between high dose-unilateral and bitemporal ECT in MDD (Semkovska et al., 2016), generally, bilateral ECT is considered more effective than right unilateral ECT (UK ECT ReviewGroup, 2003). To avoid bias, of patients receiving more than one ECT course during this period, only the first treatment course was included in the sample.

The study was conducted in accordance with the latest version of the Declaration of Helsinki and informed consent of the participants was obtained after the nature of the procedures had been fully explained. Since all data were obtained as part of standard psychiatric care, medical ethical review was not deemed necessary.

For the purpose of our analyses, patients were divided into three age groups to investigate the impact of age: young-aged (YA) patients: <50 years, middle-aged (MA) patients: ≥ 50 and <70 years, and old aged (OA) patients: ≥ 70 years. Since a recent meta-analysis showed a curvelinear relationship between age and ECT efficacy (van

Diermen et al., 2018), this categorization allows us explore non-linear relationships. We suppose a decreased efficacy of ECT in patients < 50 years.

This categorization was chosen because it can be considered as clinically relevant categories corresponding to a younger age group, a middle age group and an older age group. HAM-D items were used as indicator of the presence of unique symptoms. A score of 2, 3 or 4 on the HAM-D items 8 (psychomotor retardation) or 9 (psychomotor agitation), was classified as the presence of the symptom. A score of 0-1 on item 8 represents normal speech and thought or slight retardation and a score of 2-4 stands for at least obvious retardation at interview. A score of 0-1 on item 9 represents no agitation or fidgetiness and score of 2-4 stands for at least obvious restlessness (playing with hands, hair, moving about).

Electroconvulsive therapy

Patients were withdrawn from all psychotropic medication at least five days prior to the first ECT treatment and the majority of patients were maintained medication-free during the course of ECT. Because several patients participated in a study involving nortriptyline, 16 patients were treated with nortriptyline during the course of ECT. Approximately 3 patients in the YA group (23%), 9 patients in the MA group (18%) and 4 patients in the OA group (12%) received nortriptyline during ECT. In case of severe agitation, incidental use of haloperidol was allowed, whereas the use of benzodiazepines during ECT was not allowed.

All patients were treated with bilateral ECT. ECT was administered twice weekly with a brief-pulse constant current apparatus (Thymatron, Somatics, IL, USA). Seizure threshold, defined as the stimulus dosage that elicited a seizure of at least 25 s according to the cuff method, was determined during the first session with empirical stimulus titration. If the starting stimulus dose failed to elicit a seizure of at least 25 s, stimulus charge was increased according to the titration schedule and the patient was restimulated after 30 s. For the second treatment, the stimulus dosage was set at 1.5 times the seizure threshold. During the course of ECT, stimulus dosage settings were adjusted upward to maintain seizure duration of at least 25 s as measured with the cuff method.

Anesthesia was achieved after premedication with 0.2 mg glycopyrrolate, with intravenous administration of etomidate (0.2 mg/kg), alfentanil (7-10 microgram/kg) and succinylcholine (0.5-1.0 mg/kg). During the procedure, patients were ventilated by mask until the resumption of spontaneous respiration. Physiological

monitoring included pulse oximetry, non-invasive blood pressure measurement, electrocardiogram and electroencephalogram. The number of ECT treatments was determined by clinical observation; a minimum of 10 bilateral treatments was required before evaluation as a non-responder. ECT was continued until patients were either asymptomatic or had not shown any further improvement as measured by the HAM-D over the course of three consecutive treatments.

Evaluation of the treatment outcome

The 17-item HAM-D was used to evaluate the severity of MDD and was routinely performed 1-3 days prior to ECT and 1-3 days after treatment termination to evaluate the efficacy of ECT. High inter-rater reliability and internal consistency have been shown for this scale (Miller et al., 1985). Since the Montgomery Asberg depression rating scale (MADRS) (Montgomery and Asberg, 1979) is more sensitive to detect small changes over time (Carmody et al., 2006), the MADRS was performed weekly during ECT treatment to evaluate the time to remission. The MADRS was also performed 1-3 days prior to ECT 1-3 days after ECT. The primary outcome criteria for efficacy are mean reduction (continuous) in HAM-D scores per group and proportion of patients in remission (dichotomous) as measured by the HAM-D. The secondary outcome criterion is time to remission as measured by the MADRS. Remission was defined as a HAM-D score of ≤ 7 or a MADRS score of ≤ 9.

Response was defined as a reduction of ≥ 50% on the HAM-D score, relative to the baseline HAM-D score.

Statistical analysis

Differences with regards to socio-demographic, clinical, and outcome variables between subgroups of patients were tested with T-tests or ANOVA test for continuous variables, and Pearson's Chi-square and Fisher's Exact test (FET) for categorical variables. In case of a 2x3 contingency table, we employed the Freeman-Halton extension (Freeman and Halton, 1951) of the Fisher's Exact test.

Effect sizes were calculated to estimate the magnitude of the effect. Cohen's *d* was calculated with respect to continuous outcomes (reduction of HAM-D scores) while a Relative Risk (RR) was calculated with respect to dichotomized outcomes (proportion of patients in remission). A Cohen's *d* of 0.2 to 0.3 and a RR of 2 (or 0.50) is seen as a small effect; a Cohen's *d* around 0.5 and a RR of 3 (or 0.33) as a medium effect; and a Cohen's *d* of 0.8 and RR of 4 (or 0.25) and higher, as a large effect (Cohen, 1988).

To analyze the impact of age and clinical features on time-to-remission, survival analyses were conducted using the Kaplan-Meier method (Kaplan and Meier, 1958; Kleinbaum and Klein, 2012). Log-rank tests were used to test whether the survival curves for the age groups were equivalent. Analyses were conducted using SPSS version 21.0. Finally, we estimated the mediating effects of psychomotor agitation, retardation and psychotic symptoms in the relationship between age (three age groups) and reduction of depressive symptoms. The size and significance of all direct and indirect paths between age and symptom reduction were estimated using structural equation modelling. Robust weighted least squares estimation was used to allow the inclusion of continuous and dichotomous variables into the model (Yuan and Bentler, 2000). Path analysis was conducted using MPlus version 7.4 (Muthen and Muthen, 2015).

RESULTS

Patient characteristics

Of the 190 patients receiving ECT treatment between 2006 and 2015, 85 were excluded because they fulfilled one or more exclusion criteria, 6 patients dropped out because they refused further ECT treatment or patients were transferred to another department, and 3 patients dropped out because a reliable HAM-D and MADRS score was not obtainable due to severity of the depression with catatonic features and/or mutism. Finally, 96 patients (67% female) were included for analysis; mean age was 63.9 (SD 12.3, range 33-96) years (Figure 1). Of these patients, 57 (59%) suffered from depression with psychotic features, 29% had an episode duration >1 year, and the mean baseline HAM-D-score was 28.8 (SD 6.4).

Table 1 presents the clinical characteristics for the total patient sample and for the three age groups separately: YA: <50 years (n=13), MA: ≥50 and <70 years (n=50), and OA: ≥70 years (n=33). In the MA group, 63% had pharmacotherapy failure, significantly less than in the YA and OA group; in the OA group, 42% of the patients were previously treated with ECT, significantly more than in the YA and MA group; in the YA group, 23% of the patients had psychotic features, significantly less than in the OA and MA group; and none of the patients in the YA group had psychomotor retardation, while more than half of the MA and OA patients showed psychomotor retardation. No differences between the age groups were found for sex, episode duration >1 year, the presence of psychomotor agitation, number of ECT treatments, and baseline HAM-D score.

The mean reduction in HAM-D score was 21.3 (SD 9.0) points. Response was obtained in 82 (85%) patients, and 67 (70%) patients met the criteria for remission. The mean

number of ECT sessions was 15.0 (SD 4.8). The average ECT charge was 219.6 mC for the YA group, 302.4 mC for the MA group and 386.4 mC for the OA group.

Figure 1. Study flow diagram

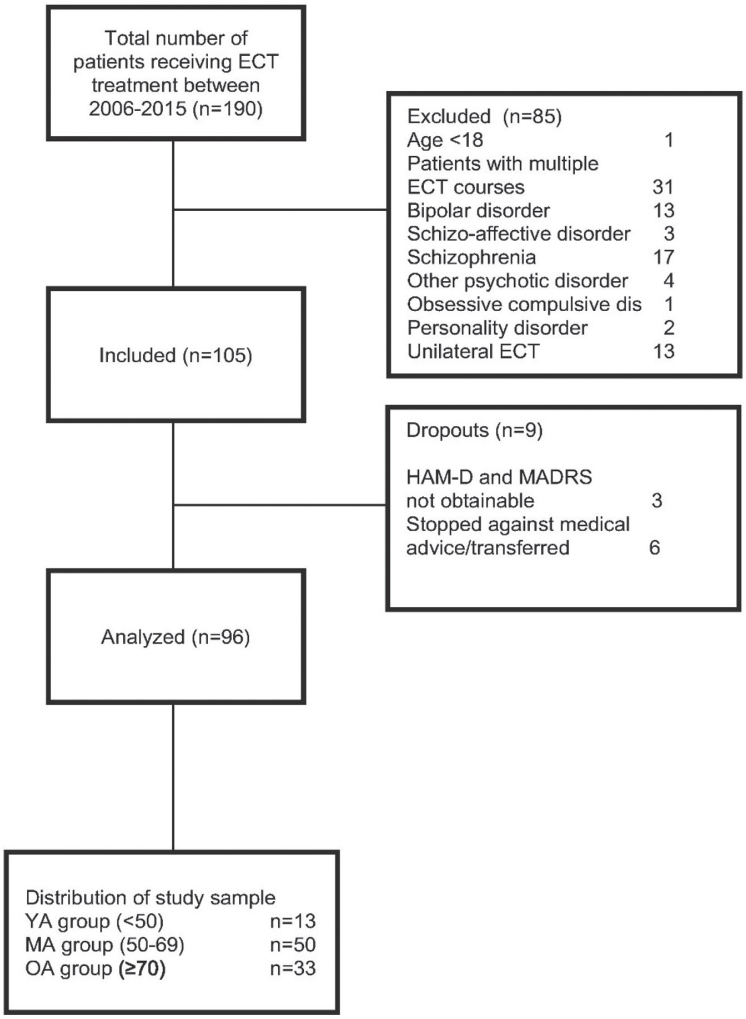

Table 1. Clinical characteristics of the study sample (n=96)

	<50 years: young age (n=13)	50-69 years: middle age (n=50)	≥70 years: old age (n=33)	Total (n=96)	Test
Female, n (%)	8 (62)	31(62)	25 (76)	64(67)	$X^2(2)=1.87$; p=0.39
Treatment history					
Episode duration >1 year, n (%)	6 (46)	13 (26)	9 (27)	28 (29)	$X^2(2)=2.12$; p=0.35
Pharmacotherapy failurea, n (%)	12 (92)	31(63)	29 (88)	72(76)	$X^2(2)=8.75$; p=0.013
Previous ECT treatment, n (%)	1 (8)	4(8)	14 (42)	19(20)	FET $X^2=14.67$; p<0.001
Phenomenology					
Psychotic features, n (%)	3 (23)	33(66)	21 (64)	57(59)	FET $X^2=7.94$; p=0.020
Psychomotor retardation[b], n (%)	0 (0)	25(64)	19 (61)	44(54)	FET $X^2=14.97$; p<0.001
Psychomotor agitation[b], n (%)	4 (40)	17(44)	8 (26)	29(36)	FET $X^2(2)=2.48$; p=0.30
Current treatment					
Mean number of ECTs (SD)	15.9 (4.1)	14.0(4.9)	15.5 (5.0)	14.7(4.8)	F(2)=1.42; p=0.25
Mean baseline HAMD score (SD)	27.5 (4.8)	29.5(7.0)	28.1 (6.3)	28.8(6.4)	F(2)=0.66; p=0.52

Notes: [a] Missing N=1; [b] Missing N=16

Effect of age on efficacy of ECT

There was no significant difference in HAM-D reduction between the three age groups. However, best treatment effect was observed in the MA group. YA showed worst effect. Difference (non-significant) between the MA and YA group was medium sized and difference between the OA and YA group was small sized. Further, the proportion of patients in remission was larger in the MA and OA group than in the YA group; however, this difference was not significant. RRs suggest a small effect between the YA and MA group and between the YA and OA group (Table 2).

Effect of age on time to remission

The average time to remission was 9.1 weeks in the YA group, 7.4 weeks in the MA group, and 7.8 weeks in the OA group. There was no significant difference in time to remission when comparing the three age groups. Pairwise comparisons showed a trend to significance in favor of the MA group over the YA group (Table 2).

Effect of symptomatology on efficacy of ECT

The efficacy of ECT, as measured by the mean reduction in HAM-D score, was significantly superior in patients with psychotic features compared to patients without psychotic features; a large effect size was found. However, there was no significant difference in the rate of patients attaining remission between patients with or without psychotic features; the RR suggests a small effect.

The mean reduction in HAM-D score was significantly larger in patients with psychomotor retardation compared to patients without psychomotor retardation, with a medium effect size. There was a trend to a significantly higher rate of patients attaining remission among inpatients with psychomotor retardation, compared with patients without retardation; the RR suggests a small effect.

Small, non-significant differences were found in mean reduction in HAM-D score and remission rate between patients with and without psychomotor agitation (Table 2).

Effect of symptomatology on time to remission

Survival analyses support these findings. That is, remission was achieved approximately one week earlier in patients with psychotic features and psychomotor retardation, and 3 to 4 days earlier in patients without psychomotor agitation. However, none of these effects reached significance (Table 2).

Mediating effects of symptomatology

Table 3 and figure 2 show the results of the path analysis. In line with earlier analysis the path analysis reports no significant association between age and reduction of depressive symptoms (total effect of age), significant direct relationships between psychomotor retardation and psychotic symptoms on symptom reduction, and no significant relationship between psychomotor agitation and symptom reduction. Regarding the indirect paths, we found a significant mediating pathway through psychomotor retardation. Psychotic symptoms showed a trend towards mediation. Both indirect paths were positive, meaning that older age was associated with more psychotic symptoms and psychomotor retardation, resulting in larger depressive symptom reduction. With regards to psychomotor agitation, we found a negative non-significant association. Overall, we found a trend (p=.058) towards mediation of the association between age and symptom reduction by clinical features. The direction of the remaining direct path between age and symptom reduction conversed to negative (older age relates to less symptom reduction), but was not significant.

Table 2. The impact of age and symptomatology on ECT treatment effect (N=96)

	N	Mean reduction HAM-D (SD)	Test/ Effect size	Remission, N (%)	Test/ Effect size	Mean time to remission in weeks (SE)	K-M Test
Age			F(2)=1.03; p=0.36		$X^2(2)$=.56; p=0.76		$X^2(1)$=.91; p=0.34
<50 yrs (YA)	13	18.3 (9.5)	YA vs MA: *d*=0.44	8 (62)	YA vs MA: RR=0.92	9.1 (0.8)	YA vs MA: $X^2(1)$=2.29; p=0.13
50-69 yrs (MA)	50	22.3 (8.8)	YA vs OA: *d*=0.30	35 (70)	YA vs OA: RR=0.86	7.4 (0.5)	YA vs OA: $X^2(1)$=1.87; p=0.17
>69 yrs (OA)	33	21.1 (9.2)	MA vs OA: *d*=0.13	24 (73)	MA vs OA:RR=0.92	7.8 (0.5)	MA vs OA: $X^2(1)$=0.13; p=0.72
Psychotic features			T(95)=4.05; p<0.001		$X^2(1)$=0.30; p=0.58		$X^2(1)$=2.97; p=0.09
Present	57	24.2 (8.7)	*d*=0.88	41 (72)	RR=1.16	7.3 (0.4)	
Absent	39	16.9 (7.8)		26 (67)	reference	8.5 (0.5)	
Psychomotor retardation[a]			T(79)=2.88; p=0.005		$X^2(1)$=2.51; p=0.11		$X^2(1)$=2.91; p=0.09
Present	44	24.6 (9.2)	*d*=0.66	33 (75)	RR=1.48	7.5 (0.4)	
Absent	36	18.9 (8.1)		21 (58)	reference	8.5 (0.6)	
Psychomotor agitation[a]			T(79)=1.35; p=0.18		$X^2(1)$=0.61; p=0.43		$X^2(1)$=0.38; p=0.54
Present	29	23.8 (8.3)	*d*=0.31	18 (62)	RR=0.87	8.3 (0.7)	
Absent	51	21.0 (9.5)		36 (71)	reference	7.8 (0.4)	

Notes: [a] Missing N=16

Figure 2. Path model of the relationship between age, clinical features and ECT efficacy on depressive symptoms. Age is modelled as ordinal variable (three age groups YA <50 yrs; MA ≥ 50 and <70 yrs; OA ≥70 yrs) (N=96). Standardized coefficients, standard error and p-value are reported. Significant paths (p<.05) are depicted as bold lines; non-significant paths are depicted as dashed lines.

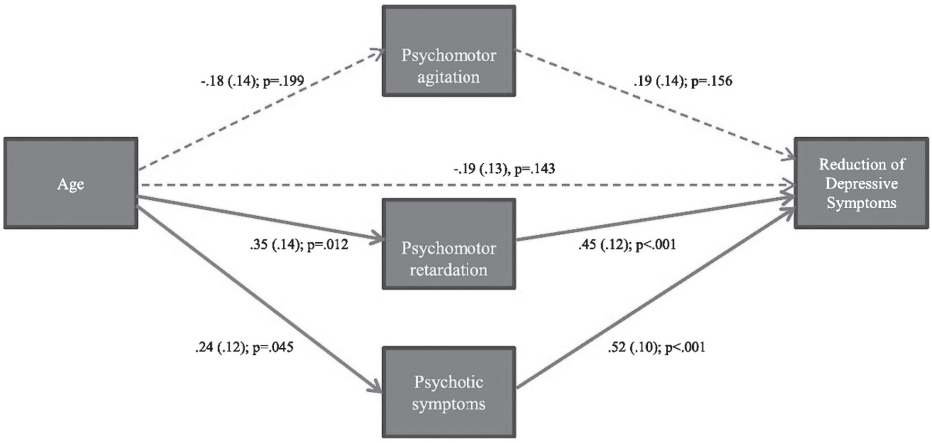

Table 3. Path model: Standardized direct and indirect effects of age and clinical features on depressive symptoms in patients treated with ECT resulting from SEM-analysis (N=96). Significant effects are in bold script.

	Reduction of Depressive Symptoms		
	Estimated	**SE**	**p-value**
Age (ordinal)			
Direct effect	-.19	.13	.143
Indirect effects	.25	.13	.058
Age-Agitation-Depressive symptoms	-.03	.04	.346
Age-Retardation-Depressive symptoms	**.16**	.08	.049
Age-Psychotic symptoms-Depressive symptoms	.13	.07	.071
Total effect	.06	.10	.580
Psychomotor agitation			
Direct effect	-.19	.14	.156
Psychomotor retardation			
Direct effect	**.45**	.12	<.001
Psychotic symptoms			
Direct effect	**.52**	.19	<.001

DISCUSSION

Effect of age on the efficacy of ECT

We failed to find a significant difference when examining the primary outcome criteria. However, medium sized differences in favor of the middle aged (MA) group and small sized differences in favor of the old aged (OA) group when compared with the young aged (YA) group suggest a correlation between older age and higher ECT efficacy.

The reduction in HAM-D scores was 3-4 points larger in the OA and MA group when compared with the YA group, which is a clinically relevant difference. No differences were found between the groups for baseline HAM-D scores. No significant difference was found according to the secondary outcome criterion. However, the MA and OA group achieved remission almost 1,5 to 2 weeks earlier than the YA group.

The differences between the YA group versus the MA and OA group most likely failed to reach significance due to the small number of patients in the YA group. Furthermore, the high rate (70%) of patients that met the criteria for remission in the total study group made it difficult to detect potential differences in efficacy (i.e. ceiling effect).

Effect of symptomatology on the efficacy of ECT

As measured by mean reduction in HAM-D score, the ECT efficacy was significantly superior in patients with psychotic features and a large difference in effect was found. The fact that no difference was found between patients with versus without psychotic features when comparing rates of patients attaining remission, is probably due to the fact that the mean HAM-D baseline score of patients with psychotic features was 6 points higher compared to the non-psychotic patients. Also, the previous mentioned high remission rate of the total group made it difficult to detect potential differences.

Patients with psychomotor retardation had higher ECT efficacy with a significant difference when measured by mean reduction in HAM-D scores and trend towards significance when measured by remission rates.

Comparison with other studies: influence of age on the efficacy of ECT

Two recent meta-analyses (Haq et al., 2015; van Diermen et al., 2018) found a positive association between older age and higher ECT efficacy, but this association was weak. Also, the results of the present study with a homogeneous patient population found a larger symptom reduction in older age, but this was non-significant. The present study found that the association between age and ECT efficacy is mediated by psychomotor retardation (p=.049) and in lesser extent by psychotic features (p=.071).

Thus heterogeneous results in previous studies (Birkenhager et al., 2010; Bloch et al., 2001; Damm et al., 2010; Nordenskjold et al., 2012; O'Connor et al., 2001; Spashett et al., 2014; Tew et al., 1999) may be explained by differences in mediatory factors between the studies.

Comparison with other studies: influence of symptomatology on the efficacy of ECT and mediating effects of symptomatology

The higher efficacy to ECT we found in patients with psychotic features is in agreement with others (Birkenhager et al., 2003; Loo et al., 2011; Petrides et al., 2001). Moreover, our finding of a higher efficacy of ECT in patients with psychomotor retardation is in accordance with Hickie et al. (1996) who found that marked psychomotor disturbance and psychotic features were independently associated with a superior response to ECT. In that study, the combination of psychotic features and marked psychomotor disturbance was associated with the best response to ECT. In depression with psychotic features, biological mechanisms such as shortened REM latency and dexamethasone non suppression are very often observed (Staner and Mendlewicz, 1991). Psychomotor disturbance is one of the strongest indicators of melancholic depression (Parker and McCraw, 2017) and melancholic features are also associated with biological mechanisms like shorter REM latency and dexamethasone non suppression (Rush and Weissenburger, 1994).

In the present study, the positive indirect pathway age-psychomotor retardation, meaning that older age was associated with more psychomotor retardation is in agreement with Brodaty et al. (1997) who found that psychomotor disturbance is more common in elderly patients.

Only a few studies investigated possible explanations for the finding that older age predicts a higher efficacy of ECT. O'Connor et al. (2001) suggested that the superior response to ECT they found in older age may be a function of a higher percentage of psychotic features in older age. In our study, we also investigated psychomotor disturbance and psychotic features as a possible explanation for the association between age and ECT efficacy. The path analysis showed that psychomotor retardation and psychotic features mediate the association between age and ECT efficacy. Therefore, the association between age and ECT efficacy may not always emerge since the presence of psychomotor retardation and psychotic features may vary between studies.

Strengths and limitations

The present study investigated a sample of severely depressed patients with a mean baseline HAM-D score of 29, of which 59% had psychotic features. The homogeneity of the diagnosis, the severity of the depressive symptoms and the wide age range of the population are considered major strengths. Further, the fact that the use of benzodiazepines during ECT was not allowed is considered a strength since benzodiazepines have a negative effect at least on the efficacy of right unilateral (RUL) ECT (Jha and Stein, 1996). This may also apply to bilateral (BT) ECT. Also, diagnosing major depression during a drug-free observation period and the prospective design are strengths of this study.

The most important limitations are the relatively small sample size and the fact that patients are not equally distributed between the three age groups, with only 14% of the patients in the young-age group and over 50% of the patients in the middle-age group. The exclusion of patients that refused further ECT treatment might have overestimated the efficacy of ECT. Our findings pertain to patients treated with BT ECT at 1ms pulse width given twice weekly. The findings may not be generalizable to RUL, BF (bifrontal) or BT ECT at different frequency.

Psychomotor retardation and agitation were defined according to item 8 and 9 of the HAM-D17, respectively, which is another limitation. In analyzing reduction in total HAM-D scores it is possible that these specific HAM-D items were partly accountable for higher baseline scores since a higher score on item 8 and/or 9 leads to a higher total baseline HAM-D score.

Future studies could investigate mediating factors with more precise evaluation tools, like the CORE for psychomotor disturbance, and the Psychotic Depression Assessment Scale (PDAS) (Ostergaard et al., 2014) for psychotic features, since these tools might provide more convincing evidence.

CONCLUSION

ECT is most effective in patients with psychotic features and patients with psychomotor retardation showed. Furthermore, our results show that these symptoms also mediate the association between older age and ECT efficacy, thereby providing a rationale for the heterogeneous results found in scientific studies for the impact of age on ECT efficacy. The observation of obvious psychomotor retardation may be an argument for treatment with ECT earlier in the treatment algorithm in severely depressed patients.

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Chapter 6

Refractory major depression successfully treated with electroconvulsive therapy in a patient with Addison disease

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Journal of ECT 2013;29:137-138

ABSTRACT

This report describes a 55-year-old woman who had 1 previous episode of major depression that responded favorably to treatment with tricyclic antidepressants. After the development of Addison disease, she experienced a new episode of major depression that failed to respond to adequate treatment with imipramine and was subsequently successfully treated with electroconvulsive therapy (ECT) with steroid cover. The patient did not experience adrenal crisis or adverse effects. After 9 ECT sessions, she attained full remission. These findings support the suggestion that ECT treatment is safe in patients with Addison disease when using 100 mg intravenous hydrocortisone as prophylaxis.

INTRODUCTION

Addison disease, or primary adrenocortical insufficiency, is a rare disorder with a mean incidence of approximately 6 new cases per million per year (1). Major depression is a frequent occurrence in patients with Addison disease (1). Although glucocorticoid replacement may alleviate major depression in these patients, some have persistent major depression despite adequate replacement therapy (2).

Major depression is associated with both hypercortisolemia and hypocortisolemia, with hypocortisolemia being more prevalent in patients with chronic major depression.

Whether the efficacy of antidepressants in patients with depression with Addison disease is similar to that in physically healthy patients with depression is unknown.

The patient we describe had 1 previous episode of major depression, which responded favorably to treatment with tricyclic antidepressants (TCAs). After the development of Addison disease, she experienced a new episode of severe major depression, which failed to respond to adequate treatment with imipramine and was subsequently successfully treated with electroconvulsive therapy (ECT).

CASE REPORT

This patient is a 55-year-old woman who developed a first major depressive episode at age 44 years. The first depressive episode responded favorably to treatment with clomipramine 150 mg/d. No recurrence of depression occurred for the next 11 years. At the age of 55 years, the patient developed Addison disease. At the same time, she developed depressive symptoms that only marginally responded to hydrocortisone treatment (30 mg). After decreasing the dose of hydrocortisone to 20 mg because of adverse side effects (tremors), the depressive symptoms increased. A depressive disorder was diagnosed, and the patient was treated at a psychiatric outpatient clinic. Subsequent treatment with clomipramine 150 mg, venlafaxine 225 mg, mirtazapine 30 mg, and amitriptyline 200 mg had no effect on the severity of her depressive symptoms.

About 2 years after the recurrence of major depression, the patient was admitted to the depression unit of the Department of Psychiatry at the Erasmus Medical Center for diagnostic evaluation and treatment. On psychiatric examination, she exhibited bradyphrenia, self-depreciation, depressed mood, psychomotor agitation, and suicidal thoughts. The diagnosis of severe major depression was confirmed. Her score

on the 17-item Hamilton Rating Scale for Depression (HAM-D) was 25. Treatment with imipramine was started and, with a daily dose of 150 mg, she attained a therapeutic plasma level (262 ng/mL). After 4 weeks of adequate treatment, there was a slight worsening of the depressive symptoms (HAM-D score, 31). The patient agreed to a trial of inpatient ECT. The imipramine was stopped before the start of ECT treatment. Bilateral ECT was performed twice a week with the Thymatron System IV. Anesthesia was achieved with intravenous etomidate (0.2 mg/kg) and succinylcholine (1.0 mg/kg) for muscle relaxation. On the advice of an endocrinologist, hydrocortisone 100 mg was administered intravenously as prophylaxis against adrenal crisis (steroid cover) just before each ECT session. The patient had no adverse effects, with the exception of retrograde amnesia and transient headache after the ECT sessions. After 9 ECT sessions, our patient attained full remission (HAM-D score, 5).

DISCUSSION

This woman had experienced several previous episodes of major depression that responded favorably to treatment with a TCA. After developing Addison disease, she developed a new episode of severe major depression; however, this time she did not respond to treatment with imipramine with therapeutic plasma concentrations but did respond favorably to ECT, attaining complete remission after 9 ECT sessions.

There are several possible pathways to an increased risk of depressive disorders in patients with Addison disease. Psychological and mood impairment has been documented in patients with primary adrenocortical insufficiency. This could result in an increased risk of depressive disorders. Another explanation is that patients with Addison disease have continuous dysregulation of the hypothalamic-pituitary-adrenal axis that might not be reversed by glucocorticoid hormone substitution (1). Glucocorticoid replacement therapy may improve depressive symptoms in Addison disease, but some patients have persistent depressive symptoms despite adequate replacement therapy (2). In addition, it is not always possible to give an optimal dose of hydrocortisone, for instance, because of adverse effects, as was the case in our patient.

It remains unclear why our patient no longer responded to TCAs after being diagnosed as having Addison disease but achieved full recovery from the depressive disorder with ECT. It is possible that the index episode in our patient was more severe than her previous episode because of the comorbid Addison disease. In addition, it is likely that a more severe depressive episode would not respond to TCAs whereas it would to ECT because ECT is a more effective antidepressant treatment compared with TCAs. Yuuki

et al showed that patients with a depressive disorder who did not respond to trials of antidepressant medication showed remission with ECT that was accompanied by resolution of the hypothalamic-pituitary-adrenal dysregulation (3). Vukadin et al (4) showed that high levels of postdexamethasone cortisol are associated with a more robust response to ECT.

Administration of ECT for major depression in patients with Addison disease has been reported in 2 other cases. (2,5). Suzuki et al (2) reported that a patient was treated with 13 ECT sessions and 100 mg hydrocortisone intravenously as prophylaxis against adrenal crisis. The depressive episode went into remission without adrenal crisis or severe adverse effects. Craddock and Zeller (5) treated their patient with a depressive disorder and Addison disease with 4 sessions of ECT without steroid cover; this patient also responded well to ECT and without adrenal crisis.

Our patient was treated with 9 bilateral ECT sessions with 100 mg hydrocortisone intravenously as prophylaxis against adrenal crisis as steroid cover without any severe adverse effects or adrenal crisis. Adrenal crisis in patients with Addison disease is a life-threatening event that might occur because of the physiologic stress that occurs during ECT. That is why we suggest to use steroid cover despite the fact that 1 patient with Addison disease was reported to be safely treated with ECT without steroid cover (5). The findings from our case report and those of Suzuki et al (2) suggest that ECT treatment is safe in patients with Addison disease with 100 mg intravenous hydrocortisone as prophylaxis.

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Chapter 8

General discussion

MAIN CONCLUSIONS OF THIS THESIS

- The efficacy of ECT in MDD is significantly superior in patients without previous pharmacotherapy failure as compared with medication resistant patients **(chapter 3)**.

- Since the overall remission rate for patients with previous pharmacotherapy failure is almost 50% **(chapter 3)** and 39% of the patients with resistance to a strong antidepressant trial (TCA and lithium addition) attain remission after ECT treatment **(chapter 2)**, severely depressed medication resistant patients can still largely benefit from subsequent ECT.

- ECT appears to be equally effective for bipolar depression as compared with unipolar depression **(chapter 4)**. This is important, since bipolar depression is hard to treat due to the doubtful effects of antidepressant add-on therapy and the additional risk of manic switches.

- Patients with MDD aged 50 or older had non-significant higher efficacy of ECT (small to medium effect sizes) compared to patients <50 years **(chapter 5)**.

- Older age was associated with more psychotic symptoms and more psychomotor retardation in MDD (**chapter 5)**.

- A superior efficacy of ECT is found in patients with psychotic features and in patients with psychomotor retardation and these symptoms mediate the association between age and ECT efficacy **(chapter 5)**. This finding provides a rationale for the heterogeneous results found in scientific studies for the impact of age on ECT efficacy in MDD.

- It is suggested that ECT treatment is safe in Addison disease with 100mg intravenous hydrocortisone as prophylaxis **(chapter 6).**

- No evidence was found for an association between cortisol values after successful bilateral ECT and early relapse **(chapter 7**). This is in line with the majority of ECT studies on the relation between persistent HPA axis hyperactivity and relapse after successful ECT.

- A strong association between HPA axis hyperactivity after successful treatment with antidepressants and relapse that was found in studies, whereas this relation

was not found in studies focusing on ECT treated patients exclusively. This suggests that ECT treatment affects the HPA axis in a fundamentally different way **(chapter 7).**

METHODOLOGICAL CONSIDERATIONS

The results of the studies should be interpreted in the lights of its strengths and its limitations.

Validity and homogeneity of psychiatric diagnosis

The accuracy of the diagnosis in the three prospective studies **(chapter 2,5,7)** due to diagnosing MDD based on clinical observation during a routinely used drug-free period is considered a strength. Further, the study samples are homogeneous samples of severely depressed patients with a mean HAM-D (17 item) baseline score between 26.0 and 28.8.

Electroconvulsive therapy

In the prospective studies **(chapter 2,5,7)**, predominantly bilateral ECT was given, which is considered to be the most effective electrode placement (1) .

Further, the use of benzodiazepines was not allowed which is considered a strength since benzodiazepines have a negative effect at least on the efficacy of right unilateral (RUL) ECT (2). This may also apply to bilateral ECT.

Since most patients were treated with bilateral ECT at 1 ms pulse width given twice weekly, the findings may not be generalizable to RUL, bifrontal ECT or bilateral ECT given a different frequency.

Study design

All three prospective studies **(chapter 2,5,7)** had relatively small sample sizes, which could have influenced the results.

In the study investigating the influence of age the mediation role and psychomotor disturbance and psychotic features on ECT efficacy **(chapter 5)** patients were not equally distributed among the three age groups, with only 14% of the patients in the YA group and >50% in the MA group. The differences between the YA group versus the MA and OA group most likely failed to reach statistical significance due to the small number of patients in the YA group.

Further, in this study, psychomotor retardation and agitation were defined according to item 8 and 9 of the HAM-D17, respectively. In analyzing reduction in total HAM-D scores it is possible that these specific HAM-D items were partly accountable for higher baseline scores, since a higher score on item 8 and/or 9 leads to a higher total baseline HAM-D score.

In the study testing the hypothesis that persistent HPA axis hyperactivity after ECT in MDD predicts early relapse (**chapter 7)**, only 17 patients were included for the analysis, which meant we could not adjust for potential confounding factors such as medication resistance, episode duration and residual symptoms. In this study we found that the majority of patients (75%) with response but without complete remission (partial remission; residual symptoms) relapsed compared to only 15% of the patients that achieved complete remission. Therefore, it is possible that partial remission is a confounding factor. This finding suggests the importance of continuing ECT treatment until full remission is achieved.

Measuring cortisol

It is possible that an influence of persistent HPA axis hyperactivity after ECT treatment on early relapse has been limited due to the high percentage of our patients with hypercortisolemia and non-suppression on the DST after ECT treatment **(chapter 7)**. Ideally, to measure the cortisol ratio, cortisol is measured at the same time before and after dexamethasone ingestion. In this study cortisol was measured at 11 AM pre dexamethasone and at 9 AM after dexamethasone ingestion the evening before. Therefore, there could have been an overestimation of the percentage of non-suppressors in this study.

Furthermore, measuring cortisol in saliva in a severely depressed population is prone to lead to missing data. It proves to be difficult to fully instruct patients to chew on the salivettes for a sufficient amount of time.

Defining medication resistance

When comparing the efficacy of ECT in medication resistant patients versus patients without medication resistance, medication resistance **(chapter 2 and 3)** was defined according to the antidepressant treatment history form. This is a physician rated instrument to assess treatment resistance. The cutoff point for treatment resistance is a score of 3 or more. This score is already attained when treated with an adequate dosage of a single selective serotonin reuptake inhibitor for 4 weeks, which generally is not considered a strong antidepressant trial.

Limitations of the meta-analyses

The findings of the meta-analyses **(chapter 3 and 4**) are based on observational studies, since a randomized controlled trial is not feasible in the situation of medication resistance and bipolar versus unipolar depression. This may result in an increased risk for some form of bias (selection bias for example) and differences in study design.

In both meta-analyses **(chapter 3 and 4)**, in several of the included studies patients were treated with right unilateral ECT with an electrical stimulus of less than 6x the seizure threshold, which is considered less effective than bilateral ECT (1). Therefore, ECT administration was less optimal in these studies compared to the remaining studies. Further, in some studies, patients were allowed to use lorazepam during the ECT course, which can also have a negative effect at least on the efficacy of right unilateral (RUL) ECT.

ECT efficacy seems to be superior in depressed patients with psychotic features compared to depressed patients without psychotic features (3, 4). In the meta-analysis comparing the efficacy of ECT in medication resistant patients versus patients without medication resistance **(chapter 3)**, the proportion of patients with psychotic depression was unequally divided between the studies: two of the included studies excluded psychotic depression (5, 6), in two studies a minority of the patients had psychotic depression and in the remaining 3 studies almost 50% of patients had a psychotic depression. Therefore, it is possible that the proportion of patients with psychotic features was a potential confounding factor.

COMPARISON WITH PREVIOUS AND RECENT LITERATURE

Medication resistance and response to subsequent electroconvulsive therapy in major depression

We found the efficacy of ECT to be significant superior in patients without previous pharmacotherapy failure as compared with medication resistant patients with a remission rate of 48% and 65% for patients with and without previous pharmacotherapy failure. This is in line with a more recent meta-analysis published in 2015 that found response rates of 58% and 70% for patients with and without medication failure respectively ($p<0.001$)(7).

Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression

Our finding that ECT appears to be equally effective for both bipolar and unipolar depression in terms of remission rates (53% versus 51% respectively) is in line with a more recent meta-analysis that found remission rates of 52% in both unipolar and bipolar depression (8). On the other hand they found a significant but small difference in terms of response rates between bipolar and unipolar depression: 77% in bipolar depression compared 74% to unipolar depression. In our study we only used the remission criterion since most patients with severe depression will show some response to ECT and therefore the response criterion may lack the sensitivity needed to detect differences in the treatment efficacy between unipolar and bipolar depression.

Influence of age on ECT efficacy in depression and the mediating role of psychomotor retardation

The findings of our study are in line of two recent meta-analyses (7, 9) that found a positive but weak association between older age and higher ECT efficacy. However, heterogeneous results are found in previous studies (10-16).

The higher efficacy to ECT we found in patients with psychotic features is in agreement with others (3, 4, 17).

Moreover, our finding of a higher efficacy of ECT in patients with psychomotor retardation is in accordance with Hickie et al. (1996)(18).

A large study published in 2018 found no difference in response or remission rate after ECT treatment between three age groups (18-45, 46-64, and 65-85 years)(19). The majority of patients suffered from a bipolar depression (89%), in contrast to our study, in which we excluded bipolar depressions. In this study, there were no significant differences in percentage of psychotic features between the 3 age groups in contrast to our study, in which the young age group (< 50 years) had significantly less psychotic features compared to the middle age (50-69) and old age (70 and over) group. Further, in this study (19) the percentage of patients with psychotic features in the middle (46-64) and older (65-85) age group was lower (28% and 35% respectively) compared to the percentage of patients with psychotic features in middle (50-69) and older (70 and older) age group (66% and 64% respectively) in our study. Since we found that the association between age and ECT efficacy is mediated by psychomotor retardation

and in lesser extend by psychotic symptoms it is possible that the association between age and ECT efficacy therefore did not emerge in the study of Socci (2018)(19).

Cortisol levels after successful electroconvulsive therapy as a predictor for early relapse in major depression

The finding of our study together with the inconclusive results from studies focusing on ECT treatment exclusively, are in contrast with the strong association that was found between post treatment non-suppression on the DST after clinical treatment response and poor long-term outcome in patients treated with antidepressants in the meta-analysis of Ribeiro et al. (1993)(20).

The difference between the results in patients treated with antidepressants and patients treated with ECT exclusively might be explained by the fact that ECT has a different effect on the HPA axis compared with treatment with antidepressants (21). This is in line with our case report (**chapter 6**). Also, ECT treatment itself might affect the HPA axis (22, 23). Therefore, the usefulness of cortisol in its present form as a biomarker for relapse after successful ECT needs further study.

GENERAL CLINICAL RECOMMENDATIONS

- Diagnose MDD, at least in inpatients, based on clinical observation during a routinely used drug-free period to increase accuracy of diagnoses

- Optimize ECT treatment in MDD: consider bilateral ECT (or RUL with an electrical stimulus of at least 6x the seizure threshold), refrain from benzodiazepines, proceed with ECT treatment as long as the patient improves

- ECT treatment should be continued in severe depression until full remission is achieved considering the higher relapse rate in partial remission

- Consider ECT treatment in severe bipolar depression earlier in the treatment algorithm, especially since this type of depression often proves to be relatively medication resistant and ECT appears to be equally effective for bipolar depression as compared with unipolar depression

- When considering ECT treatment, clinicians should focus on the presence of psychomotor retardation and psychotic features in MDD instead of focusing on the age of a patient

- The observation of obvious psychomotor retardation may be an argument for treatment with ECT earlier in the treatment algorithm in severely depressed patients

RECOMMENDATIONS FOR FURTHER RESEARCH

Predictors of ECT efficacy in major depression

Although ECT is a very effective treatment in MDD, up to 45% of the patients do not achieve full remission. Therefore, it is important to evaluate possible predictors and to investigate new predictors of ECT efficacy. Convincing predictors of ECT efficacy are absence of medication resistance, psychotic features, previous ECT treatment and shorter duration of the index episode.

In this thesis, we found evidence that psychomotor retardation and psychotic features predict ECT efficacy. However, we defined psychomotor retardation according to item 8 of the HAM-D17. Replication of this finding is warranted in larger studies with a more precise evaluation tool, like the CORE or the actiwatch since these tools might provide more convincing evidence.

Latency between sleep onset and first episode of rapid eye movement (REM) sleep is typically shortened in MDD and small studies show that ECT improves sleep parameters, increased REM sleep latency and decreased duration of REM sleep (24). Therefore, it may be of interest to investigate the relation between sleep and ECT using polysomnography to understand the mechanisms of ECT better and to assess whether sleep parameters may be interesting candidates as predictor of ECT efficacy. However, the achievability of polysomnography is questionable, since it might be a difficult procedure to fulfill in severely depressed patients.

Cortisol is another challenging predictor of ECT efficacy to investigate, since ECT treatment itself may affect the HPA axis too. Therefore, it is important first to investigate which effect ECT itself has on the HPA axis.

On the other hand, specific predictors are maybe less useful to personalize treatment strategies. Further research should focus on identifying how known clinical and biological predictors complement and interact with each other in order to build a more complex multidimensional prediction model, which may predict ECT efficacy far more accurately than the individual predictors.

Predictors of relapse after successful ECT in major depression

Further investigation of other possible predictors of relapse after successful ECT treatment in MDD is justified because of the substantial relapse rate. We did not find an association between persistent HPA axis hyperactivity after successful ECT and relapse (chapter 6). This in agreement with the majority of previous studies focusing on relapse after ECT treatment exclusively. Further, ECT itself may increase cortisol levels and there are signs that ECT treatment affects the HPA axis fundamentally different than antidepressant treatment does. Therefore, the usefulness of cortisol assessment in its present form to predict relapse after successful ECT is questionable and it needs further study. It may be useful to assess cortisol before, during and after ECT in order to understand the effect of ECT treatment on the HPA axis better. Further, we suggest assessing cortisol during the follow-up period after successful ECT since ECT treatment itself may affect the HPA axis, which may offset the expected normalization of the HPA axis.

It could also be worth investigating which treatment options, for example the combination of antidepressant therapy and a psychological treatment form like cognitive behavioral therapy, reduce the risk of relapse. Only one randomized controlled trial investigated CBT combined with antidepressants as maintenance therapy after successful ECT in depressed patients and found that this combination might be an effective continuation treatment to prevent relapse after successful ECT (25). Replication of this study is of value and assessing other forms of psychotherapy as relapse prevention after successful ECT could be of interest.

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Chapter 9

Summary / samenvatting

SUMMARY

Severe major depression (MDD) is a serious, sometimes life-threatening illness. Therefore, effective treatment is essential. ECT is a highly effective treatment in MDD. Nevertheless, up to 30-45% of the patients do not achieve full remission (1), and high relapse rates after successful ECT treatment remains a major cause for concern (2).

Reliable predictors of ECT efficacy and relapse after successful ECT treatment would be useful to guide patient treatment matching.

Therefore, we examined possible predictors of ECT efficacy and possible predictors of early relapse after successful ECT in MDD.

In chapter 2 we present an open prospective study investigating the predictive value of treatment failure to both a TCA and lithium addition with respect to the efficacy of subsequent ECT. This study included 86 patients with a mean post-ECT HAMD score of 10.7. Patients with nonresponse to a TCA and lithium addition had a mean decrease in HAM-D score during the ECT course of 16.4 compared to 19.5 in the patient group without medication resistance (p=0.2) (primary outcome criterion). Furthermore, response rates were 67% in the group adequately treated versus 77% in the inadequately treated group (p=0.3). Remission rates were 39% in the medication resistant group versus 50% in the group without medication resistance (p=0.3). Therefore, treatment failure with adequate pharmacotherapy with an TCA and lithium addition appears to be unrelated to outcome following subsequent ECT.

Since failure to respond to antidepressants is the most common indication for ECT and the literature seems to be divided as to whether medication resistance has a negative influence on the efficacy of subsequent ECT, we performed a meta-analysis (**chapter 3**) to investigate the effect of previous pharmacotherapy failure on the efficacy of subsequent ECT. We conducted a systematic literature search and included 7 prospective, observational studies in the meta-analysis. We observed the overall remission rate of patients without previous pharmacotherapy failure (64.9%) to be significantly superior to the remission rate of patients with previous pharmacotherapy failure (48%) (OR=0.52, 95% CI: 0.39-0.69). Therefore, this meta-analysis provides evidence that the efficacy of ECT appears to be superior in patients without medication resistance compared with medication-resistant patients. Despite the significant difference between patients with and without previous pharmacotherapy failure, almost 50% of medication resistant patients attain full remission with ECT

treatment. Hence, ECT seems to be an effective treatment for severely depressed patients as well as for depressed patients with previous pharmacotherapy failure.

Since possible differences in the efficacy of ECT for unipolar versus bipolar depression remain unclear, we performed a meta-analysis **(chapter 4)** to investigate the efficacy of ECT in bipolar versus unipolar major depression. We conducted a systematic literature search and included six cohort studies (5 prospective and 1 chart review) in the meta-analysis. The overall remission rate for patients with unipolar depression was similar (50.9%) to patients with bipolar depression (53.2%) (OR=1.08, 95% CI: 0.75-1.57). Accordingly, this meta-analysis provides evidence for the equal efficacy of ECT in both types of MDD. No hint for a difference in efficacy of ECT in both types of MDD emerged.

Since it is uncertain whether patients' age influences ECT efficacy in MDD, we tested the hypothesis that older age predicts a higher efficacy of ECT and a shorter time to remission in severely depressed patients (**chapter 5)**. Furthermore, we analyzed whether psychomotor disturbance and/or psychotic features mediate the relationship between age and ECT efficacy. Ninety-six patients of the PROSPECT cohort (a prospective study of depressed patients treated with ECT at the Department of Psychiatry of the Erasmus Medical Centre from January 2006 up to date) were included for analysis. Middle aged (MA; 50 to 70 years) and older aged (OA; 70 years and over) patients had non-significant larger symptom reduction compared with young aged (YA; <50 years) patients. Medium effect size was found in favor of MA (d=0.44) compared to YA and small effect size was found in favor of OA (d=0.30) compared to YA. The MA and OA group achieved remission almost 1,5 to 2 weeks earlier than the YA group; a difference that did not attain the level of statistical significance. Patients with psychotic features and patients with psychomotor retardation had significantly larger symptom reduction ($p<0.001$ and $p=0.005$, respectively, d=0.88 and d=0.66, respectively) than patients without these features. In the path-analysis that we performed we found a significant mediating pathway through psychomotor retardation ($p=0.049$) and psychotic symptoms showed a trend toward mediation ($p=0.071$). Both indirect paths were positive, meaning that older age was associated with more psychomotor retardation and psychotic symptoms resulting in larger depressive symptom reduction.

Chapter 6 is a case report that describes a 55 year old woman who had 1 previous episode of MDD that responded to treatment with a TCA. After the development of Addison disease, (primary adrenocortical insufficiently) a new episode of MDD

occurred. She experienced self-depreciation, depressed mood, bradyphrenia, psychomotor agitation and suicidal thoughts and her score on the HAM-D was 25. This episode failed to respond to a TCA (imipramine with therapeutic plasma concentrations) but with 9 sessions of bilateral ECT with steroid cover the patient experienced complete remission. The patient did not experience adrenal crisis or adverse effects. These findings support the suggestion that ECT treatment is safe in Addison disease when using 100mg intravenous hydrocortisone as prophylaxes.

Patients with Addison disease have an increased risk of MDD, possibly because these patients have a continuous dysregulation of the HPA axis that might not be reversed by glucocorticoid hormone substitution. It remains unclear why this patient with Addison disease no longer responded to a TCA but experienced full remission with ECT treatment. It is possible that this episode was more severe than her previous episode, possibly because of the Addison disease. ECT treatment is a more effective antidepressant treatment compared with a TCA. It is also possible that ECT has a different effect on the HPA axis compared with treatment with antidepressants.

Relapse after successful ECT occurs frequently in depression and therefore it is important to investigate potential predictors of relapse. The aim of **chapter 7** was to test the hypothesis that persistent HPA axis hyperactivity predicts relapse after a successful course of bilateral ECT. In total, 17 patients responded to ECT and were included in the study. In these patients salivary cortisol was collected at 10pm after successful ECT, which provides information about the basal activity. Further, information about the negative feedback system was provided by the dexamethasone (0.5mg) suppression test: salivary cortisol levels at 11 AM after successful ECT were divided by cortisol levels 10 hours after ingestion of dexamethasone 0.5mg (cortisol suppression ratio) the day after. The relation between these cortisol values and relapse 3 months after successful ECT was evaluated.

The mean cortisol level at 10 PM was 8.8 nmol/l (SD 5.2) after successful ECT, with 75% of the total patient population suffering from hypercortisolism (using an established reference range of < 6nmol/l (3)). Although not statically significant, more hypercortisolism was seen in patients without relapse at 3 months follow-up, i.e. 86% of patients without relapse (6/7) compared to 60% of patients with a relapse (3/5) =0.25, 95%CI:0.02-4.00, p=0.13), which was the opposite direction of which was hypothesized. Further, non-suppression on the DST, defined as a cortisol suppression ratio of <1.58 (in accordance with Vreeburg et al., 2009(4)) was found in >80% of the

included patients. Non-suppression rates differed not significantly between patients with or without relapse (OR=0.50, 95%CI 0.02-11.09, p=0.21).

Based on these findings, we could not confirm the hypothesis that persistent hyperactivity of the HPA axis after successful bilateral ECT is a predictor for early relapse. Therefore, no indication was found to continue ECT treatment until normalization of the HPA axis was achieved in order to minimize relapse risk.

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NEDERLANDSE SAMENVATTING

Een depressie is een ernstige en soms zelfs levensbedreigende ziekte. Daarom is een effectieve behandeling essentieel. Electroconvulsietherapie (ECT) is een zeer effectieve behandeling bij patiënten met een ernstige depressieve stoornis. Desalniettemin bereikt 30-45% van de patiënten geen volledige remissie (1), en hoge terugval percentages na een succesvolle ECT kuur blijven een reden tot zorg (2). Betrouwbare voorspellende factoren voor de effectiviteit van ECT en voorspellers van terugval na een succesvolle ECT kuur zijn zinvol om zo de patiënt-treatment matching te verbeteren. Om die reden hebben we mogelijke voorspellers van ECT effectiviteit en mogelijke voorspellers van vroege terugval na succesvolle ECT bij patiënten met ernstige depressie onderzocht en in dit proefschrift besproken.

In **hoofdstuk 2** bekeken we in een open, prospectieve studie of medicatieresistentie voor een tricyclisch antidepressivum (TCA) met lithiumadditie zorgde voor een lagere kans op een succesvolle daarna gegeven ECT kuur. In deze studie werden 86 patiënten geïncludeerd. Zij hadden een gemiddelde score op de Hamilton Depressie schaal (HAM-D) na de ECT kuur van 10.7. Patiënten die resistent waren voor een TCA met lithium additie (adequaat behandeld) voorafgaand aan de ECT kuur hadden een gemiddelde daling in HAM-D score (HAM-D score pre ECT minus HAM-D score post ECT) van 16.4 in vergelijking met 19.5 in de groep zonder medicatie resistentie (niet adequaat behandeld) (p=0.2). Het percentage patiënten met respons was 67 in de groep die adequaat behandeld was met een TCA met lithium additie versus 77 in de niet adequaat behandelde groep (p=0.3). Het percentage patiënten met remissie was 39 in de adequaat behandelde groep versus 50 in de niet adequaat behandelde groep (p=0.3).

Medicatieresistentie voor adequate farmacotherapie met een TCA met lithium additie lijkt daarom niet gerelateerd aan de effectiviteit van de daarna gegeven ECT kuur.

Tegenwoordig is medicatieresistentie de meest voorkomende indicatie voor ECT. Of medicatieresistentie een negatieve invloed heeft op de effectiviteit van daaropvolgende ECT, daar blijkt de literatuur verdeeld over te zijn. Om die reden voerden we een meta-analyse uit (**hoofdstuk 3**) om zo het effect van medicatieresistentie op de effectiviteit van daarna gegeven ECT te onderzoeken. Een systematische zoekopdracht resulteerde uiteindelijk in de inclusie van 7 prospectieve, observationele studies in de meta-analyse. Het percentage patiënten zonder medicatieresistentie die in remissie raakten met ECT (64.9%) is significant hoger dan het percentage patiënten met medicatieresistentie die in remissie raakten

(48%) (OR=0.52, 95% CI: 0.39-0.69). De meta-analyse levert dus bewijs voor hogere effectiviteit van ECT bij depressieve patiënten die niet medicatieresistent zijn in vergelijking met medicatieresistente patiënten. Ondanks dit significante verschil tussen patiënten met en zonder medicatieresistentie bereikt bijna 50% van de medicatieresistente patiënten toch nog volledige remissie na de ECT-kuur. ECT blijkt dus een effectieve behandeling voor ernstig depressieve patiënten, ook als ze eerder niet reageerden op antidepressiva.

In de literatuur bestond onduidelijkheid over een eventueel verschil in effectiviteit van ECT tussen ernstige unipolaire en bipolaire depressies. Om die reden voerden we een meta-analyse uit (**hoofdstuk 4**) om de effectiviteit van ECT bij bipolaire versus unipolaire depressieve patiënten te onderzoeken. We voerden een systematische zoekopdracht uit en includeerden 6 cohort studies (5 prospectieve studies en een retrospectief dossieronderzoek) in de meta-analyse. Het remissie percentage van patiënten met unipolaire depressie was vergelijkbaar (50.9%) met het remissie percentage van patiënten met een bipolaire depressie (53.2%) (OR=1.08, 95% CI: 0.75-1.57). Uit deze meta-analyse blijkt dus dat ECT even effectief is bij een bipolaire als bij een unipolaire depressie.

In **hoofdstuk 5** werd de voorspellende waarde van leeftijd geëvalueerd tijdens de behandeling met ECT. Tevens werd onderzocht of de veronderstelde hogere effectiviteit van ECT bij oudere depressieve patiënten (deels) verklaard werd door de aanwezigheid van psychotische kenmerken en/of psychomotore retardatie.

Zesennegentig patiënten van het PROSPECT-cohort (een prospectieve studie van depressieve patiënten behandeld met ECT op de psychiatrie afdeling van het Erasmus Medisch Centrum van januari 2006 tot heden) werden geïncludeerd voor de analyse. Patiënten van middelbare leeftijd (MA; 50 tot 70 jaar) en oudere (OA; 70 jaar en ouder) patiënten hadden een niet significant grotere symptoom reductie in vergelijking jonge (YA;< 50 jaar) patiënten. Een medium effect grootte werd gevonden ten gunste van MA (d=0.44) in vergelijking met YA en een kleine effect grootte werd gevonden ten gunste van OA (d=0.30) in vergelijking met YA. De MA en de OA groep bereikten bijna 1,5 tot 2 weken eerder remissie dan de YA groep; dit verschil was echter niet significant.

Depressieve patiënten met psychotische kenmerken en patiënten met psychomotore retardatie hadden significant grotere symptoom reductie ($p<0.001$ en $p=0.005$, respectievelijk, $d=0.88$ en $d=0.66$, respectievelijk) dan patiënten zonder deze kenmerken. In de pad-analyse die we uitvoerden, vonden we een significant effect

via psychomotore retardatie (p=0.049) en psychotische symptomen lieten een trend richting mediatie zien (p=0.07). Beiden indirecte paden waren positief, wat betekent dat een hogere leeftijd geassocieerd is met meer psychomotore retardatie en meer psychotische symptomen, wat resulteert in een grotere reductie van depressieve symptomen na ECT behandeling.

Hoofdstuk 6 is een gevalsbeschrijving waarin een 55-jarige vrouw wordt beschreven die een eerdere ernstige depressieve episode doormaakte en destijds succesvol behandeld werd met een TCA. Na het ontwikkelen van de ziekte van Addison (primaire bijnierschorsinsufficiëntie) ontstond er een nieuwe depressieve episode. Er was sprake van een sombere stemming, vertraging van het denken, schuldgevoelens, psychomotore agitatie en suïcidale gedachten. De HAM-D score was 25. Er werd gestart met een TCA (imipramine onder bloedspiegel controle), echter zonder effect. Hierna werd patiënte met ECT behandeld en na 9 sessies bilaterale ECT met steroïden dekking was er sprake van volledige remissie. Er was geen sprake van een Addison crisis of bijwerkingen tijdens de ECT kuur. Deze bevinding draagt bij aan de veronderstelling dat behandeling met ECT veilig is bij patiënten met de ziekte van Addison als er gebruikt wordt gemaakt van 100mg hydrocortison intraveneus.

Patiënten met de ziekte van Addison hebben een verhoogd risico op het ontwikkelen van een depressieve episode, mogelijk doordat deze patiënten een continue disregulatie van de HPA-as hebben die mogelijk niet hersteld kan worden door glucocorticoïd hormoon substitutie. Het blijft onduidelijk waarom deze patiënte na het ontwikkelen van de ziekte van Addison niet meer reageerde op een TCA, maar wel volledige remissie bereikte na een ECT kuur. Het is mogelijk dat deze depressieve episode ernstiger was dan haar voorgaande episode, mogelijk ook door de ziekte van Addison (die zij tijdens de eerdere episode niet had). ECT is een effectievere antidepressieve behandeling in vergelijking met een TCA. Het is ook mogelijk dat ECT een ander effect heeft op de HPA-as in vergelijking met de behandeling met antidepressiva.

Terugval na succesvolle ECT komt regelmatig voor bij depressieve patiënten. Daarom is het belangrijk mogelijke voorspellers voor terugval te onderzoeken. Het doel van **hoofdstuk 7** was om de hypothese te testen dat persisterende HPA-as hyperactiviteit direct na een succesvolle bilaterale ECT kuur terugval binnen 3 maanden voorspelt. In deze studie respondeerden in totaal 17 patiënten op ECT en deze werden geïncludeerd in de analyse. Van deze patiënten werd na succesvolle ECT speekselcortisol verzameld om 22u. Deze waarde geeft informatie over de basale activiteit. Informatie over

het negatieve feedback systeem werd gegeven door de dexamethason suppressie test (DST): speeksel cortisol waarden om 11u na een succesvolle ECT keer werden gedeeld door speeksel cortisol waarden 10 uur na inname van dexamethason 0.5mg de volgende dag (om 9u) (cortisol suppressie ratio). De relatie tussen deze cortisol waarden en terugval 3 maanden na succesvolle ECT werd geëvalueerd.

De gemiddelde cortisol waarde om 22u na succesvolle ECT behandeling was 8.8nmol/l (SD 5.2), waarbij 75% van de patiënten hypercortisolisme had (er werd gebruik gemaakt van een vastgestelde referentie range van < 6nmol/l (3)). Er werd meer hypercortisolisme gezien bij patiënten zonder terugval bij 3 maanden (86%) in vergelijking met patiënten met terugval (60%), OR= 0.25, 95%CI:0.02-4.00, p=0.13 (ns), dit was de tegenovergestelde richting van wat we verwachtten.

Non-suppressie op de DST, gedefinieerd als een cortisol suppressie ratio van <1.58 (in overeenstemming met Vreeburg et al., 2009 (4)) werd gevonden bij >80% van de geïncludeerde patiënten. Non-suppressie ratio's verschilden niet significant tussen patiënten met of zonder terugval (OR=0.50, 95%CI 0.02-11.09, p=0.21).

Op basis van deze bevindingen kon de hypothese dat persisterende hyperactiviteit van de HPA-as na succesvolle bilaterale ECT een voorspeller is voor vroege terugval niet bevestigd worden. Er werd op basis van deze studie geen indicatie gevonden om de ECT kuur na klinische verbetering verder te continueren tot normalisatie van de HPA-as wordt bereikt om op die manier de kans op een terugval te minimaliseren.

In **hoofdstuk 8** worden de belangrijkste conclusies van dit proefschrift beschreven en worden de uitkomsten van de studies vergeleken met eerdere en recente literatuur. Ook worden de methodologische tekortkomingen en sterke punten van de studies besproken. Tenslotte worden algemene klinische aanbevelingen en suggesties gedaan voor toekomstig onderzoek.

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Appendices

PUBLICATION LIST

Willemijn Heijnen, André Wierdsma, Astrid Kamperman, Witte Hoogendijk, Walter van den Broek, Tom Birkenhäger
Cortisol levels after successful electroconvulsive therapy as predictor for early relapse in major depression: a pilot study
Submitted

Willemijn T.C.J. Heijnen, Astrid M. Kamperman, Lindsay D. Tjokipro, Witte J.G. Hoogendijk, Walter W. van den Broek, Tom K. Birkenhäger.
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Handboek ECT, de Tijdstroom 2019

ABOUT THE AUTHOR

Willemijn Heijnen werd geboren op 12 maart 1982 te Maasbree, Nederland. Ze groeide op in Maasbree en behaalde haar VWO diploma in 2001 aan het Thomas college te Venlo. In 2001 werd ze uitgeloot voor de studie geneeskunde en begon toen aan de studie psychologie aan de Erasmus Universiteit te Rotterdam, waar ze haar propedeuse van behaalde. In 2002 kon ze alsnog beginnen aan haar studie geneeskunde in Rotterdam. Ze onderbrak haar studie tweemaal om meer van de wereld te zien en vrijwilligerswerk in Malawi te doen. Tijdens haar keuze-onderzoek in 2007 op de afdeling psychiatrie van het Erasmus MC maakte ze voor het eerst kennis met onderzoek in de psychiatrie (begeleid door Prof. Dr. W.W van den Broek en Dr. T.K. Birkenhäger). Dit maakte haar enthousiast voor zowel onderzoek als de psychiatrie en – mede omdat uit deze periode twee publicaties ontstonden - mondde dit uiteindelijk uit in een promotietraject.

In 2010 behaalde ze haar artsendiploma en ze begon – na opnieuw een reis in zuidelijk Afrika- in 2011 met haar opleiding tot psychiater aan de Erasmus Universiteit (bij opleider Prof. Dr. W.W. van den Broek). Dit combineerde ze met haar promotie onderzoek (co-promotor dr. T.K. Birkenhäger, promotor Prof. dr. W.J.G. Hoogendijk) in het Erasmus MC. In 2016 rondde ze haar opleiding af en begon ze haar eerste baan als psychiater bij PsyQ, Rotterdam centrum. In april 2017 keerde ze terug naar het Erasmus MC, waar ze werkzaam is als psychiater binnen de zorglijnen zwangerschapsgerelateerde psychiatrie en stemmingsstoornissen. Ze woont samen met haar man Daan en hun twee dochters Jasmijn (6) en Emma (3) in Rotterdam West.

PhD PORTFOLIO

Name PhD student:	Willemijn Heijnen
Erasmus MC Department:	Psychiatry
Research School:	ONWAR
PhD period:	2013-2019
Promotor:	Prof. dr. W.J.G. Hoogendijk
Co-promotor:	dr. T.K. Birkenhäger

1.PhD training

Courses	Year	Workload ECTS
Cursus coachen van toekomstige Erasmusartsen	2019	0.1 ECTS
2 daagse cursus psychofarmacologie (psyfar)	2018	0.6 ECTS
Cursus presenteren met theater vaardigheden	2017	0.6 ECTS
Tutortraining	2017	0.2 ECTS
Basiscursus ziekenhuismanagement	2015	0.6 ECTS
WAD cursus, 'what about stresshormones'	2014	1.0 ECTS
Corsendonck cursus, Belgium (one week)	2011	2.2 ECTS
Seminars and workshops		
31th ECNP conference Barcelona, Spain	2018	1.2 ECTS
Toxed toxicology congress, The Netherlands	2018	0.3 ECTS
Psyfar Themadag Zwangerschap en lactatie, The Netherlands	2017	0.3 ECTS
KNMG congres kwetsbaar ouderschap, The Netherlands	2017	0.3 ECTS
16th World psychiatric association congress of Psychiatry, Cape Town, South Africa	2016	1.2 ECTS
Voorjaarscongres NVVP, The Netherlands	2015	0.6 ECTS
Benecke congres persoonlijkheidsstoornissen, The Netherlands	2013	0.3 ECTS
Voorjaarscongres NVVP, The Netherlands	2012	0.9 ECTS
The American Psychiatric Association annual meeting, Hawaii, United States	2011	1.2 ECTS
Voorjaarscongres NVVP, The Netherlands	2011	0.9 ECTS
Voorjaarscongres NVVP, The Netherlands	2010	1.2 ECTS

Presentations

Junior med school oral presentation (ECT/research in psychiatry)	2017	0.5 ECTS
Keuze onderwijs medical students oral presentation (ECT)	2017	0.5 ECTS
Contribution to oral presentation ECT conference Aachen	2017	0.1 ECTS
Eindreferaat consortium, oral presentation	2016	0.5 ECTS
Researchgroup Psychiatry oral presentation	2015	0.5 ECTS
NVVP voorjaarscongres contribution to oral presentation	2011	0.1 ECTS

2.Teaching activities

Courses	Year	Workload ECTS
Consortium onderwijs stemmingsstoornissen aan artsen in opleiding tot psychiater	2017-2020	1.2 ECTS
Consortium onderwijs transculturele psychiatrie aan artsen in opleiding tot psychiater	2017-2020	0.6 ECTS
Consortium onderwijs psychofarmacologie aan artsen in opleiding tot psychiater	2018-2020	1.2 ECTS
ICK/bedside teaching co-assistenten	2017-2020	4.0 ECTS
Vaardigheidsonderwijs ‘de tuchtzaak’	2011-2020	1.2 ECTS
Vaardigheidsonderwijs ‘angststoornissen’	2011-2020	1.2 ECTS
Vaardigheidsonderwijs ‘psychiatrisch onderzoek’	2011-2020	1.2 ECTS
Maken van tentamenvragen	2018	0.5 ECTS
Superviseren van artsen in opleiding tot psychiater	2016-2020	
Superviseren van medical students (co-assistenten)	2016-2020	
Coachen van geneeskunde studenten	2018-2020