ELECTROCONVULSIVE
THERAPY FOR SEVERE
DEPRESSION

Improving efficacy and preventing relapse

Esther Pluijms

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Electroconvulsive Therapy for Severe Depression

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Elektroconvulsietherapie bij ernstige depressieve stoornis

Het verbeteren van effectiviteit en voorkomen van terugval

Proefschrift

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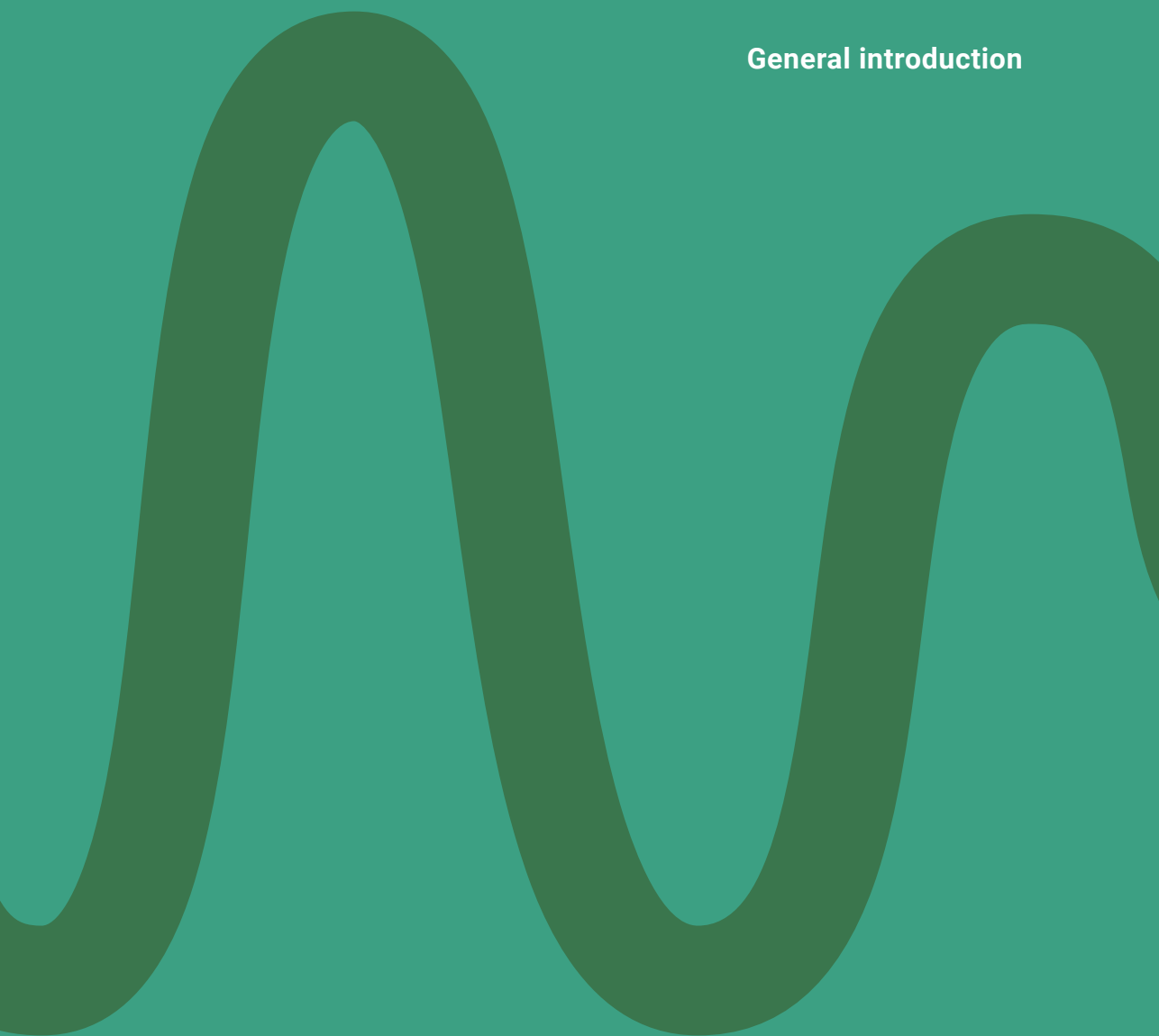
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CHAPTER 1

General introduction

MAJOR DEPRESSIVE DISORDER

Diagnosis

Major depressive disorder (major depression) is highly prevalent in the adult population throughout the world, with a lifetime prevalence of 12% (1). The NEMESIS-2 study reported a lifetime prevalence of almost 19% with a 12-month prevalence of slightly more than 5% in the Dutch general population of adults (2). Major depression has a large impact on both individuals and society. The Global Burden of Disease 2019 Study indicated that of 367 diseases and injuries considered, depressive disorders ranked 6th among adults aged 25-49 years and 14th among adults aged 50-74 years on a ranking list of causes of disability and mortality worldwide (3).

Major depression is defined in the Diagnostic and Statistical Manual (DSM); for this thesis, we used the third, revised edition (4) and fourth edition (5). The DSM is a classification system for psychiatric disorders characterized by the presence of various symptoms. Major depression is diagnosed in patients who have suffered at least one major depressive episode. Table 1 summarizes the criteria for a major depressive episode. As shown in this table, at least one of the two core symptoms of a depressive episode, i.e., depressed mood and loss of interest or pleasure in daily activities, must be present.

TABLE 1. Diagnostic criteria for a major depressive episode based on the DSM-IV (5)

A	At least five of the following symptoms have been present almost every day for at least two weeks; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure in daily activities
	1. Depressed mood or irritable most of the day, nearly every day
	2. Decreased interest or pleasure in most activities, most of each day
	3. Significant weight change or a change in appetite
	4. Insomnia or hypersomnia
	5. Psychomotor agitation or retardation
	6. Fatigue or loss of energy
	7. Feelings of worthlessness or excessive or inappropriate guilt
	8. Diminished ability to think or concentrate or indecisiveness
	9. Recurrent thoughts of death or suicide or having a suicide plan
B	The symptoms do not meet criteria for a mixed episode
C	The symptoms cause clinically significant impairment in social, occupational, or other important areas of functioning almost every day
D	The episode is not due to the effects of a substance or to another medical condition
E	The symptoms are not better explained by bereavement

During patient recruitment for our randomized controlled trial (RCT) and follow-up study, the American Psychiatric Association updated the DSM-IV criteria in the DSM-5

criteria (6). In this update, only a few minor changes were made to the criteria for a major depressive episode: the words "hopelessness" and "sad or empty" were added to the description of depressed mood, and the exclusion criterion "bereavement" was removed. Regardless of which of the two DSM versions we would have used, the identification of a depressive episode remained the same.

Melancholic and psychotic depression

Major depressive disorder is a heterogeneous disorder. In the DSM-IV, it can be subcategorized based on severity (mild, moderate, severe); course; the presence of melancholic, psychotic and atypical features; and a postpartum onset. In this thesis, we focused on patients with severe major depression, often with melancholic and/or psychotic features. In melancholic depression, patients suffer from anhedonia and/or lack of mood reactivity. Additionally, three of the following symptoms must be present: depression subjectively different from grief or loss, diurnal mood variation, early morning awakening, significant weight loss or loss of appetite, psychomotor agitation or retardation, and excessive feelings of guilt (5). Patients with psychotic depression suffer from mood-congruent delusions, such as delusions of guilt, sin and poverty, and somatic and nihilistic delusions, in addition to depressive symptoms. Hallucinations are infrequent and, if present, usually occur simultaneously with delusions (7).

ELECTROCONVULSIVE THERAPY

History

In 1938, Cerletti and Bini were the first clinicians to use an electric current to induce seizures as a treatment for schizophrenia with catatonic features (8). Shortly after, it was found to be even more effective for the treatment of mania and depression (9). Electroconvulsive therapy (ECT) quickly spread around Europe and the United States of America and was first used in the Netherlands in 1939 (10). Since then, its use has fluctuated. In the 1960s and 1970s, the use of ECT rapidly declined due to the Dutch anti-psychiatry movement, the introduction of antidepressants, and criticism about the efficacy and safety of ECT. From the 1990s onwards, the use of ECT gradually increased again due to a growing body of evidence supporting its efficacy and safety, improved ECT techniques, some decrease in stigma around ECT, and the lack of efficacy of antidepressants in some patients with major depression.

In the early years, ECT was used as a first-line treatment, whereas it is currently mainly used to treat medication-resistant patients and patients in life-threatening situations, such as those with a high suicide risk or refusing food and drink (11). In 1995, 140 Dutch patients received ECT, and in 1999, the number increased to 328. A questionnaire survey on current ECT practice in the Netherlands estimated a 16% increase from 2008-2015 and a total of 15,633 ECT sessions performed in 2015 for approximately 900 patients (11).

Technique for performing ECT

ECT is a procedure in which a small electric current is passed through the brain via two electrodes applied to the scalp, intentionally triggering a generalized seizure. Although the underlying mechanisms of action remain unclear, a generalized seizure is necessary to sort the effect.

In the Netherlands, ECT is usually administered twice weekly with a brief-pulse appa-ratus and under general anaesthesia. Anaesthesia is induced after premedication with glycopyrronium (and alfentanil), with etomidate for anaesthesia and succinylcholine for muscle relaxation. The seizure threshold is defined as the minimal electrical dose that induces a motor seizure of at least 25 s. Since marked interindividual variability exists in the seizure threshold, a course of ECT should preferably routinely involve estimation of the seizure threshold by empirical dose titration and then treatment using suprathreshold doses: the stimulus dose is set at 1.5 or at least 5 times the seizure threshold for bilateral or unilateral ECT, respectively. Other dosage strategies, such as the age method for unilateral ECT and the half-age method for bilateral ECT, are less accurate (12). The seizure threshold commonly increases during the course of ECT (13). Therefore, the stimulus dose may need to be increased during the course of ECT to maintain a motor seizure of at least 25 s.

The number of ECT sessions depends on the speed of improvement in each patient's score on the Hamilton Rating Scale for Depression (HRSD) (14). No standard number of sessions for a course of ECT or method to predict how many treatments a patient will need has been established. Most patients remit with 6 to 12 treatments, but some require far more treatments (15). ECT is completed when the patient achieves remission or when the response plateaus.

Safety and tolerability of ECT

ECT is one of the safest procedures performed under general anaesthesia. A recent study by Kaster et al. (16) found no evidence for a clinically significant increased risk for serious medical events with exposure to ECT among depressed inpatients. Although the safety of ECT is well established, adverse effects can occur. These symptoms are commonly mild

and self-limiting, such as short-term postictal confusion, headache, nausea and myalgia, and can be managed symptomatically (17). Some patients suffer from anterograde amnesia and retrograde amnesia during the course of treatment and afterwards. The patients who will experience cognitive problems and the extent of these problems are difficult to predict (18). Amnesia increases with the number of ECT sessions performed, and retrograde amnesia is most severe for events close to the ECT course (17). Memory deficits rarely persist: anterograde amnesia usually improves within days to weeks after ECT completion and retrograde amnesia within weeks to months (17). Concerns that ECT causes structural brain damage have been dispelled by both human and nonhuman primate studies (19, 20).

Efficacy of ECT

The efficacy of ECT is indisputable. It is considered the most effective treatment for patients with severe major depression (21), especially those with psychotic features (22, 23). A meta-analysis by the UK ECT review group (21) showed that ECT for major depression was more effective than both sham ECT and pharmacotherapy. Response rates declined over the years, probably due to changes in the patient population: ECT used to be a first-line treatment and is currently mainly used to treat medication-resistant patients. At the time when we conducted our retrospective chart study on medication resistance, the literature on the influence of medication resistance on ECT outcomes was inconclusive. A few uncontrolled studies found that resistance to antidepressant pharmacotherapy had no or minimal influence on the response to ECT (24-27), while the results of three controlled studies suggested a clear association between medication resistance and ECT outcomes (28-30). Since then, knowledge has expanded, and medication resistance is generally accepted to predict a decreased efficacy of ECT. A meta-analysis by Heijnen et al. (31) found remission rates of 48% in patients with medication resistance and 65% in patients without medication resistance. In a meta-analysis by Haq et al. (32), response rates were 58% and 70% in medication-resistant patients and patients without medication failure, respectively.

At the time when we conducted our retrospective chart study on episode duration, the literature supposed that a longer duration of index depressive episode is associated with decreased efficacy of ECT (26, 30, 33-38). Since then, evidence has increased, and a recent meta-analysis by Haq et al. (32) clearly showed that a shorter duration of the index episode was associated with higher response rates. However, the patients in several of the included studies differed from ours in that they were younger, more likely to have bipolar depression and less likely to suffer from psychotic depression. Additionally, ECT

administration differed in that comedication, such as benzodiazepines and antidepressant medication, was allowed in most of the included studies. Some studies used a suboptimal stimulus dose or a fixed number of ECT sessions, and the level of medication resistance was unclear. Therefore, we hypothesized that the results of previous studies might not be applicable to depressed patients who receive ECT in the Netherlands.

Influence of an adjuvant antidepressant on the efficacy of ECT

Some evidence suggests a synergy between ECT and antidepressants. An RCT by Sackeim et al. (39) showed a favourable effect of a combination of ECT and nortriptyline on remission rates. Our case report describes a patient with psychotic depression. She responded very slowly to a course of ECT monotherapy and failed to achieve full remission. After a severe relapse of psychotic depression, she very rapidly attained full remission with a second course of ECT combined with imipramine (40). Further data on the influence of antidepressant medication on the efficacy of ECT are limited, inconclusive and mostly dated. No systematic reviews or meta-analyses on the influence of an adjuvant antidepressant on the efficacy of ECT have been performed.

Guidelines vary in their recommendations regarding adjuvant antidepressant medication during ECT, probably due to limited and inconclusive data. Some guidelines recommend considering a combination treatment, particularly among patients with medication-resistant depression (41), whereas other guidelines recommend considering ceasing antidepressant medication prior to a course of ECT (42) or weighing the advantages and disadvantages of combination treatment in each individual patient and thus leaving the decision to the clinician (43). Therefore, neither routine use of an adjuvant antidepressant during ECT nor routine discontinuation of a drug prior to ECT is justified by scientific data.

Relapse after successful ECT

After successful ECT, high relapse rates are observed. A meta-analysis by Jelovac et al. (44) showed that 51% of ECT-treated patients relapsed by 12 months, with most relapsing within the first 6 months, despite continuation pharmacotherapy. Only a few studies have focused on clinical predictors for relapse post-ECT. These studies found increased relapse rates at a short-term follow-up of 6-12 months in patients with the following characteristics: younger age, female sex, less severe depression, no psychotic symptoms, medication resistance, a longer duration of the index depressive episode, achieving remission after more ECT sessions, and showing a response but not remission (45-48). Unfortunately, no prospective studies or studies with a longer-term follow-up are available.

AIMS OF THIS THESIS

The research in this thesis was designed to add to the limited and inconclusive literature on the influence of an adjuvant antidepressant on ECT outcomes, and on clinical predictors for relapse after successful ECT. We aimed (I) to determine whether the addition of nortriptyline to a course of ECT enhances its efficacy and prevents post-ECT relapse and (II) to identify clinical predictors for long-term remission after successful ECT.

ECT is considered the most effective treatment for severe major depression (21). Most patients receive ECT because they do not respond to antidepressant medication trials (15). Approximately 50% of medication-resistant patients attain remission following ECT (31). Despite continuation pharmacotherapy, almost 40% of those in remission will relapse within 6 months, and 50% will relapse within a year. Therefore, optimizing ECT in terms of both increasing remission rates and reducing relapse rates would be of considerable clinical significance. To ensure an effective, individually tailored continuation treatment after successful ECT, more extensive knowledge about predictors for relapse or sustained remission is needed. Based on our findings, we aimed to provide recommendations for clinical practice to optimize ECT.

The following main questions concerning ECT in patients with severe major depression will be addressed:

1. Are a longer episode duration and medication resistance prior to ECT predictors of poor ECT outcomes? **(Chapters 2 and 3)**
2. Does an adjuvant antidepressant during a course of ECT enhance its efficacy? **(Chapters 4, 5 and 6)**
3. Does an adjuvant antidepressant during a course of ECT prevent relapse after successful treatment? **(Chapter 6)**
4. Which clinical factors predict long-term remission after successful ECT? **(Chapter 7)**

OUTLINE OF THIS THESIS

Chapter 1 provides a general introduction to this thesis. **Chapters 2 and 3** describe the results of two retrospective chart studies on the influence of the duration of the index episode and medication resistance on the response to ECT in patients with severe major depression. **Chapter 4** is a case report in which we describe the outcomes of two consecutive treatments with ECT in a patient with major depression with psychotic features: the

first treatment was ECT monotherapy and the second treatment included ECT in combination with imipramine. **Chapter 5** is a systematic review and meta-analysis of findings from studies investigating the influence of an adjuvant antidepressant on the efficacy of ECT for major depression. In **Chapter 6,** we assess the influence of an adjuvant antidepressant on the efficacy of ECT and on the relapse rate after successful ECT for major depression. We present data from a double-blind RCT comparing nortriptyline with placebo during a course of bilateral ECT, followed by a one-year open-label treatment with nortriptyline in patients who recovered from depression during the RCT. **Chapter 7** describes the results of a retrospective cohort study on clinical predictors for sustained remission two years after a successful course of ECT. **Chapter 8** provides a general discussion of the main findings of the thesis. Additionally, we discuss clinical implications and provide recommendations for clinical practice and future research.

1

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CHAPTER 2

Influence of episode duration of major depression on response to electroconvulsive therapy

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ABSTRACT

Background

Longer duration of major depressive episode is supposed to decrease response to electro-convulsive therapy (ECT). Most studies on the subject are dated and their population differs from ours, therefore their results may not be applicable to our population of severely depressed inpatients.

Methods

We reviewed the records of 56 consecutive inpatients with major depressive disorder according to DSM-III-R criteria and assessed each patient's episode duration. We examined whether episode duration has an effect on response to ECT.

Results

Episode duration has no significant effect on response to ECT, according to both a reduction on the Hamilton Rating Scale for Depression (HRSD) of at least 50% and a post-treatment HRSD score ≤ 7 as outcome criteria. Concerning each patient's absolute change in HRSD score pre-treatment compared to post-treatment, again episode duration has no significant effect.

Limitations

The present study has a limited sample size and concerns a rather homogeneous population of severely depressed inpatients. Episode duration was established retrospectively.

Conclusions

ECT is an effective treatment for severely depressed inpatients, independent of episode duration.

INTRODUCTION

Electroconvulsive therapy (ECT) is recognised as the most effective treatment for major depressive disorder (1, 2). However, in the Netherlands ECT is still considered an exceptional treatment, administered to non-responders to antidepressant pharmacotherapy. This implies that patients receive ECT late in the course of treatment and therefore have a longer episode duration when ECT is administered.

Longer episode duration of major depressive disorder is associated with poor response to ECT (3-11). Most of these studies are dated and, by current standards, show methodological flaws. The more recent studies of Kindler et al. (10) and Prudic et al. (11) used more modern methodological standards. However, in Prudics population patients with psychotic features were excluded and half of her patients had received ECT before. In Kindlers population females are underrepresented (27%). Our patients had never been treated with ECT before and patients with mood congruent psychotic features were included. The majority was female (73%).

Because of these differences in population, results of previous studies may not be applicable to depressed patients who receive ECT in the Netherlands. Therefore, our study examines the influence of episode duration on response to ECT in a population of severely depressed inpatients, most of them being medication-resistant.

METHODS

Subjects
We reviewed the records of 56 inpatients that met the DSM-III-R (12) criteria for major depression. Diagnoses were based on clinical observation. All patients were consecutively treated with ECT between December 1993 and December 2000 at the Department of Biological Psychiatry, Parnassia Psychomedical Center, The Hague, The Netherlands. This department is reserved for patients suffering from severe depression, often medication-resistant. Patients receiving ECT were either medication-resistant or in critical condition (mutistic, refusing food). All patients were free from neurologic or serious medical illness and had never been treated with ECT before.

Electroconvulsive therapy
Of 32 patients starting with right unilateral (RUL) ECT, all but four either responded or were crossed over to bilateral (BL) ECT. Twenty-four patients received BL ECT from the

start, because of severity of illness based on clinical observation. ECT was administered with a brief-pulse, constant-current apparatus (Thymatron DGx, Somatics, Lake Bluff, IL 60044, USA) after premedication with atropine (0,5 mg i.v.) and under sodiumthiopental anaesthesia (1,0-2,5 mg/kg) and succinylcholine (1,0 mg/kg) for muscle relaxation. Patients were oxygenated (100%, positive pressure) until resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, electrocardiogram and electroencephalogram. ECT was administered at a schedule of two treatments per week with moderate to high stimulus intensity (288-504 millicoulomb). The initial stimulus dose was based on the patients' age (13) with a minimum of 288 millicoulomb in patients receiving RUL ECT. A motor seizure less than 25 seconds was considered inadequate. The number of ECT treatments was determined by clinical observation. ECT was continued until patients were either asymptomatic or had not shown further improvement over three consecutive treatments. A minimum of ten treatments was required before evaluation as non-responder.

Patients were withdrawn from all psychotropic medication before ECT and were maintained medication free during the course of ECT in all but seven cases. Those patients received droperidol 5 mg i.m. prior to ECT for severe anxiety. Three of them also received haloperidol 1-3 mg daily for severe agitation.

Evaluation of treatment outcome

Scores on the 17-item Hamilton Rating Scale for Depression (HRSD) (14) were routinely recorded in the patients' case notes prior to ECT, during ECT and following treatment termination. These HRSD scores were used in two different ways for classification of response to ECT. First, patients were classified as responder when their HRSD score showed a reduction of at least 50%. The second method requires a post-treatment score of ≤ 7 in patients with full remission. We also measured each patient's absolute change in HRSD score pre-treatment compared to post-treatment.

Duration of index episode

Duration of index episode (onset of depressive symptoms to onset of ECT) was measured retrospectively. Because choice of a cut-off point between short and long episode duration is arbitrary, we decided to analyse episode duration as a continuous variable instead as a dichotomous one.

Statistical analysis

Multiple linear regression was used to assess the relation between episode duration and absolute change in HRSD score as continuous variables. Multiple logistic regression

was used to assess the effect of episode duration on two dichotomous outcome criteria, response (at least 50% reduction of HRSD score) and remission (post-treatment HRSD score ≤ 7). In both analyses we adjusted for the following confounding variables: presence of psychotic features, presence of melancholic features (DSM-IV criteria) and adequacy of antidepressant pharmacotherapy prior to ECT. The latter was retrospectively established using the Antidepressant Treatment History Form (ATHF) (15, 16). Medication resistance might be associated with poor outcome (11, 17), whereas melancholic (18, 19) and psychotic (20, 21) features are associated with good response to ECT.

The data were analysed using SPSS 10.1 for Windows. Statistical significance was defined as $p<0.05$.

RESULTS

The patient sample consisted of 56 inpatients, 41 women and 15 men with a mean age of 50.6 years. Table 1 shows the demographic and clinical characteristics for the total patient sample. Forty patients (71.4%) were classified as responder (≥ 50% reduction of HRSD score) and twenty-two (39.3%) showed full remission (post-treatment HRSD score ≤ 7). The mean duration of illness was 23.2 months, with a range from 1 to 90 months.

TABLE 1. Demographic and clinical characteristics of total sample of patients

	Total sample (n=56)
Age in years, mean (SD)	50.6 (10.8)
Female sex, n (%)	41 (73.2)
Psychotic, n (%)	27 (48.2)
Melancholic, n (%)	43 (76.8)
Duration index episode in months, mean (SD), range	23.2 (18.8), 1-90
Score of strongest medication trial prior to ECT[a], mean (SD)	3.4 (1.2)
Pre-ECT HRSD score, mean (SD)	26.6 (5.4)
Post-ECT HRSD score, mean (SD)	10.4 (5.4)
HRSD change score, mean (SD)	16.2 (7.0)
Response (≥ 50% reduction of HRSD score), n (%)	40 (71.4)
Remission (HRSD score ≤ 7 post-ECT), n (%)	22 (39.3)

Abbreviations: ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression.

[a] Each patient's score of strongest medication trial prior to ECT was established using the Antidepressant Treatment History Form (15, 16).

Figure 1 shows the number of patients as a function of episode duration. Almost all patients (52/56, 92.9%) had an episode duration of at least six months. In thirty-eight patients (38/65, 67.9%) episode duration lasted for at least one year and in twenty-five (25/56, 44.6%) for at least two years.

FIGURE 1. Absolute frequency distribution of episode duration
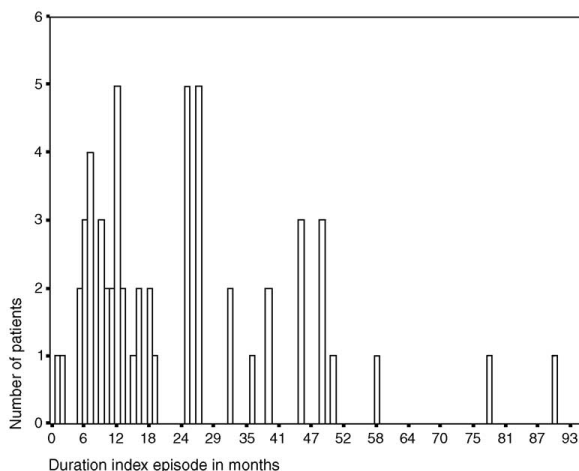
Episode duration has no significant effect on response to ECT or on remission. The odds of response increases by a factor 1.019 for each month longer duration of index episode (p=0.35, 95% CI: 0.98-1.06). The odds of remission increases by a factor 1.003 for each month longer duration of index episode (p=0.85, 95% CI: 0.97-1.04). Again, episode duration has no significant effect on each patient's absolute change in HRSD score. Each month longer duration of index episode results in an increment of 0.037 points in HRSD change score. (SE=0.05, p=0.43, 95% CI: -0.06-0.13).

DISCUSSION

In our study episode duration of major depressive disorder has no significant effect on response to ECT. This finding is contradictory to the results of several previous studies. A number of factors may account for this contradiction.

Perhaps a possible negative influence of episode duration on response to ECT is nullified in our study, because almost all patients have a relatively long episode duration. 92.9% of our patients has an episode duration of at least 6 months and 67.9% of at least

one year. However, this relatively long episode duration together with the high response rate in our study refutes a strong negative influence of episode duration.

Differences in administration of ECT can also explain for opposite results. Only two previous studies provide clear information about administration of ECT (10, 11). In these studies concomitant medication with anticonvulsant effects (chloral hydrate and lorazepam, respectively) was used during the course of ECT. In our study ECT was administered after one week washout of psychotropic drugs and without concomitant use of benzodiazepines. Moreover, we used a relatively high electrical charge and a flexible number of treatments to aim for a maximal clinical improvement. Kindler et al. (10) describes an adequate stimulus dose (150% of seizure threshold for BL ECT), whereas Prudic et al. (11) describes a stimulus dose of at least 50% above the seizure threshold for both RUL (58 out of 100 patients) and BL ECT. This may have reduced the response to ECT.

Patients in our study had never been treated with ECT before. In Prudics study (11) 46 out of 100 patients had received ECT previously. The inclusion of these patients may result both in a positive (inclusion of patients who are prone to respond to ECT) and in a negative bias (occurrence of ECT resistance) (22)

Perhaps there exists a negative, but small effect of long episode duration on response to ECT that is nullified in our study, because of the use of a highly effective treatment like ECT.

In our study, just like in previous studies, episode duration was established retrospectively. This introduces a certain inaccuracy, but cannot explain opposite results between studies.

Our limited sample size does not seem to have an influence on our results, since no effect at all was found.

In conclusion, the results of our study suggest that ECT is an effective treatment for severely depressed inpatients, independent of episode duration.

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2

Influence of resistance to antidepressant pharmacotherapy on short-term response to electroconvulsive therapy

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A B S T R A C T

Background

Few studies assessing the influence of resistance to antidepressant pharmacotherapy on the response to subsequent electroconvulsive therapy (ECT) are found in the literature. Results are somewhat conflicting and may not be applicable to the population of depressed patients in the Netherlands. The aim of this study is to assess the influence of medication resistance on the short-term response to ECT in a population of severely depressed inpatients in the Netherlands, where ECT is an exceptional treatment, often used as a final treatment option.

Methods

We reviewed the records of 41 consecutive inpatients with major depression according to DSM-III-R criteria and rated each patient's antidepressant pharmacotherapy prior to ECT. We examined the extent to which medication resistance was related to short-term response to ECT.

Results

When a reduction of at least 50% on the Hamilton Rating Scale for Depression (HRSD) post-ECT compared to pre-ECT (partial remission) is used as response criterion, medication resistant patients and patients without established medication resistance were equally likely to respond to subsequent ECT. When a post-ECT HRSD score ≤ 7 (full remission) is used as response criterion, medication resistant patients were less likely to respond to subsequent ECT (8/29=27.6%) than patients who did not receive adequate antidepressant pharmacotherapy prior to ECT (6/12=50.0%), although the difference in response rate was not statistically significant.

Limitations

This study has a retrospective nature and a relatively small sample size.

Conclusion

Antidepressant medication resistance does not seem to have an influence on the short-term response to subsequent ECT. However, when the number of patients achieving full remission is concerned, a substantial percentage of antidepressant medication resistant patients respond to ECT, although their response rate was nearly half compared to that of patients without prior adequate treatment with antidepressants. This difference in

response rate was not statistically significant. ECT seems to be an effective treatment for both patients with and without prior adequate treatment with antidepressants in this Dutch population.

3

INTRODUCTION

Before the introduction of antidepressants, electroconvulsive therapy (ECT) was recognised as the most effective treatment for major depression (1). Widespread use of antidepressant pharmacotherapy has changed the population of patients that currently receive ECT. In the Netherlands, as well as in several other countries, failure to respond to adequate antidepressant pharmacotherapy is the most common indication for ECT. However, only a few studies assessed the influence of resistance to antidepressant pharmacotherapy on the response to subsequent ECT.

Several uncontrolled studies have suggested that failure to respond to antidepressant medication has no or minimal relation to the response to subsequent ECT (2-5). These studies were uncontrolled, meaning that response to ECT was only evaluated in patients considered medication resistant. A comparison patient sample that had not received adequate antidepressant pharmacotherapy prior to ECT was not included. Other methodological flaws included marginal dose and duration of antidepressant treatment, and obscure outcome criteria.

In contrast, one controlled study of the Medical Research Council (MRC) in Great Britain (6) and two controlled studies of Prudic et al. (7, 8) suggested that resistance to antidepressant pharmacotherapy is associated with a reduced rate of response to subsequent ECT. The MRC trial compared the efficacy of four different treatments in depressed patients, namely ECT, imipramine, phenelzine and placebo. Most patients who did not respond to pharmacotherapy, received subsequent ECT. The response rate to ECT was 52% among patients who had not responded to previous antidepressant pharmacotherapy and 71% among patients who received ECT without a prior antidepressant medication trial. Weak criteria for antidepressant medication resistance were used and short-term response to ECT was measured by clinical global impression. Another methodological concern included the continuation of antidepressant pharmacotherapy during the course of ECT in some patients. The two studies of Prudic et al. (7, 8), which were the first prospective ones on the subject, were judged more valuable. The first study examined a sample of 53 depressed patients who were treated with ECT. Patients who failed an adequate antidepressant trial were less likely to respond to subsequent ECT (50%) than those who did not receive adequate antidepressant pharmacotherapy prior to ECT (86%). In the second study, the sample consisted of 100 depressed patients. Of patients with inadequate antidepressant pharmacotherapy prior to ECT, 91% were classified as responder, while 63% of medication resistant patients responded to ECT.

The results of the above studies regarding the influence of resistance to antidepressant pharmacotherapy on the response to subsequent ECT are somewhat conflicting. Some of them found no or minimal influence of medication resistance on the response to subsequent ECT, whereas others conclude that the response to ECT in medication resistant patients is inferior to that of patients without established medication resistance. Moreover, we wondered whether the results may be applicable to the population of depressed patients in the Netherlands. In our country ECT is an exceptional treatment administered almost exclusively to severely depressed inpatients in a limited number of hospitals. With a few exceptions, it is used only for patients not responding to successive adequate trials of antidepressants, i.e., consecutively, selective serotonin re-uptake inhibitor, tricyclic antidepressant, tricyclic antidepressant in combination with lithium and monoamine oxidase inhibitor. Depressed patients in a critical condition, for example mutistic and/or food refusing patients, receive ECT immediately, without prior medication trials.

The present study examines the influence of resistance to antidepressant pharmacotherapy on the short-term response to subsequent ECT in a setting where patients selected for ECT are inpatients exclusively, most of them showing a high degree of medication resistance and many of them suffering from depression with psychotic features.

METHODS

Subjects

We reviewed the records of 59 inpatients who met the DSM-III-R (9) criteria for major depression. Because a part of the patients in our sample was admitted and treated with ECT before the introduction of DSM-IV diagnostic criteria, we had to use DSM-III-R diagnostic criteria for the whole patient sample. Diagnoses were based on clinical observation, without using a structured clinical interview. All patients were successively treated with ECT between December 1993 and October 1998 at the Department of Biological Psychiatry of Parnassia Psychomedical Centre, The Hague, The Netherlands. This department is almost exclusively reserved for patients suffering from severe, medication-resistant and long-lasting depression. We restricted our sample to patients who were free from neurologic or serious medical illness and to patients who had never been treated with ECT previously, to deal with a confounding factor, namely that patients who showed medication resistance and good response to subsequent ECT in previous depressive episodes are particularly likely to receive ECT in their current episode without prior pharmacotherapy. If patients received more than one course of ECT during the study

period, only the first course of ECT was reviewed. The final study sample consisted of 41 inpatients.

Electroconvulsive therapy

Fourteen patients received right unilateral ECT only, 17 patients initially received right unilateral ECT and were crossed over to bilateral ECT, because of an inadequate response after three to 11 treatments, and ten patients received bilateral ECT from the start, because of severity of illness based on clinical observation. ECT was administered with a brief-pulse, constant-current apparatus (Thymatron, Somatics, Inc., 910 Sherwood Drive, Lake Bluff, IL 60044) after premedication with atropine (0.5 mg i.v.) and under sodium thiopental anaesthesia (1.0–2.5 mg/kg) and succinylcholine (1.0 mg/kg) for muscle relaxation at a schedule of two treatments per week with moderate to high stimulus intensity (288–504 millicoulomb), without measuring seizure threshold by empirical stimulus titration. Motor and EEG seizure duration were monitored and conservative criteria for adequacy were used (10). The number of ECT treatments was determined by clinical observation, the maximum being 27 treatments in this sample.

Patients were withdrawn from all psychotropic medication before ECT and were maintained medication free during the course of ECT in all but three cases. Those patients received droperidol 5 mg i.m. prior to ECT to control severe anxiety. One of them also received lorazepam 1 mg and haloperidol 2 mg daily to control severe agitation.

Evaluation of medication resistance

Each patient's strongest antidepressant medication trial prior to ECT was independently evaluated and rated by one psychiatrist (T.K.B.) and one resident (E.M.P.) using the Antidepressant Treatment History Form (ATHF), a 0–5 scale originally developed by Keller et al. (11) and modified by Sackeim et al. (12). When patients did not receive psychotropic medication prior to ECT a score of 0 is given. Any antidepressant trial with a duration of less than 4 weeks or monotherapy with benzodiazepines or antipsychotics scores 1. A score of 2 corresponds to an inadequate dose of antidepressant medication for at least 4 weeks, whereas a score of 3 corresponds to an adequate dose, for example at least 200 mg/day of imipramine, 20 mg/day of fluoxetine and more than 60 mg/day of phenelzine for a minimum of 4 weeks. An antidepressant trial that meets level 3 criteria scores 4 when lithium augmentation is performed. This score is also given when the trial meets more stringent dose criteria, for example at least 300 mg/day of imipramine or 40 mg/day of fluoxetine for a minimum of 4 weeks. When lithium is added to an antidepressant trial that is classified as score 4 the score becomes 5. Patients whose score was 3 or more

were classified as having had adequate antidepressant pharmacotherapy (established medication resistance) prior to ECT, whereas patients with scores less than 3 were classified as having had inadequate antidepressant pharmacotherapy prior to ECT. The scores of both raters were identical in all but one case, which they jointly re-evaluated reaching consensus.

Evaluation of treatment outcome

Scores on the 17-item Hamilton Rating Scale for Depression (HRSD) (13) were routinely recorded within the patients' case notes prior to ECT and following treatment termination. These HRSD scores were used in two different ways for classification of response to ECT. First, patients were classified as responders when their HRSD score shows a reduction of at least 50% post-treatment compared to pre-treatment. The second method requires a post-treatment HRSD score ≤ 7 in patients with full remission.

Statistical analysis

Fisher's exact tests were used to analyse the differences in response rate to ECT between patients who received adequate antidepressant pharmacotherapy prior to ECT (established medication resistance, ATHF score ≥ 3) and patients who received inadequate antidepressant pharmacotherapy prior to ECT (ATHF < 3). Furthermore, a χ^2-analysis was used to test the association between short-term response to ECT and the potency of the strongest medication trial prior to ECT, ranging from 1 (not resistant to medication) to 5 (very resistant to medication) according to the ATHF. Statistical analyses were performed using SPSS-PC (version 7.5).

RESULTS

The patient sample consisted of 41 inpatients, 31 women and ten men with a mean age of 51.5 years. Subclassification reveals that 20 patients suffered from severe depression with psychotic features, among which two had a bipolar depression. Twenty patients suffered from severe depression without psychotic features and one from depression not otherwise specified. Table 1 presents the demographic and clinical characteristics for the total patient sample and as a function of inadequate and adequate treatment (established medication resistance) with antidepressants prior to ECT. Twelve patients received inadequate treatment with antidepressants prior to ECT, whereas 29 patients received adequate treatment and were classified as medication resistant.

A comparison of both groups reveals no significant differences with regard to age, sex and number of previous depressive episodes. Patients who failed to respond to adequate antidepressant medication prior to ECT had a longer duration of their current depressive episode than patients who received inadequate antidepressant medication. This factor may influence the results in disadvantage of the medication resistant group, because in general the response to antidepressant medication and ECT in depressed patients decreases with a longer duration of the depressive episode (14). This cannot be ruled out, although we found no difference in duration of the current depressive episode between ECT responders and nonresponders among medication resistant patients. There was no significant difference in the number of psychotic patients between the patient sample that received adequate treatment prior to ECT and the patient sample that did not. This is an important point, because it is possible that depression with psychotic features has a better rate of response to ECT than depression without psychotic features (15, 16).

TABLE 1. Demographic and clinical characteristics of the patient sample

Variable	Total sample (n=41)	Inadequate treatment prior to ECT (n=12)	Adequate treatment prior to ECT (medication resistance) (n=29)
Age in years, mean (SD)	51.5 (9.5)	49.3 (11.9)	52.4 (8.4)
Female sex, n (%)	31 (75.6)	9 (75.0)	22 (75.9)
Psychotic, n (%)	20 (48.8)	5 (41.7)	15 (51.7)
Bipolar, n (%)	2 (4.9)	1 (8.3)	1 (3.4)
Length of index episode in months, mean (SD)	22.9 (20.4)	13.3 (10.9)	26.8 (22.2)
Number of previous depressive episodes, mean (range)	1.5 (0−6)	1.7 (0−5)	1.5 (0−6)

Abbreviations: ECT, electroconvulsive therapy.

Table 2 presents the HRSD scores prior to ECT and following treatment termination for the total patient sample and as a function of inadequate and adequate treatment (established medication resistance) with antidepressants prior to ECT. It also shows the number of patients responding to ECT, classified in two different ways, namely a 50% reduction on the HRSD score post-treatment compared to pre-treatment and a post-treatment HRSD score ≤ 7.

Both groups showed no significant difference in scores on the HRSD prior to ECT. When a reduction on the HRSD score of at least 50% is used as response criterion, patients who have had adequate antidepressant pharmacotherapy prior to ECT and

patients who have not, were equally likely to be classified as responder to ECT (Fisher's exact test: *p*>0.2). When a HRSD score ≤ 7 is used as response criterion, patients who received adequate antidepressant pharmacotherapy were less likely to be classified as responder to ECT (8/29=27.6%) than patients without established medication resistance (6/12=50.0%), although the difference in response rate was not statistically significant (Fisher's exact test: *p*>0.2). In general, most patients with severe major depression show some response to ECT. Therefore, in classifying response to ECT, a reduction on the HRSD score post-treatment compared to pre-treatment of at least 50% seems easier to achieve and possibly less relevant than a post-treatment HRSD score ≤ 7.

TABLE 2. Pre-ECT and post-ECT scores on HRSD and number of patients responding to ECT

Variable	Total sample (n=41)	Inadequate treatment prior to ECT (n=12)	Adequate treatment prior to ECT (medication resistance) (n=29)
Pre-ECT HRSD score, mean (SD)	26.3 (5.6)	29.3 (5.7)	25.1 (5.2)
Post-ECT HRSD score, mean (SD)	10.5 (5.5)	10.8 (6.4)	10.4 (5.1)
≥ 50% reduction of HRSD score, n (%)	29 (70.7)	8 (66.7)	21 (72.4)
HRSD score ≤ 7 post-ECT, n (%)	14 (34.1)	6 (50.0)	8 (27.6)

Abbreviations: HRSD, Hamilton Rating Scale for Depression; ECT, electroconvulsive therapy.

Tables 3 and 4 present the score for the strongest medication trial prior to ECT as a function of response and nonresponse to ECT. In Table 3, response is classified as a reduction on the HRSD score of at least 50% post-treatment compared to pre-treatment and in Table 4, it is classified as a post-treatment HRSD score ≤ 7. When a HRSD score ≤ 7 is used as response criterion, there is no significant difference between number of responders and nonresponders to ECT within each of five groups of patients having the same score for the strongest medication trial prior to ECT (χ^2=6.17, df=4, *p*=0.187). When a reduction on the HRSD score of at least 50% is used as response criterion, again no significant difference is found between number of responders and nonresponders to ECT within each of five groups of patients having the same score for the strongest medication trial prior to ECT, although patients with a score of 5 on the ATHF seem to be less likely to be classified as responder to ECT than patients with a score of 4 or less (χ^2=8.36, df=4, *p*=0.079). This can be due to the small number of patients within each of five groups.

TABLE 3. Number of patients responding to ECT (HRSD reduction post-treatment compared to pretreatment ≥ 50%) as a function of their score of strongest medication trial prior to ECT

Variable	Score of strongest medication trial prior to ECT[a]					Total
	1	2	3	4	5	
	(n=7)	(n=5)	(n=7)	(n=17)	(n=5)	(n=41)
Response to ECT, n (%)	5 (71.4)	3 (60.0)	6 (85.7)	14 (82.4)	1 (20.0)	29 (70.7)
Non-response to ECT, n (%)	2 (28.6)	2 (40.0)	1 (14.3)	3 (17.6)	4 (80.0)	12 (29.3)

Abbreviations: ECT, electroconvulsive therapy.

[a] *Each patient's score of strongest medication trial prior to ECT was established using the Antidepressant Treatment History Form (10, 11).*

TABLE 4. Number of patients responding to ECT (post-treatment HRSD ≤ 7) as a function of their score of strongest medication trial prior to ECT

Variable	Score of strongest medication trial prior to ECT[a]					Total
	1	2	3	4	5	
	(n=7)	(n=5)	(n=7)	(n=17)	(n=5)	(n=41)
Response to ECT, n (%)	4 (57.1)	2 (40.0)	0 (0)	7 (41.2)	1 (20.0)	14 (34.1)
Non-response to ECT, n (%)	3 (42.9)	3 (60.0)	7 (100)	10 (58.8)	4 (80.0)	27 (65.9)

Abbreviations: ECT, electroconvulsive therapy.

[a] *Each patient's score of strongest medication trial prior to ECT was established using the Antidepressant Treatment History Form (10, 11).*

DISCUSSION

In the Netherlands, as well as in several other countries, resistance to adequate antidepressant pharmacotherapy is the most common indication for ECT. Until recently, it was assumed that resistance to antidepressant pharmacotherapy had no or minimal influence on the response to subsequent ECT. This assumption was based on a few uncontrolled studies (2-5), while the results of three controlled studies (6-8) suggested that resistance to antidepressant pharmacotherapy is associated with a reduced rate of response to subsequent ECT.

In our study, resistance to adequate antidepressant pharmacotherapy either as a dichotomous or as a continuous measure does not seem to have an influence on the response to subsequent ECT, when an at least 50% reduction on the 17-item HRSD score

post-treatment compared to pre-treatment is used as response criterion. As compared to other studies, the response rate to ECT in the medication resistant group was somewhat higher than expected, while it was somewhat lower than expected in the group that received inadequate antidepressant pharmacotherapy prior to ECT. This can be due to a number of factors, besides antidepressant pharmacotherapy, that are likely to have influence on the response to ECT, such as severity of illness, duration of the index depressive episode and the presence of psychotic features (17, 18). Differences in these factors among studies can explain for different results. Thus, some caution is needed in drawing conclusions based on the results of our study, also because of the small number of patients.

In our sample, despite the fact that the mean pre-ECT HRSD score did not show a significant difference between both groups, patients who received inadequate antidepressant pharmacotherapy prior to ECT seemed more severely depressed than patients who received adequate medication. Most of them were mutistic and/or refused food and others had attempted to commit suicide during their stay on the ward. Their condition was critical to such an extent that successive medication trials were judged not feasible. According to Table 1 only 41.7% of these patients suffered from depression with psychotic features, while we expected an overrepresentation of patients with psychotic depression in this group, as in the first study of Prudic et al. (7).

Another possible explanation for our failure to find a significant difference in rate of response to ECT between medication resistant patients and patients without established medication resistance is that most patients with major depression show some response to ECT. Therefore, some patients will fulfill the response criterion of an at least 50% reduction on the HRSD score post-treatment compared to pre-treatment, but will not achieve a full remission (post-treatment HRSD score ≤ 7). Thus, the stricter response criterion of a post-treatment HRSD score ≤ 7 may be more suitable to differentiate ECT responders from nonresponders.

When the number of patients achieving full remission (post-ECT HRSD score ≤ 7) is considered, a substantial percentage of antidepressant medication resistant patients in our sample respond to subsequent ECT, although their response rate was nearly half compared to that of patients without established medication resistance. However, this difference in response rate was not statistically significant, possibly because of the small patient sample. Nevertheless, ECT seems to be an effective treatment for both patients with and without prior adequate treatment with antidepressants in this Dutch population.

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CHAPTER 4

Possible synergy between electroconvulsive therapy and imipramine: a case report

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ABSTRACT

This report describes a 63-year-old woman, who had experienced 3 previous episodes of severe major depressive disorder. The first 2 episodes responded to treatment with antidepressants, whereas the third episode was accompanied by psychotic features and responded well to treatment with electroconvulsive therapy (ECT). After a severe relapse, the patient responded very slowly to a second course of ECT and failed to achieve full remission. Within a few weeks, she had another severe relapse and responded very rapidly to a combination of ECT and imipramine. The possible enhancement of the antidepressant efficacy of ECT by combining it with a tricyclic antidepressant (TCA) has received little study, although the literature provides some evidence for a synergy between ECT and TCAs. Combining ECT with a TCA may be a useful strategy in patients who fail to achieve full remission or who experience a rapid relapse.

INTRODUCTION

Electroconvulsive therapy (ECT) is generally considered the most effective treatment for severe major depressive disorder, with a reported response rate of 60% to 90% (1). Patients who have previously failed to respond to pharmacotherapy have lower remission rates with ECT compared with patients who did not receive adequate treatment with antidepressant medications (2). Furthermore, previous failure to respond to pharmacotherapy may be associated with a greater risk of relapse after ECT (3). The patient described in this case report had experienced 3 previous episodes of severe major depression. The most recent episode was successfully treated with ECT in 2012. However, when she developed a subsequent major depressive episode, the patient responded slowly to a second course of ECT and did not achieve full remission. She then had a severe relapse within a few weeks after completing the ECT course and showed a very rapid response to combination treatment with ECT and imipramine.

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CASE DESCRIPTION

The patient is a 63-year-old woman, who developed her first major depressive episode when she was 56 years old. Both her first and second depressive episodes responded to treatment with clomipramine 200 mg/d. A third episode of major depression with psychotic features developed when the patient was 60 years of age. She was treated with bilateral ECT between December 2011 and January 2012 and, after 8 sessions, she attained full remission. Following this course of ECT, the patient received continuation treatment with imipramine 200 mg/d and lithium 600 mg/d, achieving therapeutic plasma levels of both medications. However, in August 2014, when the patient was 63 years of age, she experienced a depressive recurrence despite the fact that she had continued to take therapeutic doses of imipramine and lithium. She was admitted to the depression unit of the Department of Psychiatry of the Erasmus Medical Center for diagnostic evaluation and treatment. The patient experienced depressive mood, hopelessness, psychomotor retardation, decreased appetite, and nihilistic delusions. Her score on the 17-item Hamilton Rating Scale for Depression (HAM-D) (4) was 24. Given the patient's apparent failure to respond to pharmacotherapy and the severity of her depression, a course of bilateral ECT was started. Treatments were given twice weekly from August 14 to October 20, 2014 with a brief-pulse constant current apparatus (Thymatron System IV, Somatics, IL). Because it is routine practice to discontinue selected psychotropic drugs before the start of ECT,

both imipramine and lithium were stopped. Anesthesia was achieved with intravenous etomidate (0.2 mg/kg), after premedication with 0.2 mg glycopyrrolate. Rocuronium 30 mg (antagonized with 200 mg sugammadex) was used for muscle relaxation, as the patient has pseudocholinesterase deficiency. The stimulus dose-titration method (5) was used to determine the seizure threshold during the first ECT session. The stimulus dosage was set at 50% above the threshold dosage during the second session. Because of the severity of the patient's psychotic depression, 2 mg haloperidol was added after 4 ECT sessions and stopped after 18 sessions. The patient improved very gradually during the ECT course, which was stopped after 22 sessions. At that time she had a score of 8 on the HAM-D. Continuation treatment with imipramine 200 mg/d was prescribed. Despite adequate treatment with imipramine, the patient had a severe relapse 3 weeks after the discontinuation of ECT, with a score of 25 on the HAM-D and a reappearance of her nihilistic delusions. She received a second course of bilateral ECT, again, twice weekly, from November 6 to 20. However, during this course of ECT, treatment with imipramine 200 mg/d (plasma level of imipramine + desmethylimipramine: 268 ng/mL) was continued, although the haloperidol was not restarted. The anesthetic drugs and the dosing strategy were the same as in the previous ECT course. The patient showed a remarkably rapid response to the combination of bilateral ECT and imipramine, achieving full remission (HAM-D score of 3) after 5 ECT sessions. She then received continuation treatment involving a combination of imipramine 200 mg/d and once weekly ECT.

The maintenance ECT was continued once weekly for another 9 months. Two attempts to decrease the frequency to every 2 weeks after 4 and 8 months resulted in a relapse into depression, which remitted again with weekly treatment. After 9 months, we succeeded in decreasing the frequency of ECT to once every 10 days for 1 month and then to every 2 weeks without a reappearance of depressive symptoms. With regard to cognitive side effects, although the patient did not complain about amnesia, when tested she exhibited anterograde amnesia, which improved somewhat when the ECT frequency was decreased from twice to once weekly. She had no disturbances of her long-term memory.

DISCUSSION

This patient had shown a rapid and favorable response to her first course of ECT in 2012. She received a second course of ECT after having a severe recurrence of depression 2½ years later. Although her depression was not actually resistant to this ECT course, the

patient showed a very gradual response and did not attain full remission. Subsequently, after a severe relapse of psychotic depression, she attained full remission very rapidly with a combination of bilateral ECT and imipramine. Was this result purely coincidental, or is there evidence for a synergy between ECT and antidepressants, including tricyclic antidepressants (TCAs)?

In a retrospective study, Nelson and Benjamin (6) found superior antidepressant efficacy with the combination of a TCA and ECT compared with ECT monotherapy. In a second retrospective study, Baghai et al. (7) found a better response when the ECT course was combined with a TCA, a selective serotonin reuptake inhibitor, or mirtazapine compared with ECT monotherapy. In a prospective double-blind study (8), with a rather complicated design involving 2 separate randomization procedures, a combination of imipramine and ECT proved to be more effective than paroxetine plus ECT, which was more effective than ECT monotherapy. In a large, prospective double-blind study, a combination of nortriptyline and ECT was superior to ECT monotherapy, whereas no difference in efficacy was found between ECT plus venlafaxine and ECT monotherapy (9). However, Mayur et al. (10) conducted a rather small prospective naturalistic study, in which half of the patients continued treatment with TCAs during an ECT course, while TCAs were discontinued in the other 50% of patients before the start of ECT, and no difference in efficacy was found between the 2 groups. Most of the studies described here had methodological flaws (e.g., a small sample size, a retrospective design, poorly defined outcome criteria, no determination of TCA plasma levels).

The mechanism underlying an additive effect of TCAs and ECT is unknown. Animal studies revealed a synergistic effect on beta-adrenergic and 5-HT2 receptors. Furthermore, ECT and TCAs appear to have similar effects on GABA-B receptors (6). In summary, although this topic has received very little study, the literature provides some evidence for an actual synergy between ECT and TCAs (and possibly also other antidepressants). The most relevant observation in this report is probably not that the patient attained remission with combination therapy, but the strikingly fast remission that was achieved when ECT was combined with imipramine.

Therefore, psychiatrists may want to consider combining ECT with a TCA in patients with severe major depression, especially in depressed patients who fail to achieve a full remission during a course of ECT. Likewise, in patients who experience a rapid relapse after successful ECT, combining ECT with a TCA may be a useful strategy.

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Influence of an adjuvant antidepressant on the efficacy of electroconvulsive therapy: a systematic review and meta-analysis

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ABSTRACT

Objective

The primary indication for electroconvulsive therapy is medication-resistant major depression. There is some evidence that combining electroconvulsive therapy with an antidepressant, instead of electroconvulsive therapy monotherapy, might improve remission rates. However, data on this topic have not been systematically studied. We undertook a systematic review and meta-analysis to determine the effectiveness of an adjuvant antidepressant during electroconvulsive therapy for major depression.

Methods

Embase, Medline Ovid, Web of Science, Cochrane Central, PsychINFO Ovid and Google Scholar were searched up to January 2019. Randomized controlled trials and cohort studies reporting on the influence of an adjuvant antidepressant on the efficacy of electroconvulsive therapy for major depression were included. Authors independently screened records, extracted data and assessed study quality. We reported this systematic review and meta-analysis following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results

Nine studies were included in the meta-analysis. The meta-analysis revealed a significant advantage of adjuvant antidepressants versus placebo. The overall effect size per category of antidepressant was as follows: tricyclic antidepressants: Hedges' g 0.32 (95% confidence interval: [0.14, 0.51]) (k=6) with low heterogeneity (I^2: 4%, p=0.39); selective serotonin reuptake inhibitors/serotonin noradrenaline reuptake inhibitors: Hedges' g 0.27 (95% confidence interval: [0.03, 0.52]) (k=2) with a lack of heterogeneity (I^2: 0%, p=0.89); and monoamine oxidase inhibitors: Hedges' g 0.35 (95% confidence interval: [−0.07, 0.77]) with moderate heterogeneity (I^2: 43%, p=0.17) (k=3).

Conclusion

An adjuvant antidepressant enhances the efficacy of electroconvulsive therapy for major depression. Tricyclic antidepressants, selective serotonin reuptake inhibitors/serotonin noradrenaline reuptake inhibitors and monoamine oxidase inhibitors showed the same effect size. However, the effect sizes of tricyclic antidepressants and monoamine oxidase inhibitors are most likely underestimated, due to insufficient doses in most of the included studies. We recommend the routine use of an adequately dosed antidepressant during electroconvulsive therapy for major depression.

INTRODUCTION

Electroconvulsive therapy (ECT) is considered the most effective treatment for severe major depression (1). The majority of patients receive ECT because they do not respond to antidepressant medication trials (2), although there is evidence that medication resistance can negatively influence the efficacy of ECT. Recent meta-analyses have found remission rates of 48% and 58% for patients with medication-resistant depression (3, 4). Improving these remission rates would be of great clinical benefit. Moreover, continuing an antidepressant instead of ceasing the drug prior to ECT prevents withdrawal symptoms, saves time and reduces the risk of full relapse.

There is some evidence to suggest a synergy between ECT and antidepressants. A randomized controlled trial (RCT) by Sackeim et al. (5) showed a favourable effect of a combination of ECT and nortriptyline on remission rates. A recent case report described a patient with psychotic depression. She responded very slowly to ECT monotherapy and failed to achieve full remission. After a severe relapse of psychotic depression, she very rapidly attained full remission with a combination of ECT and imipramine (6). Further data on the influence of antidepressant medication on the efficacy of ECT are limited and inconclusive. Even guidelines vary in their recommendations regarding adjuvant antidepressant medication during ECT. Some guidelines recommend considering a combination treatment, particularly among patients with medication-resistant depression (7), whereas other guidelines recommend considering ceasing antidepressant medication prior to ECT (8) or weighing the advantages and disadvantages of combination treatment in each individual patient and thus leaving the decision to the clinician (9). The British guidance on the use of ECT does not give specific recommendations, although it states that the combination of ECT and pharmacotherapy is not superior to ECT alone (10).

To our knowledge, there are no systematic reviews or meta-analyses on the influence of an adjuvant antidepressant on the efficacy of ECT. Thus, neither the routine use of an adjuvant antidepressant during ECT nor the routine discontinuation of the drug prior to ECT is justified by sound scientific data. We addressed the question of whether ECT should be routinely combined with an antidepressant to improve its efficacy. We conducted this systematic review and meta-analysis to provide well-founded recommendations for clinical practice.

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METHODS

This systematic review and meta-analysis was registered in the Research Registry (reviewregistry763) (11) and it adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12).

Search strategy

One author (EP) and an experienced biomedical information specialist searched the electronic databases Embase, Medline Ovid, Web of Science, Cochrane Central, PsychINFO Ovid and Google Scholar for relevant English-language studies up to January 15, 2019. Supplementary Table 1 provides the exact search strategies. The electronic database search was supplemented by a manual review of reference lists from eligible articles.

Inclusion criteria

The inclusion criteria were as follows: (1) an RCT or a prospective/retrospective cohort study; (2) a diagnosis of major depressive disorder; (3) a course of ECT; (4) intervention condition: an adjuvant antidepressant during ECT; and (5) control condition: a placebo or an active placebo during ECT or ECT monotherapy in retrospective cohort studies. Both unipolar and bipolar depression were included. For the diagnosis of depression, the diagnostic criteria according to the International Classification of Diseases, tenth edition (ICD-10) (13), Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) (14), Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (15), Diagnostic and Statistical Manual of Mental Disorders, the text revision of the fourth edition (DSM-IV-TR) (16) and Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM 5) (17) were accepted, as well as diagnoses based on clinical observation. There was no restriction on the type or dose of antidepressant.

Study selection

After removing duplicates, two authors (E.M.P. and W.W.v.d.B.) independently screened all articles on the basis of title and abstract. Articles that were deemed potentially relevant by at least one author were selected. The same authors independently reviewed the full text of the selected articles and assessed their eligibility. We resolved any disagreements by discussion and consensus with a third author (T.K.B.). All eligible articles, both RCTs and cohort studies, were used for qualitative analysis. For quantitative analysis, we only included RCTs.

Data extraction

We used a structured data extraction form to collect the following information from all eligible articles: (1) study characteristics, e.g., study design, study setting, patient population and sample size; (2) ECT method, e.g., electrode placement, waveform, dose strategy, frequency and duration of ECT; (3) details of the intervention condition, e.g., type, dose and monitoring of adjuvant antidepressant; (4) type of control condition, e.g., placebo or type of active placebo or ECT monotherapy; (5) outcome measures and (6) overall results. Additionally, we extracted data on the study quality of the studies included for quantitative analysis (see Methods, section 'Quality assessment').

If studies reported multiple outcome measures, we included the outcome measure that operationalized the clinical psychiatric symptoms the best. We preferred instruments that are validated for the assessment of depressive symptoms, such as the Hamilton Rating Scale for Depression (HRSD)[18] and the Montgomery Asberg Depression Rating Scale (MADRS) [19]. We preferred interviewer-reported questionnaires to self-reported questionnaires. We also accepted outcomes assessed by means of the Clinical Global Impression (CGI) rating scale [20] or clinical observation. If available, we opted for data from an intention-to-treat analysis.

Quality assessment

RCTs. Two authors (E.M.P. and W.W.v.d.B.) independently assessed the risk of bias for each RCT in the quantitative analysis using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (21). We estimated the risk of bias according to the following eight quality criteria: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) use of intention-to-treat analysis and incomplete data; (6) selective reporting; (7) baseline imbalance and (8) other bias, i.e., intervention or treatment fidelity, which is the extent to which the intervention or treatment is delivered as it should be according to current standards. We judged each potential source of bias as high, low or unclear. If a study had a crossover design, we only considered the part before the crossover. For studies that reported on an acute and a continuation phase, we only included the acute phase of ECT. We resolved any disagreements by discussion and consensus with a third author (A.M.K.).

Cohort studies. Two authors (E.M.P. and A.M.K.) independently rated the strength of each cohort study using the checklist outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (22). We resolved any disagreements by discussion and consensus with a third author (T.K.B.).

Statistical analysis

Per category of adjuvant antidepressant, we calculated pooled effect size estimates between the intervention group and the control group over a minimum of two trials. We distinguished three categories of adjuvant antidepressants, i.e., tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors/serotonin noradrenaline reuptake inhibitors (SSRIs/SNRIs) and monoamine oxidase inhibitors (MAOIs). SSRIs and SNRIs were pooled, because the mean dose of venlafaxine used in the study by Sackeim et al. (2009) was 187 mg/day. At doses below 225 mg/day, venlafaxine acts as an SSRI (23). Effect sizes were reported using Hedges' *g* and corresponding 95% confidence intervals (24). The results for each category of adjuvant antidepressant were plotted in a forest plot. In cases of substantial heterogeneity, random-effects analyses were used to estimate an overall treatment effect. Cochran's *Q*-test and the I^2 and T^2 statistics were used to quantify heterogeneity across trials. Heterogeneity was further explored by conducting sensitivity analyses. Specifically, we calculated the overall treatment effect using both fixed- and random-effects modelling and evaluated the impact of the modelling procedure on the overall treatment effect. Additionally, we created subgroups of trials based on type of electrode placement, outcome measures (standardized questionnaires versus other types of rating scales versus clinical observations), and the criteria included in the risk of bias evaluation. We assessed the impact of these moderator variables on the overall effect of adjuvant medication. The effect of the year of publication on the overall treatment effect was assessed using meta-regression analysis. Standardized effect sizes were calculated using comprehensive meta-analysis (CMA). Statistical analyses were performed using the 'metan' package in Stata 15 (25). Differences in the mean treatment effect between subgroups were estimated using the 'metaf' macro (26).

Publication bias was assessed visually with a funnel plot. Additionally, we formally assessed whether the effect size decreased in proportion to increasing sample size using Egger's test (27). In case of an asymmetrical funnel plot, missing data were imputed using the trim-and-fill method (28).

R E S U L T S

Study selection

After removing duplicates, the database search identified 3026 abstracts. Further results of the study selection are shown in the PRISMA flow diagram (Figure 1). We excluded 22 out of 30 eligible articles for the reasons as outlined in Figure 1. Eight articles met our

inclusion criteria. We identified four additional articles via a cross-reference check. Thus, 12 studies were included in our systematic review for qualitative analysis. Since we only included RCTs in our meta-analysis, the quantitative analysis was based on nine studies. The raw interrater agreement suggested substantial interrater reliability (kappa=0.78; 95% CI: [0.63, 0.93]).

FIGURE 1. Flow diagram of the study selection
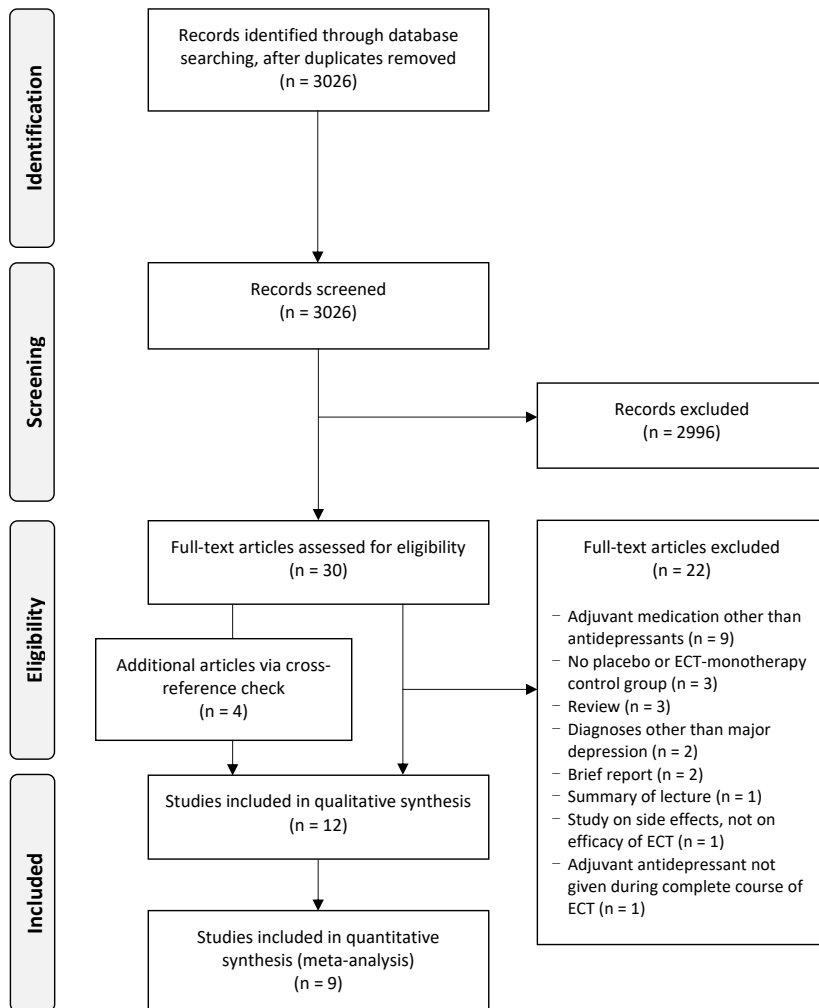
Abbreviations: ECT, electroconvulsive therapy.

Characteristics of included studies

Twelve studies met our inclusion criteria: nine RCTs (5, 29-36) and three retrospective cohort studies (37-39). We found no prospective cohort studies. Table 1 shows detailed information about the study characteristics. There is a remarkably lack of data from the last decade.

RCTs. Most studies reported on one category of antidepressant. Only two studies reported on two different categories of antidepressants (5, 29). One study specified the type of depression, including both unipolar and bipolar depression (5). Three studies provided data on electrode placement: in one study, all patients received unilateral ECT (31); in the second study, patients received either unilateral or bilateral ECT (5); and in the third study, an atypical ECT protocol was used, i.e., all patients were switched from bilateral to unilateral ECT after three sessions (34). ECT dose strategies were described in two studies (5, 31). Only one of these studies described an adequate dose strategy of 1.5 times the seizure threshold in bilateral ECT and 6 times the seizure threshold in unilateral ECT (5). In eight studies, patients were randomized into groups that either received an adjuvant antidepressant or received an adjuvant placebo or active placebo during ECT. In these studies, ECT and the antidepressant or placebo were started simultaneously. One RCT used a different design; patients were randomized into groups that either continued an ongoing treatment with antidepressant medication or withdrew from antidepressant medication with placebo substitution at the start of ECT (31).

Retrospective cohort studies. The studies included unipolar depressed patients (39) or both unipolar and bipolar depressed patients (37, 38). All studies provided information on electrode placement and their ECT dose strategy. None of the studies used an adequate dose strategy, according to current standards. None of the studies provided information on the way antidepressants were combined with ECT. It is unclear if ECT was added to an ongoing treatment with an antidepressant or if antidepressants and ECT were started simultaneously.

Outcomes of included studies

Table 1 shows detailed information about the study outcomes.

RCTs. Sackeim et al. (2009) found a trend in remission rate in favour of nortriptyline relative to placebo. Muller (1961) showed a significant difference in decrease in symptoms on a '25 point scale' in favour of phenelzine relative to placebo. Six studies failed to demonstrate a

significant advantage of an adjuvant TCA (29-32), SSRI (34), SNRI (5) or MAOI (29) during ECT. Two studies did not perform a statistical analysis (33, 35).

Retrospective cohort studies. The studies by Nelson and Benjamin (1989) and Baghai et al. (2006) showed an advantage of an adjuvant antidepressant during ECT. Nelson and Benjamin reported a significant difference in improvement on a clinical observation scale in favour of ECT + TCA relative to ECT monotherapy. Baghai et al. found a higher efficacy of ECT + TCA, SSRI or mirtazapine relative to ECT monotherapy. Kho et al. (2005) failed to demonstrate a significant difference in remission rate between patients using TCA or not during ECT.

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TABLE 1. Characteristics of the included studies

Study	Design, setting and country	Patients and sample size	ECT method	Intervention	Control condition	Outcome measures of interest	Results
Randomized controlled trials on adjuvant TCA							
Imlah et al., 1965[a]	RCT, inpatient clinic, UK	Depressive disorder (clinical observation) Total sample n=150 ECT + placebo n=50 ECT + IMI n=50 ECT + PHE n=50	No information available on electrode placement, waveform and dose strategy; 2 ECT sessions/week until favourable clinical response, maximum of 12 treatments.	ECT + IMI 75 mg	ECT + placebo	Number of ECT sessions until response, based on '5-point scale'	Mean Number of ECT sessions until response: ECT + placebo 7.93 ECT + IMI 7.15 ECT + PHE 6.90 No significant difference between intervention and control group.
Kay et al., 1970	RCT, inpatient clinic, UK	Depressive disorder (clinical observation) Total sample n=132 ECT + diazepam n=73 ECT + AMI n=59	No information available on ECT method.	ECT + AMI 50-150 mg	ECT + diazepam 4-12mg	HRSD	Mean decrease in HRSD score at 1 month: ECT + diazepam 24.4 ECT + AMI 28.7 No significant difference between intervention and control group.
Mayur et al., 2000[a]	RCT (discontinuation study), inpatient clinic, India	Major depressive disorder (DSM-IV) Total sample n=30 ECT + placebo n=15 ECT + TCA n=15	UL; pulse, square wave; dose titration (stimulus: 2.5x ST); 3 ECT sessions/week for 4 weeks or until remission, whichever was earlier.	ECT + TCA	ECT + placebo	17-item HRSD, MADRS	Mean HRSD score and mean MADRS score at week 4 not reported. No significant differences between intervention and control group.
Sackeim et al., 2009[b]	RCT, inpatient clinic, USA	Major depressive disorder (DSM-IV) Total sample n=319 ECT + placebo n=135 ECT + NOR n=93 ECT + VEN n=91	RUL or BL; pulse, square wave; dose titration (stimulus RUL 6x ST, BL 1.5x ST); 3 ECT sessions/week until remission.	ECT + NOR (mean blood level 82.1 ± 52.2 ng/ml)	ECT + placebo	24-item HRSD Remission: reduction HRSD score ≥ 60% and post-ECT HRSD ≤ 10	Remission rate: ECT + placebo 41.4% ECT + NOR 54.8% ECT + VEN 52.8% Difference between intervention and control group shows trend in favour of NOR. Mean post-ECT HRSD score: ECT + placebo 15.9 ± 10.7 ECT + NOR 12.6 ± 9.8 ECT + VEN 13.0 ± 9.7 Significant difference between ECT + NOR and ECT + placebo in favour of NOR; ECT + VEN did not differ from the other conditions.
Seager et al., 1962[a]	RCT, inpatient clinic, UK	Depressive disorder (clinical observation) Total sample n=43, analysed sample n=40 (drop-outs excluded for analysis) ECT + placebo n=21 ECT + IMI n=19	No information available on electrode placement and dose strategy; sine wave; 2 ECT sessions/week until favourable clinical response.	ECT + IMI 150 mg	ECT + placebo	Number of ECT sessions until response, based on clinical observation	Mean number of ECT sessions until response: ECT + placebo 7.0 ECT + IMI 6.3 No significant difference between intervention and control group.

Study	Design, setting and country	Patients and sample size	ECT method	Intervention	Control condition	Outcome measures of interest	Results
Wilson et al., 1963[c]	RCT, inpatient clinic, USA	Depressive disorder (clinical observation) Total sample n=10 ECT + atropine n=6 ECT + IMI n=4	No information available on electrode placement, waveform and dose strategy; 2 ECT sessions/week for 6 treatments.	ECT + IMI 150 mg	ECT + atropine 0.1 mg	HRSD	Mean decrease in HRSD score at week 5: ECT + atropine 22.3 ± 1.6 ECT + IMI 20.7 ± 1.9 Difference between intervention and control group not statistically analysed.
Randomized controlled trials on adjuvant SSRI/SNRI							
Lauritzen et al., 1996[a,d]	RCT, inpatient clinic, Denmark	Major depressive disorder (DSM-III-R) Total sample n=87, of which n=35 in this study arm ECT + placebo n=17 ECT + PAR n=18	First 3 ECT sessions BL, thereafter UL; pulse, square wave; no information available on dose strategy; 3 ECT sessions/week until remission.	ECT + PAR 30 mg	ECT + placebo	HRSD, number of ECT sessions	Mean post-ECT HRSD score: ECT + placebo 9.2 ± 3.4 ECT + PAR 8.9 ± 4.7 Mean number of ECT sessions until response: ECT + placebo 11.1 ± 3.8 ECT + PAR 12.1 ± 6.3 No significant difference between intervention and control group in mean post-ECT HRSD score and number of ECT sessions until response.
Sackeim et al., 2009[b]	RCT, inpatient clinic, USA	Major depressive disorder (DSM-IV) Total sample n=319 ECT + placebo n=135 ECT + NOR n=93 ECT + VEN n=91	RUL or BL; pulse, square wave; dose titration (stimulus RUL 6x ST, BL 1.5x ST); 3 ECT sessions/week until remission.	ECT + VEN (mean dose 187 mg/day)	ECT + placebo	24-item HRSD Remission: reduction HRSD score ≥ 60% and post-ECT HRSD ≤ 10	Remission rate: ECT + placebo 41.4% ECT + NOR 54.8% ECT + VEN 52.8% Difference between intervention and control group shows trend in favour of NOR. Mean post-ECT HRSD score: ECT + placebo 15.9 ± 10.7 ECT + NOR 12.6 ± 9.8 ECT + VEN 13.0 ± 9.7 Significant difference between ECT + NOR and ECT + placebo in favour of NOR; ECT + VEN did not differ from the other conditions.
Randomized controlled trials on adjuvant MAOI							
Imlah et al., 1965[a]	RCT, inpatient clinic, UK	Depressive disorder (clinical observation) Total sample n=150 ECT + placebo n=50 ECT + IMI n=50 ECT + PHE n=50	No information available on electrode placement, waveform and dose strategy; 2 ECT sessions/week until favourable clinical response, maximum of 12 treatments.	ECT + PHE 45 mg	ECT + placebo	Number of ECT sessions until response, based on '5-point scale'	Mean Number of ECT sessions until response: ECT + placebo 7.93 ECT + IMI 7.15 ECT + PHE 6.90 No significant difference between intervention and control group.

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Study	Design, setting and country	Patients and sample size	ECT method	Intervention	Control condition	Outcome measures of interest	Results
Monaco et al., 1964[b]	RCT, inpatient clinic, USA	Depressive disorder (clinical observation) Total sample n=26 ECT + placebo n=12 ECT + TRA n=14	No information available on ECT method.	ECT + TRA 20 mg	ECT + placebo	Clinical observation	Improvement rate at week 4: ECT + placebo 91.7% ECT + TRA 78.6% Difference between intervention and control group not statistically analysed.
Muller et al., 1961	RCT, outpatient clinic, UK	Depressive disorder (clinical observation) Total sample n=100 ECT + placebo n=45 ECT + PHE n=55	No information available on electrode placement, waveform and dose strategy; 2 ECT sessions/week until clinical response.	ECT + PHE 45 mg	ECT + placebo	'25-point scale'	Mean post-ECT score on '25-point scale': ECT + placebo 6.62 ± 4.04 ECT + PHE 4.82 ± 2.75 Mean decrease on '25 point scale' at end of ECT: ECT + placebo 4.31 ± 5.28 ECT + PHE 7.24 ± 4.37 Significant differences between intervention and control group in mean post-ECT score and mean decrease on '25-point scale'.
Retrospective cohort studies							
Baghai et al., 2006	Cohort study, inpatient clinic, Germany	Major depression (ICD-10) Total sample n=358 ECT alone n=170 ECT + TCA n=78 ECT + TTCA n=40 ECT + SSRI n=30 ECT + other AD n=40	UL or BL; pulse, square wave; dose titration in <5% of patients; dose strategy in remaining patients: based on age in UL, based on half-age in BL; 2.8 ECT sessions/week (mean).	ECT + AD	ECT alone	CGI	Scores on CGI not reported. Significantly higher severity of illness and less improvement in control group and ECT + SNRI group compared to ECT + TCA, ECT + TTCA and ECT + SSRI groups.
Kho et al., 2005	Cohort study, setting unclear, The Netherlands	Major depressive disorder (DSM-IV) Total sample n=73 ECT alone n=26 ECT + TCA n=19 ECT + SSRI n=12 ECT + combination treatment and or lithium and or antipsychotic medication n=49	UL, UL>BL, or BL; pulse, square wave; dose strategy based on age, adjusted upwards if patients used benzodiazepines and or anticonvulsants; 2 ECT sessions/week until remission.	ECT + psychotropic medication (among which AD)	ECT alone	17-item HRSD Remission: reduction HRSD score ≥ 60% and post-ECT HRSD < 8	Remission rate: ECT alone 61.5% ECT + psychotropic 68.1% No significant difference between intervention and control group.

Study	Design, setting and country	Patients and sample size	ECT method	Intervention	Control condition	Outcome measures of interest	Results
Nelson et al., 1989	Cohort study, inpatient clinic, USA	Depressive disorder (clinical observation) Total sample n=84 ECT alone n=44 ECT + partial TCA n=23 ECT + full TCA n=17	UL; pulse, square wave; dose strategy: "initial middle setting" so that seizures of > 30s were obtained; no information available on frequency of ECT; ECT sessions administered until favourable clinical response.	ECT + partial TCA (IMI blood level 75-149 ng/ml or daily dose 50-99 mg) ECT + full TCA (IMI blood level 150-300 ng/ ml or daily dose >100 mg)	ECT alone	Number of ECT sessions, 'clinical observation scale' (no (0), slight (1), moderate (2) and marked (3) improvement)	Mean post-ECT score on "clinical observation scale" ECT alone 2.0 ECT + partial TCA 2.4 ECT + full TCA 2.6 Significant difference between ECT + full TCA and ECT alone; no significant difference between ECT + partial TCA and ECT alone. Mean number of ECT sessions until response: ECT alone 9.8 ECT + partial TCA 8.0 ECT + full TCA 8.2 Significant difference between control group and both intervention groups; no significant difference between ECT + partial TCA and ECT + full ECT.

Abbreviations: RCT, randomized controlled trial; UK, United Kingdom; USA, United States of America; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor; MAOI, monoamine oxidase inhibitor; TTCA, tetracyclic antidepressant; AD, antidepressant; IMI, imipramine; AMI, amitriptyline; NOR, nortriptyline; PAR, paroxetine; VEN, venlafaxine; PHE, phenelzine; TRA, tranylcypromine; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; UL, unilateral ECT; BL, bilateral ECT; ST, seizure threshold; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery Asberg Depression Rating Scale; CGI, Clinical Global Impression.

[a] These studies consisted of two phases: (1) acute treatment and (2) follow-up. We only included the first phase in our systematic review and meta-analysis.

[b] These studies had a crossover design. We only included the part prior to crossover in our systematic review and meta-analysis.

[c] This study consisted of two phases: (1) ECT + IMI versus ECT + IMI versus ECT + atropine and sham ECT + IMI versus sham ECT + atropine and (2) ECT + atropine versus IMI alone. We only included the ECT + IMI versus ECT + atropine arm of the first phase in our systematic review and meta-analysis.

[d] This study consisted of two study arms: (1) ECT + PAR versus ECT + placebo and (2) ECT + IMI versus ECT + PAR. We only included the first study arm in our systematic review and meta-analysis.

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Quality assessment

RCTs. Figure 2 shows the results of the assessment of the risk of bias for each RCT included in this systematic review.

Regarding the individual RCTs, the study by Sackeim et al. (2009) is the only study that showed a low risk of bias in the majority of quality criteria. In this study, only intervention or treatment fidelity showed bias, since almost 90% of the patients randomized to the unilateral ECT group received a suboptimal stimulus dose due to the maximum settings on the device. The other eight RCTs showed an unclear or a high risk of bias in the majority of quality criteria, since most of these studies did not report on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, use of intention-to-treat analysis and incomplete data, and baseline imbalance. Moreover, study protocols were frequently lacking, outcome measures were not always prespecified, statistical analyses were not always described, and low doses of TCAs and MAOIs were used.

Regarding the individual quality criteria, the most prevalent risk of bias was found for selective reporting and intervention or treatment fidelity. Selective reporting showed bias in seven out of nine studies (29-33, 35, 36). These studies did not describe a study protocol. In all studies, except for the study by Lauritzen et al. (1996), intervention or treatment fidelity showed bias. In these studies, according to current standards, inadequate doses of antidepressants or ECT were used.

Retrospective cohort studies. The strength of the study by Nelson and Benjamin (1989) was rated as moderate. In this study, the dose of TCA was based on plasma levels in an unspecified number of patients. In the remaining patients, doses of imipramine > 100 mg/ day were classified as 'full TCA'. These doses might have been insufficient (40). Moreover, this study relied on the number of ECT sessions and an invalidated clinical outcome scale as outcome measures. The strengths of the studies by Kho et al. (2005) and Baghai et al. (2006) were rated as poor. Kho et al. focused on predictors for the efficacy of ECT. The efficacy of an adjuvant antidepressant was just a small part of this study. The type, dose and plasma levels of TCAs were not reported. An unspecified number of patients received a variety of psychotropic drugs in addition to antidepressants, including benzodiazepines and anticonvulsants. These drugs may interfere with the efficacy of ECT (41-43). Baghai et al. used different types of antidepressants. Doses or plasma levels of TCAs were not reported. More than half of the patients received other psychotropic drugs in addition to antidepressants. Almost 30% of the patients received two to six other psychotropic drugs.
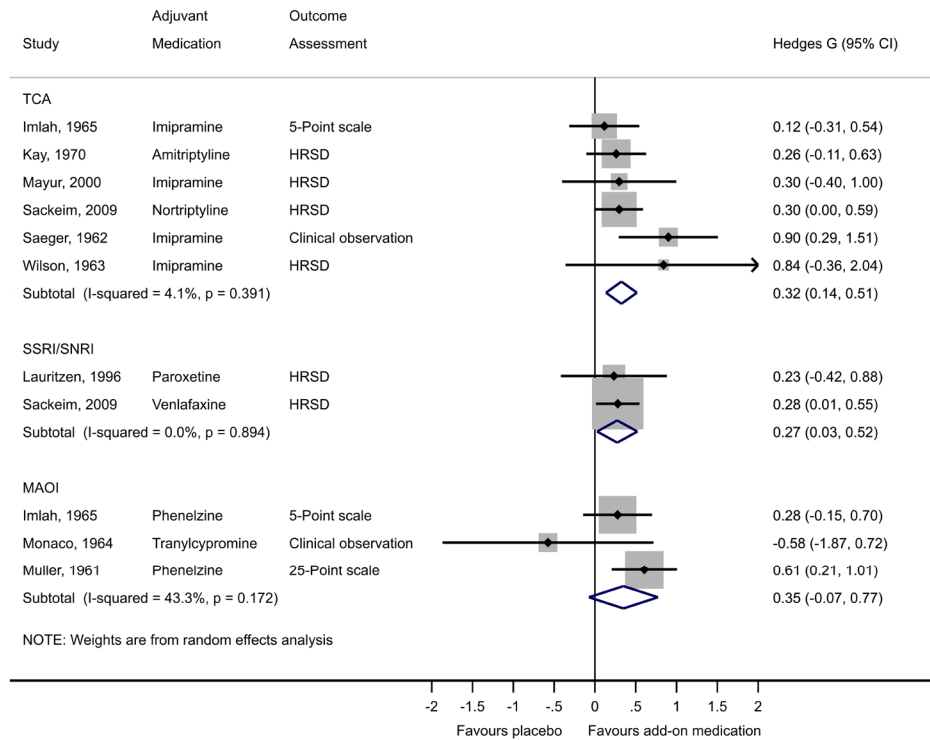
FIGURE 2. Risks of bias of studies included in the quantitative analysis
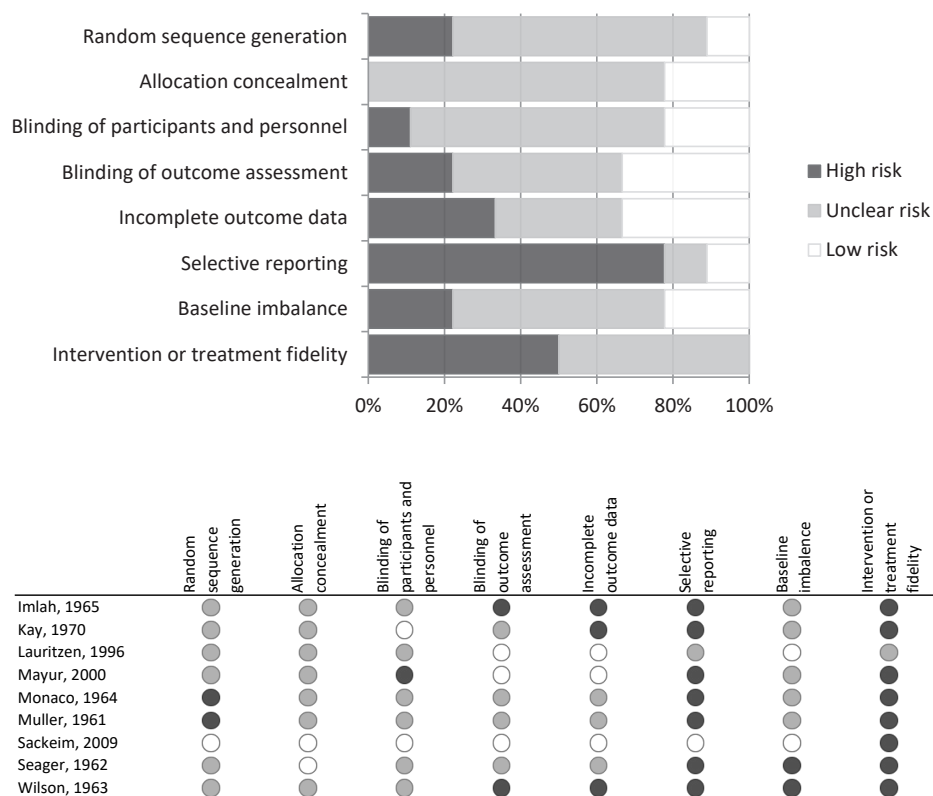
Meta-analysis

A total of 9 RCTs, estimating 11 effect sizes, were included in the meta-analysis. Figure 3 shows the effect of an adjuvant TCA, SSRI/SNRI and MAOI. The overall effect size of TCAs was Hedges' g 0.32 (95% CI: [0.14, 0.51]) (k=6) using random-effects estimation. Heterogeneity was low (I^2: 4%, p=0.39). Fixed- and random-effects estimations resulted in identical effect size estimates. The overall effect size of SSRI/SNRI was Hedges' g 0.27 (95% CI: [0.03, 0.52]) with a lack of heterogeneity (I^2: 0%, p=0.89) (k=2). Fixed- and random-effects estimations resulted in identical effect size estimates. Finally, MAOI showed an overall effect size of Hedges' g 0.35 (95% CI: [-0.07, 0.77]) using random-effects estimation (k=3). Heterogeneity was moderate (I^2: 43%, p=0.17). Fixed-effects estimation resulted in a higher effect size with a smaller confidence interval (Hedges' g: 0.40; 95% CI: [0.12, 0.69]).

FIGURE 3. Forest plot showing meta-analytic results of efficacy of an adjuvant TCA, SSRI/SNRI and MAOI versus placebo or active placebo on ECT

Study	Adjuvant Medication	Outcome Assessment	Hedges G (95% CI)
TCA			
Imlah, 1965	Imipramine	5-Point scale	0.12 (-0.31, 0.54)
Kay, 1970	Amitriptyline	HRSD	0.26 (-0.11, 0.63)
Mayur, 2000	Imipramine	HRSD	0.30 (-0.40, 1.00)
Sackeim, 2009	Nortriptyline	HRSD	0.30 (0.00, 0.59)
Saeger, 1962	Imipramine	Clinical observation	0.90 (0.29, 1.51)
Wilson, 1963	Imipramine	HRSD	0.84 (-0.36, 2.04)
Subtotal (I-squared = 4.1%, p = 0.391)			0.32 (0.14, 0.51)
SSRI/SNRI			
Lauritzen, 1996	Paroxetine	HRSD	0.23 (-0.42, 0.88)
Sackeim, 2009	Venlafaxine	HRSD	0.28 (0.01, 0.55)
Subtotal (I-squared = 0.0%, p = 0.894)			0.27 (0.03, 0.52)
MAOI			
Imlah, 1965	Phenelzine	5-Point scale	0.28 (-0.15, 0.70)
Monaco, 1964	Tranylcypromine	Clinical observation	-0.58 (-1.87, 0.72)
Muller, 1961	Phenelzine	25-Point scale	0.61 (0.21, 1.01)
Subtotal (I-squared = 43.3%, p = 0.172)			0.35 (-0.07, 0.77)

NOTE: Weights are from random effects analysis

-2 -1.5 -1 -.5 0 .5 1 1.5 2

Favours placebo   Favours add-on medication

Abbreviations: TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor; MAOI, monoamine oxidase inhibitor; HRSD, Hamilton Rating Scale for Depression.

The funnel plot including the effect sizes extracted from the RCTs was symmetrically shaped (Figure 4), suggesting no indication of publication bias. The Egger's test supported this finding (β=0.15; 95% CI: [-1.69, 1.99]; *p*=0.85). Results remained unchanged using the trim-and-fill method.

FIGURE 4. Funnel plot of included studies
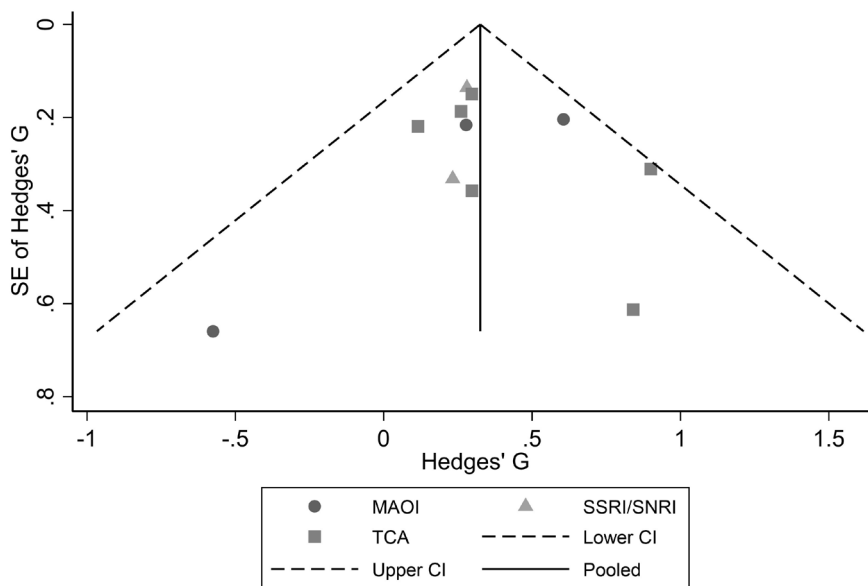
Abbreviations: MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor.

A sensitivity analysis was performed regarding design characteristics, study quality, and year of publication. We were not able to estimate the impact of the type of electrode placement, due to insufficient data. More recent studies showed more homogeneity compared to early studies. However, we found no indication of a linear association between year of publication and reported add-on medication effect (β=-0.002; 95% CI: [-0.009, 0.005]; p=0.498). We found no indication of an impact of the instrument used for outcome assessment on the overall effect (Q=0.89, df=9, p=0.99). The randomization procedure did not significantly impact the overall effect (Q=0.99, df=8, p=0.99), nor did the allocation procedure (Q=0.80, df=10, p=0.99), blinding of personnel (Q=0.73, df=9, p=0.99), blinding of the assessor (Q=0.80, df=10, p=0.99), incomplete data (Q=0.80, df=10, p=0.99), or baseline imbalance (Q=0.89, df=9, p=0.99). We were not able to estimate the impact of intervention or treatment fidelity due to insufficient variation between studies.

DISCUSSION

Main findings

The results of our meta-analysis indicate that an adjuvant antidepressant, compared to placebo or active placebo, enhances the efficacy of ECT in patients with major depression. Although effect sizes were small to moderate, they are clinically relevant, since they reflect an add-on effect to ECT, which is considered the most effective treatment for major depression (1).

Different categories of antidepressants, i.e., TCAs, SSRIs/SNRIs, and MAOIs, showed approximately the same effect size. Given the previously established evidence of the superior efficacy of TCAs compared to SSRIs in severely depressed inpatients (44), we expected to find TCAs to be more effective than SSRIs and venlafaxine at doses below 225 mg/day. Insufficient doses of TCAs and MAOIs in most of the included studies versus adequate doses of SSRIs and SNRI most likely resulted in underestimated effect sizes for adjuvant treatment with TCAs and MAOIs. This is supported by the study by Sackeim et al. (2009), the only study in our meta-analysis in which a TCA was given at doses that were aimed to achieve therapeutic plasma levels. This study showed a positive effect of adding nortriptyline to unilateral or bilateral ECT.

Limitations

The prime limitation of our meta-analysis is that most included studies are relatively old. Five out of nine studies were conducted in the sixties before the introduction of modern techniques for administering ECT (29, 32, 33, 35, 36). ECT dosage and waveform have changed over the last decades, and anaesthetics have been introduced. In early studies, the administration of ECT might have been suboptimal, at least in unilateral ECT. Additionally, the patient population receiving ECT has changed a great deal. ECT used to be a first-line antidepressant treatment, but medication resistance is currently an important indication for its inclusion. This may have resulted in an overestimation of the effect of an adjuvant antidepressant during ECT. On the other hand, in early studies, the doses of antidepressants were often subtherapeutic. The inclusion of patients with bipolar depression in at least one large study (5), may have decreased the efficacy of the adjuvant antidepressants. Six studies investigated adjuvant treatment with a TCA (5, 29-33). Of those, five did not use plasma-level targeted dosing (29-33). In three studies, imipramine was given at a dose of 75-150 mg/day (29, 32, 33), which is insufficient for the large majority of patients (40). Three studies investigated adjuvant treatment with a MAOI (29, 35, 36). These studies used low doses of phenelzine (45 mg/day) or a very low dose

of tranylcypromine (20 mg/day). These subtherapeutic antidepressant doses may have resulted in an underestimation of the effect of an adjuvant antidepressant during ECT. In eight out of nine RCTs, antidepressants and ECT were started simultaneously. In one study, ECT was added to an ongoing treatment with an antidepressant (31). Since there is hardly any variation regarding this methodological aspect, it probably has a negligible influence on the result.

All studies, except for the study by Sackeim et al. (2009), were deemed to be of poor to moderate quality. Six out of nine RCTs were conducted in the sixties and seventies (29, 30, 32, 33, 35, 36). At that time, reports on studies were less transparent. Among other things, these studies lack information on their study protocol, randomization procedure and allocation concealment. This makes it difficult to appraise the quality of these studies and their subsequent results. Despite these flaws, we found no statistical association between year of publication and reported add-on effect. Moreover, the same six RCTs did not report on electrode placement. Due to insufficient data, it is impossible to make a statement on the impact of the type of electrode placement on the results.

Another limitation of our meta-analysis is the small number of included studies and the fact that two of studies (5, 29) reported on two categories of adjuvant antidepressants. A larger number of studies might have provided better evidence. Despite a lack of significance in almost all individual studies, our meta-analysis shows a homogeneous and positive effect in favour of an adjuvant antidepressant in all but one study. This indicates an underlying effect of an adjuvant antidepressant on the efficacy of ECT. Additionally, we found no indication of publication bias. For future research, a comparison trial of different types of adjuvant antidepressants during ECT would be very relevant.

Conclusion

Our results suggest that an adjuvant antidepressant enhances the efficacy of ECT in patients with major depression. Although the included studies had some methodological limitations, effect sizes were consistently small to moderate. We speculate that modern day-controlled trials using adequately dosed TCAs and MAOIs will most likely result in larger effect sizes. From a clinical point of view, we prefer an adjuvant TCA to an adjuvant MAOI, since TCAs are generally safe to use with ECT (2, 5, 37, 45), whereas MAOIs warrant precautions during anaesthesia for ECT (45, 46). Moreover, MAOIs are prescribed far less commonly than TCAs and the use of a MAOI requires dietary restrictions.

Thus, if ECT is indicated for a patient with major depression, we recommend the routine use of an adequately dosed adjuvant antidepressant to improve the efficacy of ECT. We leave the choice between a TCA, an SSRI/SNRI and a MAOI up to the clinician.

Our findings warrant renewed interest in adjuvant pharmacotherapy during ECT for major depression.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Search strategy per database

Embase

('electroconvulsive therapy'/exp OR 'electroconvulsive therapy unit'/de OR 'electric shock'/de OR (electroconvulsi* OR electr*-convulsi* OR electroshock OR (electr* NEAR/3 shock) OR ect OR spECTrum-5000Q OR Thymatron):ab,ti) AND ('depression'/exp OR 'antidepressant agent'/exp OR (depress* OR antidepress*):ab,ti) AND ('drug therapy'/ de OR 'drug therapy':lnk OR 'antidepressant agent'/exp OR 'serotonin uptake inhibitor'/ exp OR 'serotonin noradrenalin reuptake inhibitor'/exp OR 'lithium'/de OR 'psychotropic agent'/de OR (drug OR antidepress* OR anti-depress* OR (pharmaco* NEAR/3 (therap* OR treat)) OR pharmaco* OR Psychopharmaco* OR (serotonin NEAR/3 (uptake OR reuptake) NEAR/3 inhibitor*) OR ssri OR ssri OR venlafaxine OR lithium OR psychotropic*):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/ de OR 'Single-blind procedure'/de OR 'cohort analysis'/de OR 'longitudinal study'/de OR 'prospective study'/de OR 'retrospective study'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups OR cohort OR longitudinal* OR prospectiv* OR retrospectiv*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ('case report'/de OR 'case report':ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/ lim OR [Editorial]/lim) AND [english]/lim

MEDLINE Ovid

(Electroconvulsive Therapy/ OR (electroconvulsi* OR electr*-convulsi* OR electroshock OR (electr* ADJ3 shock) OR ect OR spECTrum-5000Q OR Thymatron).ab,ti.) AND (depression/ OR exp Depressive Disorder/ OR exp Antidepressive Agents/ OR (depress* OR antidepress*).ab,ti.) AND (drug therapy/ OR drug therapy.xs. OR exp Antidepressive Agents/ OR exp Serotonin Uptake Inhibitors/ OR lithium/ OR exp Psychotropic Drugs/ OR (drug OR antidepress* OR anti-depress* OR (pharmaco* ADJ3 (therap* OR treat)) OR pharmaco* OR Psychopharmaco* OR (serotonin ADJ3 (uptake OR reuptake) ADJ3 inhibitor*) OR ssri OR ssri OR venlafaxine OR lithium OR psychotropic*).ab,ti.) AND (Exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR exp Cohort Studies/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups OR cohort OR longitudinal* OR prospectiv* OR retrospectiv*).ab,ti.) NOT

(exp animals/ NOT humans/) NOT (case report/ OR case report.ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

PsycINFO Ovid

(Electroconvulsive Shock Therapy/ OR (electroconvulsi* OR electr*-convulsi* OR electroshock OR (electr* ADJ3 shock) OR ect OR spECTrum-5000Q OR Thymatron).ab,ti.) AND ("depression (emotion)"/ OR exp Major Depression/ OR exp Antidepressant Drugs/ OR (depress* OR antidepress*).ab,ti.) AND (drug therapy/ OR exp Antidepressant Drugs/ OR exp Serotonin Reuptake Inhibitors/ OR lithium/ OR (drug OR antidepress* OR anti-depress* OR (pharmaco* ADJ3 (therap* OR treat)) OR pharmaco* OR Psychopharmaco* OR (serotonin ADJ3 (uptake OR reuptake) ADJ3 inhibitor*) OR ssri OR ssri OR venlafaxine OR lithium OR psychotropic*).ab,ti.) AND ((random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups OR cohort OR longitudinal* OR prospectiv* OR retrospectiv*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (case report.ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts OR books).pt. AND english.la.

Cochrane Central

((electroconvulsi* OR (electr* NEXT/1 convulsi*) OR electroshock OR (electr* NEAR/3 shock) OR ect OR spECTrum-5000Q OR Thymatron):ab,ti) AND ((depress* OR antidepress*):ab,ti) AND ((drug OR antidepress* OR anti-depress* OR (pharmaco* NEAR/3 (therap* OR treat)) OR pharmaco* OR Psychopharmaco* OR (serotonin NEAR/3 (uptake OR reuptake) NEAR/3 inhibitor*) OR ssri OR ssri OR venlafaxine OR lithium OR psychotropic*):ab,ti)

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TS=(((electroconvulsi* OR electr*-convulsi* OR electroshock OR (electr* NEAR/2 shock) OR ect OR spECTrum-5000Q OR Thymatron)) AND ((depress* OR antidepress*)) AND ((drug OR antidepress* OR anti-depress* OR (pharmaco* NEAR/2 (therap* OR treat)) OR pharmaco* OR Psychopharmaco* OR (serotonin NEAR/2 (uptake OR reuptake) NEAR/2 inhibitor*) OR ssri OR ssri OR venlafaxine OR lithium OR psychotropic*)) AND ((random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR placebo* OR ((doubl* OR singl*) NEAR/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups OR cohort OR longitudinal* OR prospectiv* OR retrospectiv*)) NOT ("case report") NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR

swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird*) NOT (human* OR patient*))) AND DT=(article) AND LA=(english)

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electroconvulsion|electroconvulsive|electroshock|"spECTrum-5000Q"|Thymatron depression|depressive|antidepressive drug|antidepressve|pharmacotherapy|Psycho pharmacology|"serotonin uptake|reuptake inhibitors|inhibitor"|psychotropics intitle:trial| randomized|rct

Influence of adjuvant nortriptyline on the efficacy of electroconvulsive therapy: a randomized controlled trial and 1-year follow-up

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ABSTRACT

Objective

There is limited evidence that adding an antidepressant to electroconvulsive therapy (ECT), compared with ECT monotherapy, improves outcomes. We aimed to determine whether the addition of nortriptyline to ECT enhances its efficacy and prevents post-ECT relapse.

Methods

We conducted a randomized, double-blind, placebo-controlled trial (RCT). Patients with major depressive disorder and an indication for ECT received either nortriptyline or placebo during a bilateral ECT course. Outcome measures were mean decrease in Hamilton Rating Scale for Depression (HRSD) score, response, remission, and time to response and remission. Patients who attained remission participated in a one-year follow-up study with open-label nortriptyline. Outcome measures were relapse and time to relapse.

Results

We included 47 patients in the RCT. In the nortriptyline group, 83% showed response, 74% attained remission, and the mean decrease in HRSD score was 21.6 points. In the placebo group these figures were, respectively, 81% (p=0.945), 73% (p=0.928) and 20.7 points (p=0.748). Thirty-one patients participated in the follow-up study. In patients who had received nortriptyline during the RCT, 47% relapsed at a mean of 34.2 weeks. Patients who had received placebo showed similar treatment results. In both study phases no statistically significant differences between the nortriptyline and the placebo group were found.

Conclusion

In our sample of severely depressed patients who were often medication resistant and suffering from psychotic depression, the addition of nortriptyline to ECT did not enhance its efficacy or prevent post-ECT relapse. Encouragingly, even in these patients, ECT was highly effective and relapse rates were relatively low.

Significant outcomes
- Adjuvant nortriptyline during the course of ECT did not enhance its efficacy.
- Adjuvant nortriptyline during the course of ECT did not prevent post-ECT relapse.
- In severely depressed patients who were often medication resistant and suffering from psychotic depression, ECT was shown to be a highly effective treatment with a relatively good long-term prognosis.

Limitations
- A relatively small sample size.
- Limited generalizability due to a specific patient sample, consisting of severely depressed inpatients who were often medication resistant and suffering from psychotic depression.
- Our findings may not apply to unilateral ECT since all patients received bilateral ECT.

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INTRODUCTION

Electroconvulsive therapy (ECT) is considered the most effective treatment for severe major depression (1). It is mainly used to treat medication-resistant patients (2), although medication resistance can reduce the efficacy of ECT. Recent meta-analyses have found a remission rate of 48% and a response rate of 58% for patients with medication-resistant depression (3, 4).

We recently published a meta-analysis that provides limited evidence that the efficacy of ECT for major depression might be improved by adding an antidepressant (5). We found a small to moderate clinical benefit among adjuvant selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Effect sizes were approximately the same for all types of antidepressants. However, effect sizes of TCAs and MAOIs were probably underestimated. Most of the studies included were dated, and therefore, they did not meet today's standards — neither for conducting randomized controlled trials (RCTs) nor for the treatment of major depression with antidepressants and ECT. Six of the studies conducted a trial on adjuvant treatment with a TCA. Five of them did not use plasma level targeted dosing. For example, in three studies, imipramine was given at a dose of 75-150 mg/day, which is a suboptimal dose for most patients (6). In the single study that used plasma level targeted dosing, ECT was administered with an optimal stimulus dose in approximately 10% of the patients who received right unilateral ECT (7). Three of the studies reported adjuvant treatment with an MAOI. All of these studies used low (phenelzine 45 mg/day) or very low (tranylcypromine 20 mg/day) doses.

Given the previously established evidence on the superior efficacy of TCAs compared to SSRIs in depressed inpatients (8), we assumed that TCAs and MAOIs might be more effective as adjuvant antidepressants during ECT than SSRIs. From a clinical perspective, we preferred an adjuvant TCA to an adjuvant MAOI, since MAOIs are prescribed far less commonly than TCAs because of their potentially severe drug-drug and drug-food interactions; in addition, MAOIs warrant precautions during anaesthesia for ECT (9, 10). Moreover, TCAs are safe to use with ECT and do not affect ECT tolerability (2, 7, 11).

Maintaining remission following ECT completion is a major challenge. While continuation treatment with antidepressant medication reduces the relapse rate, many patients still relapse: a meta-analysis by Jelovac et al. showed that 37% of ECT responders will relapse within the first 6 months after ECT completion and 51% by the end of the first year (12). Starting an antidepressant from the onset of ECT, as opposed to after ECT completion, might further reduce relapse rates. There are only a few RCTs that have tried

to demonstrate a reduction of the relapse rate by starting an antidepressant at the onset of ECT and continuing that medication after ECT completion. These studies showed that a 6-month continuation of paroxetine (13); a 6-month continuation of nortriptyline or venlafaxine, both with lithium added (14); and a 12-week continuation of agomelatine (15) did not significantly affect the relapse rates. To our knowledge, there are no longer-term outcome data.

We conducted a double-blind RCT comparing nortriptyline with placebo during a course of ECT for major depression, followed by a one-year open-label study with nortriptyline in patients who recovered from depression during the RCT.

Aims of the study

Our trial was designed to add to the currently limited literature and to test the hypotheses that starting nortriptyline at the onset of ECT, rather than after ECT completion, would result in (I) a larger decrease in depressive symptoms, (II) an increase in the response and remission rates, (III) a faster time to response and remission, (IV) a decrease in the relapse rate, and (V) a slower time to relapse.

MATERIAL AND METHODS

The study consisted of two phases: a double-blind RCT comparing nortriptyline with placebo during the course of ECT for major depression, followed by a one-year open-label treatment with nortriptyline in patients who recovered from depression during the RCT. The study was registered at the Dutch Trial Register (NTR5579).

Ethics

All procedures involving patients were approved by the Erasmus MC Medical Ethics Review Committee (MEC-2009-176) and complied with the Helsinki Declaration of 1975, as revised in 2008. After the study procedures were fully explained, patients provided written informed consent. We obtained written informed consent for both study phases separately and immediately prior to the start of each phase. Regarding the informed consent procedure for the RCT, if a patient was not capable of giving consent, written informed consent was obtained from the legally acceptable representative. In these patients, written informed consent was then obtained as soon as they were able to give consent. In conditions involving a legally acceptable representative's informed consent, the patient was informed regarding this consent, and any objection was heeded.

Participants

The RCT and the follow-up study were conducted at the inpatient and outpatient depression units of the Department of Psychiatry at the Erasmus Medical Centre – University Hospital in Rotterdam, The Netherlands.

Patients were eligible to participate in the RCT if they were ≥ 18 years old; had a DSM-IV-TR (16) diagnosis of major depressive disorder as assessed with the Schedule for Affective Disorders and Schizophrenia (SADS) (17) during a routine drug-free observation period; had a score of ≥ 18 on the Hamilton Rating Scale for Depression (18); and had an indication for ECT. If a patient was ≥ 65 years old, the first depressive episode had to have been diagnosed before the age of 65, and the score on the Mini Mental State Examination (MMSE) (19) had to be ≥ 24. The drug-free observation period of one week was part of the routine clinical practice and was used for diagnosing and screening for eligibility. It was routinely shortened to at least five days if ECT could not be delayed due to symptom severity, and it was routinely extended with another week if discontinuation symptoms interfered with the diagnostic process. Indications for ECT were life-threatening situations, for example, high suicide risk and the refusal of food and drink; and medication resistance, that is, at least an inadequate response to a plasma level targeted dosage of TCA for ≥ 4 weeks or venlafaxine > 225 mg/day for ≥ 4 weeks. Patients were excluded if they had a history of bipolar disorder, schizoaffective disorder or schizophrenia; had alcohol or drug dependence in the previous 3 months; had a serious neurological illness; had a contraindication for nortriptyline; were taking anti-epileptics; were pregnant; or had an insufficient command of the Dutch language.

Patients were eligible to participate in the follow-up study if they attained remission following ECT. All eligible patients were approached and asked to participate.

RCT

Patients were withdrawn from all psychotropic medications, including benzodiazepines, at least five days prior to the first ECT treatment. Except for trial medication, patients were kept medication free during the course of ECT. In cases of severe agitation, incidental use of haloperidol up to 2 mg/day was allowed.

Patients were randomized to receive either nortriptyline or placebo during the course of ECT, starting five days prior to the first ECT treatment. All patients received an initial daily administration of two pills for five days, followed by a daily administration of four pills. Each pill was manufactured by the trial pharmacy, looked identical and contained 25 mg of nortriptyline or placebo. To maintain blinding, plasma levels were measured weekly during the course of ECT in both the nortriptyline group and the placebo group. A trial

pharmacist provided real plasma levels for patients receiving nortriptyline and fictitious plasma levels for patients receiving placebo. In the patient records, both nortriptyline and placebo were marked as 'study medication', so the treating psychiatrist was blind to the pharmacotherapy assignment. The dosage of 'study medication' was adjusted by the treating psychiatrist to achieve therapeutic nortriptyline plasma levels of 50-150 µg/L.

All patients were treated twice weekly with bilateral ECT, administered with a brief-pulse, constant-current device (Thymatron DGx, Somatics, Lake Bluff, Illinois, USA). The seizure threshold, defined as the stimulus dose that elicited a seizure of at least 25 s as measured with the cuff method, was determined during the first ECT treatment with empirical stimulus titration. If the starting stimulus dose failed to elicit a seizure of at least 25 s, the stimulus charge was increased according to the titration schedule, and the patient was restimulated after 30 s. For the second ECT treatment, the stimulus dose was set at 1.5 times the seizure threshold. During the course of ECT, stimulus dose settings were adjusted upward to maintain a seizure duration of at least 25 s as measured with the cuff method. Anaesthesia was induced after premedication with 0.2 mg glycopyrronium and 0.5 mg alfentanil, with intravenous administration of etomidate (0.2 mg/kg) for anaesthesia and succinylcholine (0.5-1.0 mg/kg) for muscle relaxation. During the procedure, patients were ventilated by a mask until the resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, noninvasive blood pressure measurement, electrocardiography, and electroencephalography. The number of ECT treatments depended on the improvement in each patient's HRSD score. ECT was terminated if a patient attained full remission or if there was no further improvement in HRSD score over 3 consecutive ECT treatments. A minimum of 10 bilateral ECT treatments was required before a patient was determined to be a non-responder.

Follow-up study

One week after ECT completion, the 'study medication' was replaced by open-label nortriptyline. To maintain blinding for whether the patient was treated with nortriptyline or placebo in the RCT, a trial pharmacist indicated the dosage of nortriptyline to be prescribed for each patient. In doing so, the trial pharmacist adhered to the following: the patients who had received nortriptyline in the RCT continued taking this medication at the same dosage, whereas the patients who had received placebo were started on nortriptyline. Nortriptyline plasma levels were measured weekly during the first month and then every four weeks for a year or until relapse. If necessary, the dosage of nortriptyline was adjusted to maintain therapeutic plasma levels of 50-150 µg/L. Patients were kept free from all psychotropic medications aside from nortriptyline.

Randomization and blinding

We used a 1:1 permuted block randomization with block lengths of 6. The randomization sequence was created by a trial pharmacist. Patients, the treatment team and the outcome assessor were blind to the pharmacotherapy assignment in the RCT until the end of the follow-up study.

Assessments

RCT. Prior to ECT, weekly during the course of ECT and at ECT completion, a trial psychiatrist (EP) completed the HRSD and the Clinical Global Impression Scale (CGI) (20) to quantify the severity of each patient's depression. We filled in the Antidepressant Treatment History Form (ATHF) (21) to assess medication resistance during the index episode. The presence of delusions of guilt or sin, persecution and poverty, somatic and nihilistic delusions, and hallucinations was determined by examining the scores on relevant SADS items. We classified patients as having a depressive disorder with psychotic features if there was at least a positive score on one type of delusion, along with a positive score on the SADS item on mood-congruent psychotic features. During the course of ECT, we constantly monitored for adverse events, and we assessed side effects weekly by inquiring about any unpleasant feeling and, if present, rated mild, moderate or severe on a self-assembled checklist.

Follow-up study. Weekly during the first month and then every four weeks, a trial psychiatrist (EP) completed the HRSD and CGI to determine the presence and severity of each patient's depressive symptoms. These questionnaires were completed for one year or until relapse. Adverse events and side effects were monitored at the same intervals. We assessed side effects by inquiring about any unpleasant feeling and, if present, rated mild, moderate or severe on a self-assembled checklist.

Outcome measures

RCT. Our primary outcome measure was the mean decrease in HRSD score, defined as the difference in the HRSD score between baseline and at ECT completion. Our secondary outcome measures were (I) response, defined as a reduction in HRSD score of ≥ 50% relative to baseline; (II) remission, defined as an HRSD score of ≤ 7 within one week of ECT completion; and (III) the time to response and the time to remission, defined as the number of weeks between the first ECT treatment and the first HRSD assessment indicating response or remission, respectively.

Follow-up study. Our primary outcome measure was relapse, defined as a CGI score of at least 'much worse' compared to the baseline CGI assessment at ECT completion; or an HRSD score ≥ 16; or when the study psychiatrist (EP) decided, based on a worsening in depressive symptoms, that it was in the patient's clinical interest to exit the protocol and to change the treatment regimen. Additionally, patients had to meet the DSM-IV-TR criteria for major depression for ≥ 2 weeks. In patients who had been diagnosed with psychotic depression prior to the start of the RCT, the presence of psychotic features was not necessary to determine relapse. Our secondary outcome measure was the time to relapse, defined as the number of weeks between the baseline CGI assessment at ECT completion and the first CGI assessment indicating relapse.

Sample size

The power calculation is based on the primary outcome measure, the mean decrease in HRSD score. A difference of ≥ 3 points between the nortriptyline group and the placebo group is considered clinically relevant. Previous research showed that the standard deviation of the mean decrease in HRSD score was approximately 5 (Cohen's *d*=0.54). In a power analysis employing a level of significance of 5% and a power of 80%, the minimum sample size to reach statistical significance was 45 participants in each group. The sample size was calculated by means of Table 6A, *Sample size per group for comparing two means* from Hulley SB et al., Designing Clinical Research, 3rd edition, 2007 (22). Due to the relatively slow recruitment rate, new study medication had to be made after 4 years. In 2017, again, the study medication expired, and we lacked financial support to order new trial medication. Therefore, we were forced to stop the recruitment of patients after seven years. At that time, 47 patients were included in the RCT. Post hoc power analysis showed that with 47 patients, we were able to detect a difference between the nortriptyline group and the placebo group of ≥ 4 points (pooled SD=5.0, *d*=0.84 (large)) with a power of 80% and level of significance of 5% (two-sided).

Statistical analyses

RCT. The difference between the nortriptyline group and the placebo group in the mean decrease in HRSD score was tested using a *t*-test and by testing the time*condition interaction term using a mixed linear model, including a random intercept, autoregressive (AR1) covariance matrix. For the purpose of the mixed model analysis, follow-up assessments were included up to 15 weeks of treatment, as this was the longest course of ECT in our patient sample. The scores of the patients for whom ECT treatment ended before 15 weeks, either because remission was reached or because the patient failed to

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respond after at least 10 ECT treatments, were imputed using the last observation carried forward. The autoregressive covariance structure (constant measurement variability over time combined with an exponential decrease of the correlation between measurements over time) best describes the assumed symptom trajectory. Before conduct of the analysis we tested whether the parameters met the assumptions for a generalized linear mixed model. Differences between the nortriptyline group and the placebo group in the percentage of responders and remitters were tested using χ^2 tests. Differences in the time to remission and the time to response were tested using Kaplan–Meier curves in combination with log rank χ^2 tests.

Baseline differences were tested using univariable tests, that is, t-tests and Mann-Whitney for continuous variables and χ^2 tests for dichotomous variables.

By means of post hoc analyses, we explored whether patient characteristics, known to predict ECT outcome (23), that is, age, sex, the presence of psychotic features, and medication resistance, might have impacted our overall results. For this purpose, we added an interaction term (patient characteristic*time) to a linear mixed model analysis including the patient characteristic and time as fixed effects (random intercept, AR1 covariance matrix). If the interaction-term was significant, we plotted the estimated marginal means of the term to interpret the interaction term. Additionally, we used χ^2 tests and Kaplan–Meier curves in the stratified sample to explore differences. Since medication resistance and episode duration often correlate strongly (24), they were not both incorporated in our post-hoc analyses.

Follow-up study. The differences between the nortriptyline group and the placebo group in the mean CGI score and the mean HRSD score at the end of the follow-up study were tested using a t-test. The scores of the patients who dropped out were imputed using the last observation carried forward. The difference between the nortriptyline group and the placebo group in the percentage of relapse was tested using a χ^2 test. The difference in the time to relapse was tested using a Kaplan–Meier curve in combination with a log rank χ^2 test.

R E S U L T S

Participants

Between March 2010 and March 2017, 97 patients were assessed for eligibility. Figure 1 presents the CONSORT flow diagram of the patient recruitment. Twenty-nine patients did

not meet the inclusion criteria, and 21 patients declined to participate. Among the latter group, almost all patients were incapable of giving consent due to psychotic features. Their legally acceptable representatives found it difficult to decide on ECT treatment, let alone on participation in an ECT trial. Therefore, they were not willing to provide proxy consent. A total of 47 patients were enrolled in the RCT, of whom 23 were assigned to the nortriptyline group and 24 were assigned to the placebo group. Thirty patients were capable of giving written informed consent. For 17 patients, written informed consent was obtained through a legally acceptable representative. None of these patients objected to the conduct of the study, and all patients gave written informed consent as soon as they were capable of doing so. Three patients dropped out, all from the placebo group. Two of them withdrew informed consent prior to baseline assessment, and one patient refused trial medication after the first ECT treatment. Table 1 summarizes the demographic and baseline clinical characteristics of the total sample and of the nortriptyline group and the placebo group separately. Since we were unable to collect any clinical data from the two patients who withdrew informed consent prior to baseline assessment, baseline clinical characteristics from these patients are missing, and these patients were excluded from the analysis. As a result, only 45 patients were included in the analyses.

**TABLE 1.** Demographic and baseline clinical characteristics

	Nortriptyline (n=23)	Placebo (n=24)	Total sample (n=47)	*P*-value
Age, mean (SD), years	63.2 (11.6)	59.2 (10.2)	61.2 (11.0)	0.210
Female, n (%)	12 (52.2)	13 (54.2)	25 (53.2)	0.891
Psychotic, n (%)[a]	12 (52.2)	8 (36.4)	20 (44.4)	0.450
Melancholic, n (%)[a]	12 (52.2)	13 (59.1)	25 (55.6)	0.218
Duration of current episode, median (IQR), weeks[a]	50.0 (20.0-68.0)	31.0 (12.0-103.0)	35.0 (16.0-74.5)	0.708
Number of previous depressive episodes, mean (SD)[a]	1.6 (1.4)	1.4 (1.2)	1.5 (1.3)	0.606
ATHF score, mean (SD)[a]	2.5 (2.0)	3.1 (1.7)	2.8 (1.8)	0.299
Medication resistant, n (%)[b]	11 (47.8)	15 (68.2)	26 (57.8)	0.167
Number of adequate medication trials, mean (SD)[b]	1.3 (1.6)	1.3 (1.2)	1.3 (1.4)	0.974
Pre-ECT HRSD score, mean (SD)[a]	29.0 (5.5)	28.5 (5.2)	28.7 (5.3)	0.727

Abbreviations: ATHF, Antidepressant Treatment History Form; ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression.

[a] *For this characteristic, the data from two patients in the placebo group are missing.*

[b] *According to the ATHF.*

FIGURE 1. CONSORT flow diagram of the patient inclusion
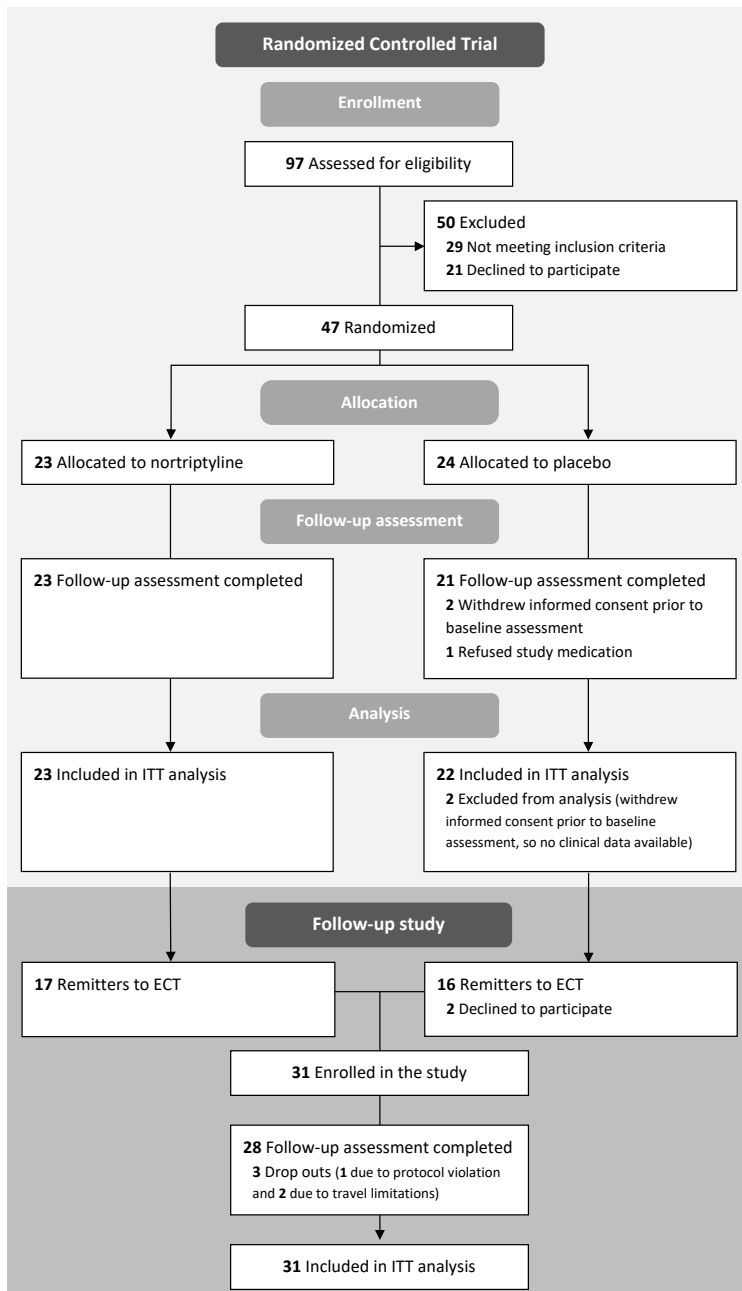
Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; ECT, electroconvulsive therapy; ITT, intent-to-treat.

After the completion of the RCT, 33 patients were eligible to participate in the follow-up study. Two patients declined to participate: one due to travel limitations and the other due to a preference to be treated by the referring psychiatrist. Thus, 31 patients were enrolled in the follow-up study. Three patients dropped out. For one of them, her general practitioner initiated a course of psychotropic medication for memory problems. The other two patients discontinued with follow-up due to travel limitations. A total of 31 patients were included in the analyses.

Interventions

RCT. Except for trial medication, all but six patients were kept medication free during the course of ECT. These six patients incidentally received haloperidol 1 mg/day (n=4) or 2 mg/day (n=2) due to severe agitation. In the nortriptyline group, all patients achieved a therapeutic plasma level of nortriptyline. ECT was performed as described in the *Material and methods* section. In all patients, seizure durations of at least 25 s were elicited. No adverse events or serious side effects were reported.

Follow-up study. Except for nortriptyline, all patients were kept medication free and had a therapeutic plasma level of nortriptyline. No adverse events or serious side effects were reported.

Outcomes

RCT. Table 2 shows the results of our efficacy analyses. In patients treated with a combination of ECT and nortriptyline, the mean HRSD score at ECT completion was 7.4, and the mean decrease in HRSD score was 21.6 points. A total of 83% showed response at a mean of 5.6 weeks of ECT, and 74% attained full remission at a mean of 7.2 weeks. Similar treatment results were found in patients treated with a combination of ECT and placebo. Testing showed no significant difference in the mean decrease in HRSD score, neither by means of a *t*-test nor by general linear mixed model analysis (time*condition interaction: B=-0.05; 95% CI=-0.48 to 0.37; *p*=0.802). Additionally, we found no significant differences between the nortriptyline group and the placebo group with respect to the response and remission rates or the accompanying time to response and time to remission analyses. Figure 2 shows the Kaplan–Meier survival curve for the time to remission.

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TABLE 2. Outcomes and results of efficacy analyses from the RCT

	Nortriptyline (n=23)	Placebo (n=22)	Test
HRSD score after treatment, mean (SD)	7.4 (6.6)	7.7 (7.4)	T(43)=0.160; p=0.873
HRSD score change over treatment, mean (SD)	-21.6 (9.3)	-20.7 (9.3)	T(43)=0.324; p=0.748
Response, n (%)	19 (82.6)	18 (81.2)	χ^2(1)=0.005; p=0.945
Mean week to response (SE)	5.6 (1.01)	6.7 (0.96)	Log rank χ^2(1)=1.015; p=0.314
Remission, n (%)	17 (73.9)	16 (72.7)	χ^2(1)=0.008; p=0.928
Mean week to remission (SE)	7.2 (0.89)	8.0 (0.92)	Log rank χ^2(1)=0.27; p=0.602

Abbreviations: HRSD, Hamilton Rating Scale for Depression.

FIGURE 2. Kaplan–Meier survival curves for the RCT (left) and for the follow-up study (right)
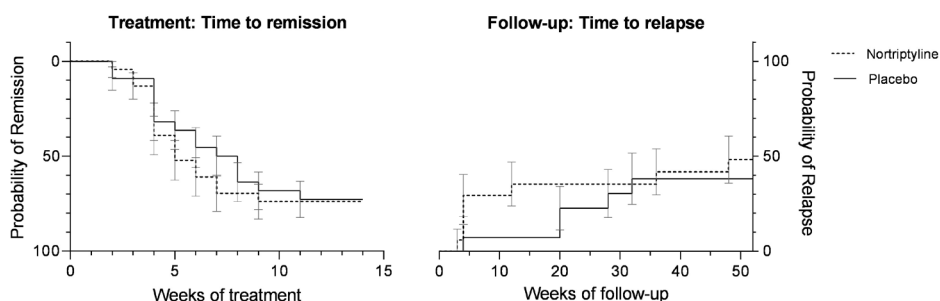
By means of post hoc analyses, we explored whether patient characteristics might have impacted the efficacy of ECT in combination with either nortriptyline or placebo. We found no significant interaction effects of sex with time (B=-0.12; 95% CI=-0.54 to 0.31; p=0.592) or age with time (B=-0.01; 95% CI=-0.03 to 0.006; p=0.191), suggesting that the course of depressive symptomatology as a result of ECT was not impacted by these factors. We found that patients with psychotic features reported a higher HRSD score before the start of treatment (B=5.85; 95% CI=1.07 to 10.62; p=0.016) and showed a more rapid decrease in HRSD score than patients without psychotic features (B=-0.52; 95% CI=-0.95 to -0.10; p=0.015). We found an indication of a lower percentage of remitters among medication-resistant patients (69%) than among patients without medication resistance (79%), with a mean time to remission of 8.6 weeks in medication-resistant patients compared to 6.2 weeks in patients without medication resistance. Again, these

differences did not reach significance ($\chi^2(1)$=0.530; *p*=0.467 and K-M log rank $\chi^2(1)$=2.796; *p*=0.094).

Follow-up study. Table 3 shows the results of our efficacy analyses. In patients who had received nortriptyline during the RCT, the mean HRSD score and the mean CGI score at the end of the follow-up study were 9.0 and 4.8, respectively. Forty-seven percent relapsed at a mean of 34.2 weeks after ECT completion. Similar treatment results were found in patients who had received placebo during the RCT. Testing showed no significant difference in the mean HRSD score and the mean CGI score at the end of the follow-up study. Additionally, we found no significant differences between the nortriptyline group and the placebo group with respect to the relapse rate or the accompanying time to relapse analyses ($\chi^2(1)$=0.408; *p*=0.524 and K-M log rank $\chi^2(1)$=0.437; *p*=0.509). Figure 2 shows the Kaplan–Meier survival curve for the time to relapse.

TABLE 3. Outcomes and results of efficacy analyses from the follow-up study

	Nortriptyline (n=17)	Placebo (n=14)	Test
HRSD score at end of FU, mean (SD)	9.0 (7.5)	6.1 (8.2)	T(29)=1.013; *p*=0.320
CGI score at end of FU, mean (SD)	4.8 (1.0)	4.2 (1.1)	T(29)=1.587; *p*=0.123
Relapse, n (%)	8 (47.1)	5 (35.7)	$\chi^2(1)$=0.406; *p*=0.524
Mean week to relapse (SE)	34.2 (5.3)	40.2 (4.4)	Log rank $\chi^2(1)$=0.437; *p*=0.509

Abbreviations: HRSD, Hamilton Rating Scale for Depression; FU, follow-up; CGI, Clinical Global Impression Scale.

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DISCUSSION

In this study, there was no significant difference in the mean decrease in HRSD score between the nortriptyline group and the placebo group at ECT completion. Additionally, the proportion of responders and remitters and the speed of response and remission did not differ significantly between the groups. These findings did not support the study hypotheses and were not in line with the results of our recently published meta-analysis that showed that an adjuvant antidepressant might increase the efficacy of ECT (5).

In our patient sample, ECT was shown to be a highly effective treatment for both the nortriptyline group and the placebo group. In the nortriptyline group, 83% of the patients responded to ECT, and 74% attained full remission; in the placebo group, these num-

bers were 81% and 73%, respectively. As commented by Ottosson et al. (25), such high response and remission rates make it exceptionally difficult to further raise the proportion of responders and remitters by any additional treatment. Thus, our highly effective ECT might have prevented us from finding an effect of adjuvant nortriptyline. Another reason that might explain why we did not find an add-on effect of nortriptyline to ECT is that 58% of our patients were medication resistant. As discussed by Heijnen et al. (3), it seems reasonable that patients with difficult-to-treat severe major depression will respond less well to subsequent treatment, including an adjuvant antidepressant during the course of ECT.

Previous RCTs on the influence of an antidepressant on the efficacy of ECT are limited. In our recently published meta-analysis (5), only nine RCTs met the inclusion criteria. The results of eight of these studies were difficult to compare with ours for various reasons. For example, Mayur et al. (26) used a different design, Imlah et al. (27) used a very low and fixed dose of imipramine, Kay et al. (28) used diazepam as active placebo, and Wilson et al. (29) did not statistically analyse their results.

Only one study included in our meta-analysis was deemed to be of good quality. This study by Sackeim et al. (7) was the only RCT in which an adjuvant TCA was given at doses that aimed to achieve therapeutic plasma levels. Approximately half of the patients in that study received bilateral ECT, and the other half received right unilateral ECT. ECT was administered with an optimal stimulus dose in approximately 10% of the patients who received right unilateral ECT. Sackeim et al. reported a superior outcome with ECT plus nortriptyline relative to ECT plus placebo, with a remission rate of 41% in patients receiving placebo and 55% in patients receiving nortriptyline. Compared to the study by Sackeim et al. (7), our remission rates were considerably higher, possibly due to a larger proportion of patients with psychotic features (44% in our study versus 20% in the study by Sackeim et al.) and the use of adequately dosed bilateral ECT in all patients. Bilateral ECT might be superior to right unilateral ECT (1); however, there are studies that do not support this (30). Furthermore, Sackeim et al. did not describe the proportion of medication-resistant patients; instead, they reported a mean number of adequate medication trials of 1.3 (SD 1.3). Although this figure appeared similar to our mean number of adequate medication trials, it does not provide information about the number of treatment resistant patients in their sample. In our patient sample, 58% of the patients were medication resistant according to the ATHF. We speculate that our patient sample consisted of a higher proportion of medication-resistant patients than Sackeim et al.'s patient sample. The difference in both the remission rate and the level of medication resistance may explain

why Sackeim et al. were able to demonstrate an add-on effect of nortriptyline to ECT, while we were not.

The study by Lin et al. (15), not included in our meta-analysis due to its recent publication date, did not find an add-on effect of agomelatine to ECT. Their results are difficult to compare with ours, since Lin et al. used a modern antidepressant as add-on medication to ECT and they included younger patients with a larger number of previous depressive episodes. Moreover, their ECT method differed from ours; they used an age-based and gender-adjusted method to determine the initial stimulus dose, and the maximum number of treatments was limited to twelve.

Another finding of our study was that the mean HRSD score and the mean CGI score at the end of the one-year follow-up study did not significantly differ between the patients who had received nortriptyline and the patients who had received placebo during the RCT. Additionally, the relapse rate and the time to relapse did not significantly differ between the groups. Again, these findings did not support the study hypotheses. However, they are in line with previous studies (13-15).

Compared to these previous studies, our results are somewhat more favourable. In our patients who had received nortriptyline during ECT and who continued taking this medication after ECT completion, the relapse rate at one year was 47%. At both 12 weeks and 6 months, our relapse rate was 35%, whereas Lauritzen et al. (13) and Prudic et al. (14) found higher relapse rates at 6 months, and Lin et al. (15) found a higher relapse rate at 12 weeks. Our relapse rates were comparable with those from a meta-analysis of Jelovac et al. (12). However, their results were based on predominantly small, underpowered, observational studies. Our patients not only seem to have responded well to ECT but also had a relatively good long-term prognosis. The older age of our patients and the large proportion of patients with psychotic features might account for this long-term sustained remission (31), although this is still under debate (32). The optimal continuation pharmacotherapy following successful ECT in patients with psychotic depression has been studied scarcely. The combination of an antidepressant and an antipsychotic is commonly prescribed (33), but showed no advantage over antidepressant monotherapy in preventing post-ECT relapse in a previous study in elderly patients (34). Future research might determine which patient-, illness- or treatment-related characteristics predict long-term sustained remission.

An important strength of this study is its prospective, randomized, double-blind and placebo-controlled design and its long-term follow-up period of one year. We included even the most severely depressed patients. These patients are often excluded from studies, while their inclusion ensures a more realistic reflection of all patients eligible for ECT.

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Furthermore, ECT was performed according to current standards, which included empirical stimulus titration at the first session. Except for trial medication and the incidental use of low doses of haloperidol in six patients, our patients were kept medication free prior to and during the course of ECT. Thus, benzodiazepines, which may have a negative effect on the outcome of ECT (35, 36), although a recent study found an opposite effect (37), were not allowed. During the follow-up study, no psychotropic medication other than nortriptyline was permitted.

A limitation of this study is the lack of power caused by its smaller than anticipated number of included patients; recruitment ended before we reached our inclusion targets. The limited power might have caused us to overlook small effect sizes. However, given the effect sizes found in this study we would have needed an extremely large sample size to reach significance with regard to the decrease in depressive symptoms during the course of ECT. Our specific patient sample, consisting of severely depressed inpatients who were often medication resistant and suffering from psychotic depression, limits the generalizability of our findings. The presence of psychotic features, medication resistance and episode duration are known to predict ECT outcome (4, 23) and should be considered as relevant confounders. A larger proportion of patients with psychotic features and a smaller proportion of medication resistant patients within the nortriptyline group, might have resulted in overestimating the effect of nortriptyline. Contrary, the effect of nortriptyline might have been underestimated due to a longer episode duration in the nortriptyline group. However, baseline differences in the presence of psychotic features, medication resistance and episode duration were not statistically significant. Moreover, our findings were based on patients treated with bilateral ECT and may not apply to patients treated with right unilateral ECT.

Our findings do not support the addition of nortriptyline to ECT in severely depressed patients, who are medication resistant and suffering from psychotic depression. In this patient group, ECT was shown to be a highly effective treatment to which an antidepressant had no added value. Nevertheless, considering that TCAs are generally safe to use with ECT (2, 7, 9, 10), we recommend starting a TCA during the course of ECT in these patients to ensure an adequate plasma level at ECT completion, which may be crucial in preventing relapse (38, 39). The long-term prognosis on continuation treatment with nortriptyline was relatively good in our patient sample, although adjuvant nortriptyline during the course of ECT did not prevent relapse.

To conclude, this study adds to the limited literature on the influence of an adjuvant antidepressant on the efficacy of ECT and on relapse after ECT completion. We were not able to demonstrate an add-on effect of nortriptyline during the course of ECT in our patient

sample, which consisted of severely depressed patients who were often medication resistant and suffering from psychotic depression. It is encouraging that in these patients, ECT was highly effective, and post-ECT sustained remission was better than expected. Therefore, this study provides renewed evidence that ECT is a highly effective treatment, even for patients with medication-resistant severe major depressive disorder.

Acknowledgements

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Relapse two years after electroconvulsive therapy for major depression: relevant clinical predictors

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ABSTRACT

Background

High relapse rates are observed after electroconvulsive therapy (ECT) for major depression. Identifying patients who are at increased risk for relapse to intensify their treatment regimen post-ECT might reduce relapse rates.

Aims

We aimed to determine clinical characteristics that are associated with relapse within two years after successful ECT.

Method

Patients who remitted to ECT in a randomized controlled trial comparing adjuvant nortriptyline and placebo during a course of bilateral ECT were followed-up prospectively for one year with open-label nortriptyline (Dutch Trial Register NTR5579). Second-year follow-up data were collected retrospectively. Thirty-four patients were included in this follow-up cohort. To examine the association between clinical characteristics and the risk of relapse, unadjusted hazard ratios (HRs) were calculated.

Results

At two years post-ECT, the overall relapse rate was 50%, and the HRs for relapse in patients with psychotic features, a higher severity of depression, and medication resistance prior to ECT were 0.33 (CI 0.12−0.89; p=0.029), 0.88 (CI 0.80−0.98; p=0.014), and 4.48 (CI 1.28−15.73, p=0.019), respectively. No effect was found for age, sex or episode duration on the relapse rate.

Conclusions

Depressed patients with psychotic features, with higher symptom severity and without medication resistance prior to ECT have a significantly decreased risk of relapse after successful ECT. A sustained remission rate of 50% over two years in patients with severe major depression who were treated with nortriptyline monotherapy after successful ECT is encouraging.

INTRODUCTION

Electroconvulsive therapy (ECT) is a highly effective treatment for patients with severe major depression (1). After successful ECT, high relapse rates are observed. A meta-analysis showed that, despite continuation pharmacotherapy, 51% of patients relapsed within 12 months following successful ECT, with the majority relapsing within the first 6 months (2). It would be of great clinical benefit to be able to identify patients who are at increased risk of relapse. These patients can then be monitored more carefully and receive a more intensive continuation treatment after successful ECT to reduce their relapse rate. Only a few studies have focused on clinical predictors for relapse post-ECT. Some of them found that an older age (3, 4) and the presence of psychotic features prior to ECT (2-6) are associated with a lower relapse rate and that medication resistance prior to ECT is associated with a higher risk of relapse (7-9). However, other studies were not able to replicate these findings regarding older age (10, 11), psychotic features (7, 10) and medication resistance (3, 4). Female sex (9), a larger number of previous depressive episodes (3, 12), a longer duration of the index episode (13), and achieving response but not remission to ECT (9) have also been identified as risk factors for relapse. A higher severity of depression prior to ECT might reduce the relapse rate, although this is based on our clinical impression and has not yet been studied. All previous studies on clinical predictors for relapse after successful ECT had a short-term follow-up period of 3-12 months. Unfortunately, there are no studies with a longer-term follow-up.

Aim of the study

To add to the currently limited and inconclusive literature, we conducted a cohort study to determine clinical predictors for relapse after successful ECT. We hypothesized that older age, male sex, a shorter duration of the index episode, a higher severity of the index episode, the presence of psychotic features prior to ECT, and the absence of medication resistance prior to ECT predict long-term, i.e., two years, remission after successful ECT.

METHOD

Design

The current cohort study is embedded in a randomized controlled trial (RCT) comparing adjuvant nortriptyline and placebo during a course of bilateral ECT and a subsequent prospective one-year follow-up study with open-label nortriptyline in patients who attained

remission to ECT (Dutch Trial Register NTR5579) (14). We used prospective data from this follow-up study, i.e., data up to 12 months post-ECT. Additionally, we retrospectively collected data up to two years post-ECT. The RCT and subsequent 12-month prospective follow-up assessments were carried out from 2010-2018. The retrospective data collection took place from 2018-2019, i.e., 2-8 years since initial treatment with ECT.

Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving patients were approved by the Erasmus MC Medical Ethics Review Committee (prospective data collection: MEC-2009-176; retrospective data collection: MEC-2018-1120). All patients provided written informed consent.

Patients

All patients included in the current study participated in an RCT comparing adjuvant nortriptyline and placebo during a course of bilateral ECT and attained remission with ECT. Remission was defined as a score of ≤ 7 on the 17-item Hamilton Rating Scale for Depression (HRSD) (15) within one week of ECT completion. On average, they had achieved remission after 13 ECT sessions, and they had shown a response (50% reduction in HRSD score) at the 6th session.

Patients were eligible to participate in the RCT if they were ≥ 18 years old; had a DSM-IV-TR (16) diagnosis of major depressive disorder as assessed with the Schedule for Affective Disorders and Schizophrenia (SADS) (17) during a routine drug-free observation period; had a score of ≥ 18 on the 17-item HRSD (15); and had an indication for ECT. Indications for ECT were life-threatening situations and medication resistance, i.e., at least an inadequate response to a plasma level targeted dosage of a tricyclic antidepressant for ≥ 4 weeks or venlafaxine > 225 mg/day for ≥ 4 weeks. Exclusion criteria were a history of bipolar disorder, schizoaffective disorder or schizophrenia; alcohol or drug dependence in the previous 3 months; a serious neurological illness; a contraindication for nortriptyline; taking anti-epileptics; pregnancy; or an insufficient command of the Dutch language.

The current study was conducted at the outpatient depression unit of the Department of Psychiatry at the Erasmus Medical Centre – University Hospital in Rotterdam, The Netherlands.

ECT procedure

All patients were treated twice weekly with bilateral ECT administered with a brief pulse constant current device (Thymatron DGx, Somatics, Lake Bluff, Ill, USA). During the first ECT treatment, the seizure threshold was determined with empirical stimulus titration. The seizure threshold was defined as the stimulus dose that elicited a seizure of at least 25 seconds (s) as measured with the cuff method. If the starting stimulus dose failed to elicit a seizure of at least 25 s as measured with the cuff method, the stimulus charge was increased according to the titration schedule, and the patient was restimulated after 30 s. For the second ECT treatment, the stimulus dose was set at 1.5 times the seizure threshold. During the course of ECT, stimulus dose settings were adjusted upwards to maintain a seizure duration of at least 25 s as measured with the cuff method. Anaesthesia was performed after premedication with 0.2 mg glycopyrronium and 0.5 mg alfentanil, with intravenous administration of etomidate (0.2 mg/kg) for anaesthesia and succinylcholine (0.5-1.0 mg/kg) for muscle relaxation. During the procedure, patients were ventilated by mask until the resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, noninvasive blood pressure measurement, electrocardiography, and electroencephalography. The number of ECT treatments depended on improvement in the HRSD score. ECT was continued until a patient attained full remission or if there was no further improvement in HRSD score over 3 consecutive ECT treatments. A minimum of 10 bilateral ECT treatments was required before classification as a nonresponder.

Medication during follow-up

According to the protocol, all patients were treated with nortriptyline at a target plasma level of 50-150 μg/L. They were kept free from all psychotropic medications aside from nortriptyline. After 12 months, the medication regimen was re-evaluated. The majority of patients (90%) continued to take nortriptyline monotherapy over the subsequent 12-month period.

Assessments and data collection

Clinical characteristics

Prior to the RCT, demographic and clinical characteristics were recorded. The age, sex and duration of the index episode were obtained by an interview and double checked by chart review. The 17-item HRSD (15) was completed to measure the severity of depression. The presence of mood-congruent delusions and hallucinations was determined by examining the scores on relevant SADS (17) items. Patients were classified as having a depressive disorder with psychotic features if there was at least a positive score on one type of

delusion, along with a positive score on the SADS item on mood-congruent psychotic features. The Antidepressant Treatment History Form (ATHF) (18) was completed to assess medication resistance during the index episode; scores of ≥ 3 indicate medication resistance.

Depressive symptoms
Depressive symptoms were collected prospectively for up to 12 months. The 17-item HRSD (15) and the Clinical Global Impression Scale (CGI) (19) were completed weekly during the first month and then every four weeks to determine the occurrence and severity of each patient's depressive symptoms. These questionnaires were completed until relapse. Retrospective data were collected up to 24 months and obtained through each patient's general practitioner or, if the patient was still in psychiatric care, the treating psychiatrist or mental health care provider. If possible, information was cross validated in an interview with the patient. We preferred a face-to-face interview but also accepted an interview by telephone. We inquired about current and previous episodes of depression and changes in treatment regimen due to depressive symptoms since the end of initial treatment with ECT. During the interview with the patient, we completed the Structured Clinical Interview for DSM-IV (SCID-I) (20), the part concerning mood disorders, to determine the occurrence of depressive episodes.

Outcome measures
Our primary outcome measure was time to relapse. We used the term 'relapse' for the occurrence of depressive symptoms after successful ECT, regardless of when these symptoms occurred. In prospective assessments, this was defined as the number of weeks between the moment of remission and the first CGI (19) or 17-item HRSD (15) assessment indicating relapse, i.e., a CGI score of at least 'much worse' or an HRSD score ≥ 16, or between the moment of remission and when the study psychiatrist decided, based on a worsening in depressive symptoms, that it was in the patient's clinical interest to exit the prospective follow-up study protocol and to change the treatment regimen. Additionally, patients had to meet the DSM-IV-TR criteria for major depression for at least 2 weeks. During the retrospective data collection, time to relapse was defined as the number of weeks between the moment of remission and the first occurrence of a depressive episode as indicated by the general practitioner, treating psychiatrist or mental health care provider and, if available, cross validated with the SCID. Additionally, the worsening of depressive symptoms must have led to a change in the treatment regimen.

Statistical analyses

Descriptive statistics were tested for normality using the Shapiro–Wilk test. For normally distributed continuous variables, means and standard deviations (SD) were presented. Otherwise, medians, including the 25th and 75th percentiles, were given. Categorical variables were reported as absolutes and percentages. To examine the relationship between clinical characteristics and the risk of relapse, unadjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated using univariable Cox regression survival analyses incorporating the following variables: age, sex, duration of the index episode (episode duration), severity of the index episode (severity of depression), presence of psychotic features prior to ECT (psychotic features), and medication resistance prior to ECT (medication resistance). Multivariable Cox regression survival analyses could not be performed due to the limited sample size. For categorical variables, i.e., sex, psychotic features, and medication resistance, survival distributions were plotted using the Kaplan–Meier method to visually verify proportional hazard assumptions. For continuous variables, i.e., age, episode duration and severity of depression, time-dependent variables were created, Schoenfeld ("partial" in SPSS) residuals were checked for significance, and Q-Q plots were visually verified. All statistical analyses were performed using IBM SPSS version 27.

RESULTS

Thirty-four patients reached remission during the RCT and were included in the current cohort study. Prospective data on the first-year follow-up were available in all but two cases. In these cases, we relied on retrospective data only.

Nineteen patients showed sustained remission over the first 12 months of prospective data collection. In these cases, retrospective data were needed to determine relapse and time to relapse over the period up to 24 months. Concerning these data, in one patient, the general practitioner provided us with information, and in seventeen cases, we obtained information from the patient's treating psychiatrist or mental health care provider. One patient wrote us a letter to declare sustained remission but refused both further data collection through a physician and an interview. In fourteen patients, we cross-validated the information in an interview with the patient. Five patients refused or could not participate in an interview. One patient was lost to follow-up at 57 weeks and had not relapsed. All 34 patients were included in the analyses.

Table 1 summarizes the demographic and baseline clinical characteristics of the total sample. The mean age was 63 years, and 56% were female. The median HRSD score prior to ECT was 28, and the median duration of the index episode was 36 weeks. Psychotic features and medication resistance were observed in 56% and 59% of the patients, respectively. Among medication-resistant patients, 52.6% and 31.6% had ATHF scores of 4 and 5, respectively. In only 15.8% of medication-resistant patients, the ATHF score was 3. Thus, the level of medication resistance was relatively high.

TABLE 1. Demographic and baseline clinical characteristics

Variable	Total sample (n=34)
Age, mean (SD), years	63 (11)
Female sex, n (%)	19 (56)
Episode duration, median (25th; 75th percentile), weeks	36 (16; 73)
HRSD score prior to ECT, median (25th; 75th percentile)	28 (25; 35)
Psychotic features, n (%)	19 (56)
Medication resistance, n (%)	20 (59)

Abbreviations: HRSD, Hamilton Rating Scale for Depression; ECT, electroconvulsive therapy.

All patients received nortriptyline with a plasma level within the target range. Of 19 patients who entered the second-year follow-up in remission, 17 continued on nortriptyline throughout the period up to 24 months. One patient stopped after the first year, and for the remaining patient, the status is unknown.

Seventeen patients (50%) relapsed within 2 years after successful ECT. The relapse rates at 6 months and at one year were 32% and 44%, respectively. Among patients who relapsed, 64.7% did so within the first 6 months, another 23.5% relapsed during the second half of the first-year follow-up, and only two patients (11.8%) relapsed during the second-year follow-up. The median time to relapse for the total sample was 18 weeks (25th; 75th percentile: 5; 41).

Table 2 summarizes the outcomes of the univariable Cox regression survival analyses. These analyses showed no significant impact of age, sex or episode duration prior to ECT on the relapse rate. In patients with psychotic features, in more severely depressed patients, and in patients who were medication resistant prior to ECT, the hazard ratios for relapse at 2 years post-ECT were 0.33 (CI 0.12−0.89; *p*=0.029), 0.88 (CI 0.80−0.98; *p*=0.014), and 4.48 (CI 1.28−15.73, *p*=0.019), respectively, indicating that the presence of psychotic features, a higher severity of depression, and absence of medication resistance

prior to ECT predict long-term remission. Cox proportional hazards assumptions were met. Figure 1 shows the survival plots for the significant clinical predictors.

TABLE 2. Univariable Cox regression survival analyses of risk factors for relapse after successful ECT

Variable	HR	95% CI	*P*-value
Age	1.01	0.96−1.05	0.953
Female sex	1.66	0.62−4.50	0.316
Episode duration	1.00	0.99−1.01	0.617
Severity of depression (HRSD score prior to ECT)	0.88	0.80−0.98	**0.014**
Psychotic features	0.33	0.12−0.89	**0.029**
Medication resistance	4.48	1.28−15.73	**0.019**

Abbreviations: ECT, electroconvulsive therapy; HR, hazard ratio.
Statistically significant p-values are highlighted in bold.

FIGURE 1. Survival plots for the significant clinical predictors
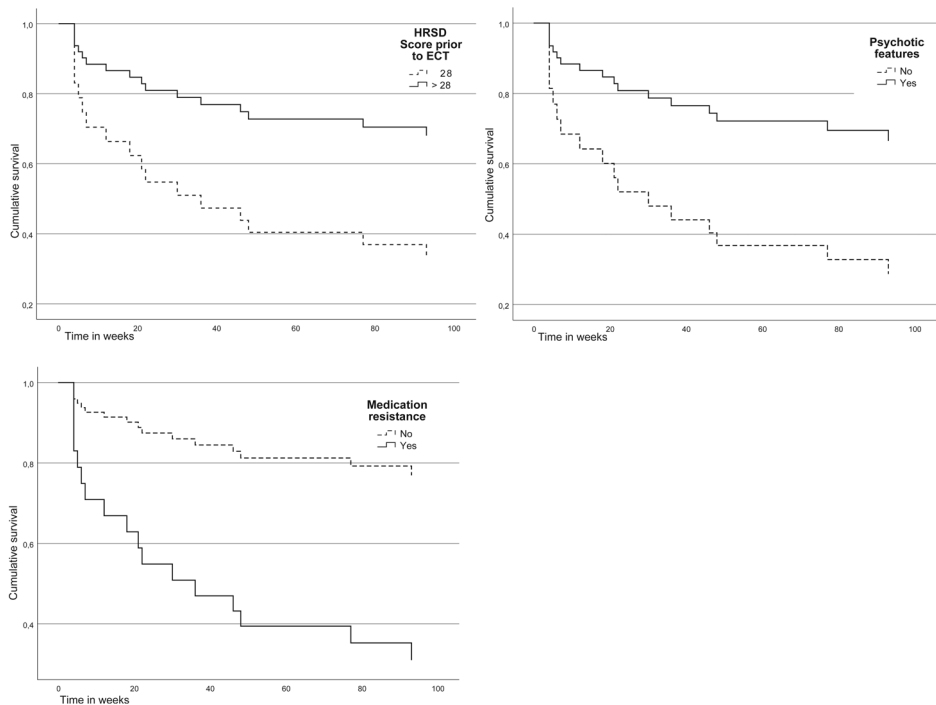
Abbreviations: HRSD, Hamilton Rating Scale for Depression; ECT, electroconvulsive therapy.
For the purpose of visualisation, the HRSD score prior to ECT (symptom severity) was dichotomized using a median split.

DISCUSSION

Main findings

In patients with severe major depression who attained remission to a course of bilateral ECT, the relapse rate at two years was 50%. Among patients who relapsed, 64.7% did so within the first 6 months, another 23.5% relapsed during the second half of the first-year follow-up, and only two patients (11.8%) relapsed during the second-year follow-up. The median time to relapse was 18 weeks. The two-year outcome was significantly more favourable in patients with psychotic features, with a higher severity of depression, and without medication resistance prior to ECT. In the current study, age, sex and episode duration did not affect the relapse rate.

Comparison with previous studies

Previous prospective studies on predictors of relapse after successful ECT for major depression are limited, and none of them had a follow-up period longer than a year. In a 6-month follow-up study by Sackeim et al. (9), remitters to ECT were randomized to receive either placebo or nortriptyline or nortriptyline-lithium. The relapse rates were 84%, 60% and 39%, respectively. In a 6-month follow-up study by Prudic et al. (4), 50% of remitters to ECT receiving nortriptyline-lithium or venlafaxine-lithium relapsed. In a 3-month follow-up study by Yang et al. (12), 58% of remitters to ECT receiving treatment-as-usual relapsed. Compared to these three studies, our relapse rates of 32% at 6 months and 44% at 1 year were considerably lower. Our relapse rate at 6 months (32%) was even more favourable than the relapse rate in Sackeim's nortriptyline-lithium group (39%). Our favourable outcomes might be explained by a larger proportion of patients with psychotic features in our study (56%). In Sackeim's nortriptyline group, Sackeim's nortriptyline-lithium group, and Prudic's study, 37%, 43% and 25% of patients suffered from psychotic depression, respectively. Yang et al. did not mention the proportion of patients with psychotic features. Their excessive relapse rate at 3 months might be due to suboptimal continuation pharmacotherapy; almost all patients received a modern antidepressant post-ECT. Jelovac et al. (3) conducted a one-year follow-up study in which remitters to ECT received treatment as usual. In addition to antidepressants, patients frequently used lithium (44%), antipsychotics (61%), anticonvulsants (28%), benzodiazepines (34%) and Z-hypnotics (46%). Lithium, antipsychotics and anticonvulsants might reduce relapse rates, especially in patients with bipolar depression (21), diagnosed in 23% of patients. Benzodiazepines and Z-hypnotics might mask relapse. Our relapse rate at one year (44%) was approximately equal to the relapse rate found by Jelovac et al. (39%). In interpreting

these figures, it should be taken into account that our patients received nortriptyline monotherapy, whereas Jelovac's patients used multiple psychotropic drugs. In a 6-month naturalistic follow-up study by Wagenmakers et al. (6), 33% of ECT remitters relapsed. Our relapse rate at 6 months (32%) was comparable; however, our patients were treated with nortriptyline monotherapy, whereas almost 40% of their patients received a combination pharmacotherapy, and approximately 10% received continuation ECT.

In line with most previous studies, we found that the presence of psychotic features, a higher severity of depression, and absence of medication resistance prior to ECT were predictors of long-term remission after successful ECT. Concerning medication resistance, the studies by Jelovac et al. (3) and Prudic et al. (4) failed to demonstrate an effect of medication resistance on relapse post-ECT. This might be explained by the fact that in our patient sample, the level of medication resistance was relatively high, possibly higher than in the study by Jelovac et al. and Prudic et al. We did not find an effect of age, sex or episode duration on relapse after successful ECT. In our sample, the mean age was 63 years, and only 3 patients were younger than 50 years. Concerning age, our rather homogeneous patient sample might have prevented us from finding an association between age and relapse post-ECT. The same might apply to episode duration; most patients in our sample had an episode duration of at least 6 months (68%), and in many patients, the index episode lasted for at least one year (44%). Heijnen et al. (22) found that psychotic features and psychomotor retardation mediate the association between older age and ECT efficacy. Perhaps this is also true for the association between age and relapse post-ECT, providing a rationale for heterogeneous results found in the literature for the effect of age on relapse post-ECT. The associations between sex and relapse post-ECT and between episode duration and relapse post-ECT might also be mediated by other factors, explaining inconsistent findings (8-11, 13) in the literature.

Strengths and limitations

A strength of the current study is that prior to follow-up, all patients participated in an RCT comparing nortriptyline and placebo during a course of bilateral ECT. Strict criteria were used to diagnose major depression. Almost all patients (94%) also participated in a one-year prospective follow-up study with plasma level targeted open-label nortriptyline. Patients were kept free from all psychotropic medications aside from nortriptyline. In the second-year follow-up, 90% of the patients continued on nortriptyline monotherapy. Another strength is the relatively long duration of the follow-up period of two years.

Limitations of the current study are the small sample size and the retrospective data collection for the second-year follow-up. One could argue that relapses might have been

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missed in the second-year follow-up. However, this has probably not had a great effect on our results, since most patients relapsed in the first 6 months post-ECT. In addition, during the second-year follow-up, most people were under psychiatric outpatient care, so any relapse would likely have been noticed.

Clinical implications

Research shows that ECT for major depression is particularly effective in patients with psychotic features, a higher severity of depression and without medication resistance prior to ECT (23, 24). In our and other studies, these patients also had a favourable long-term prognosis post-ECT. Therefore, in this specific group of depressed patients, ECT should be considered as a first-step treatment. Our study showed that most relapses post-ECT occurred within the first 6 months, which is a well replicated finding (2-4, 6, 9, 10). Thus, in this period, patients and treating psychiatrists need to be especially alert to early symptoms of relapse. In general, psychiatrists tend to intensify follow-up after successful ECT in patients who were the most severely depressed prior to ECT. Counterintuitively, our study showed that patients without psychotic features and with a lower severity of depression require at least equal or even closer attention during follow-up treatment because they are at higher risk of relapse. These patients probably need more intensive continuation treatment post-ECT. Whether this involves antidepressant medication or continuation ECT or both is a scope for future research. Finally, a sustained remission rate of 50% over two years in patients with severe major depression who were treated with nortriptyline monotherapy after successful ECT is encouraging.

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CHAPTER 8

General discussion

GENERAL DISCUSSION

The research in this thesis was designed to add to the limited and inconclusive literature on the influence of an adjuvant antidepressant on electroconvulsive therapy (ECT) outcomes, and on clinical predictors for relapse after successful ECT. We aimed (I) to determine whether the addition of nortriptyline to a course of ECT enhances its efficacy and prevents post-ECT relapse and (II) to identify clinical predictors for long-term remission after successful ECT.

ECT is considered the most effective treatment for severe major depression (1). Most patients receive ECT because they do not respond to antidepressant medication trials (2). Approximately 50% of medication-resistant patients attain remission following ECT (3). Despite continuation pharmacotherapy, almost 40% of those in remission will relapse within 6 months, and 50% will relapse within a year (4). Therefore, optimizing ECT in terms of both increasing remission rates and reducing relapse rates would be of considerable clinical significance. To ensure an effective, individually tailored continuation treatment after successful ECT, more extensive knowledge about predictors for relapse or sustained remission is needed. Based on our findings, we aimed to provide recommendations for clinical practice to optimize ECT.

The following main questions concerning ECT in patients with severe major depression will be addressed:
1. Are a longer episode duration and medication resistance prior to ECT predictors of poor ECT outcomes?
2. Does an adjuvant antidepressant during a course of ECT enhance its efficacy?
3. Does an adjuvant antidepressant during a course of ECT prevent relapse after successful treatment?
4. Which clinical factors predict long-term remission after successful ECT?

This chapter will provide a general discussion of the main findings, including methodological considerations. We will discuss how our results relate to the literature. Additionally, we will provide recommendations for clinical practice and future research.

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MAIN FINDINGS

Are a longer episode duration and medication resistance prior to ECT predictors of poor ECT outcomes in patients with severe major depression?

The limited literature on the influence of episode duration on ECT outcomes (5-12) at the time prompted the retrospective chart study described in **Chapter 2.** We reviewed 56 patient records to investigate the influence of episode duration on response and remission to ECT. The odds of response and remission increased by a factor of 1.019 (p=0.35, 95% CI: 0.98−1.06) and 1.003 (p=0.85, 95% CI: 0.97−1.04), respectively, for each additional month in an episode.

Our findings suggest that a longer episode duration does not predict poor ECT outcomes, which is inconsistent with recent literature showing that a longer episode duration predicts decreased efficacy of ECT (13, 14). The homogeneity of our patient sample might have prevented us from demonstrating this association; almost all patients in our study had a relatively long episode duration (93% ≥ 6 months and 68% ≥ 1 year). Remarkably, despite this long episode duration, the response rate (71%) and remission rate (40%) were relatively high. Unlike some other studies (9, 10), we refrained from giving patients benzodiazepines during the course of ECT, we used bilateral ECT in almost all patients, and the ECT course was continued as long as the patient improved. These factors might have contributed to our favourable findings. Episode duration was assessed retrospectively, which introduced a certain inaccuracy, representing a limitation of our study. Our limited sample size did not seem to have had an influence on our results since we found no effect at all.

We conducted another retrospective chart study, described in **Chapter 3**, since the literature on the influence of medication resistance was limited and inconclusive at the time (15-18). We reviewed 41 patient records to investigate the influence of medication resistance on response and remission rates to ECT. Response rates in patients with and without medication resistance were 72% and 67%, respectively (Fisher's exact test: p>0.2). The remission rate in patients without medication resistance (50%) was almost twice the remission rate in medication-resistant patients (28%). However, this difference was not statistically significant (Fisher's exact test: p>0.2).

Our findings suggest that medication resistance is not associated with a decreased response rate for ECT and that an association with a decreased remission rate with ECT may exist. The latter finding is consistent with the current literature; two recent meta-analyses (3, 13) clearly showed that medication resistance is strongly associated with a poor ECT outcome. The meta-analysis by Heijnen et al. (3) showed remission rates of 48% and 65% in patients with and without medication resistance, respectively. The meta-

analysis by Haq et al. (13) showed response rates of 58% and 70% in patients with and without medication resistance, respectively. In our study, a larger sample size might have resulted in a significant effect. Another limitation of our study was that medication resistance was established retrospectively, which is less accurate.

In conclusion, based on the current body of knowledge, both a longer episode duration and medication resistance are generally accepted to predict decreased efficacy of ECT for severe major depression. We were not able to identify these associations, probably due to methodological shortcomings. A longer episode duration and medication resistance often correlate (14). Since both factors are strongly associated with poor ECT outcomes, one should avoid taking too long for pharmacological treatment prior to ECT. Since studies on the duration of major depression are limited, the definition of a long episode duration remains unresolved. We suggest that patients with severe major depression, especially those with psychomotor symptoms (14), should be referred for ECT within 6 months of the onset of depression.

Does an adjuvant antidepressant during a course of ECT for severe major depression enhance its efficacy?

The patient described in **Chapter 4** showed a slow and limited response to ECT mono-therapy and a fast and good response to a subsequent course of ECT combined with imipramine, which suggests a synergy between ECT and imipramine.

Seeking evidence to support the findings from our case report, we performed a systematic review and meta-analysis. In **Chapter 5,** we present the resulting overview of the literature regarding the influence of an adjuvant antidepressant on the efficacy of ECT. Nine mostly dated randomized controlled trials (RCTs) met the inclusion criteria, only one of which was assessed to be of good quality. Thus, methodological concerns limit the interpretation of the results of the RCTs. Three categories of antidepressants showed the same small to moderate effect sizes, i.e., tricyclic antidepressants (TCAs): Hedges' g 0.32 (95% CI: 0.14 to 0.51) (k = 6), with low heterogeneity (I^2: 4%, p=0.39); selective serotonin reuptake inhibitors/serotonin noradrenaline reuptake inhibitors (SSRIs/SNRIs): Hedges' g 0.27 (95% CI: 0.03 to 0.52) (k = 2), with a lack of heterogeneity (I^2: 0%, p=0.89); and monoamine oxidase inhibitors (MAOIs): Hedges' g 0.35 (95% CI: -0.07 to 0.77), with moderate heterogeneity (I^2: 43%, p=0.17) (k = 3). The effect sizes of TCAs and MAOIs were most likely underestimated due to insufficient doses in most of the included studies. Overall, these findings are in line with our case report and suggest that an adjuvant antidepressant might increase the efficacy of ECT. Although effect sizes are small to moderate, they are clinically relevant since they reflect an add-on effect to ECT.

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Since only one RCT, i.e., the study by Sackeim et al. (19), included in our systematic review and meta-analysis was assessed to be of good quality, we designed a trial to add to the limited literature. In **Chapter 6,** we investigated the influence of adjuvant nortriptyline on the efficacy of ECT. One could argue that imipramine as a reuptake inhibitor of both serotonin and noradrenaline might be more effective than nortriptyline as a reuptake inhibitor of noradrenaline alone. However, clear evidence for the superior efficacy of imipramine compared with nortriptyline in treating major depression is lacking. Only one study compared both antidepressants head to head and showed that imipramine and nortriptyline were equally effective; 74 female outpatients with 'primary depressive illness' were treated with either nortriptyline 150 mg/day or imipramine 150 mg/day for a period of up to 6 weeks (20). Concerning side effects, nortriptyline is known to be tolerated better than imipramine, since it has a relatively lower affinity for histamine H1 and muscarinic M1 receptors (21). Therefore, if a TCA is indicated, nortriptyline is generally preferred in elderly patients (22, 23). We chose nortriptyline instead of imipramine since a superior effect of imipramine has not been demonstrated, and at our department, many elderly patients are indicated for ECT. Moreover, by using nortriptyline, we were able to compare our results with the results from the study by Sackeim et al. (19) in which nortriptyline was used.

We performed a double-blind, placebo-controlled RCT to test the hypotheses that starting nortriptyline at the onset of ECT, rather than after ECT completion, would result in (I) increases in the response and remission rates and (II) faster times to response and remission. We included 47 patients with severe major depression who received either nortriptyline or placebo during a course of bilateral ECT. In the nortriptyline group, 83% of patients showed a response, and 74% attained remission. In the placebo group, these figures were 81% ($\chi^2(1) = 0.005$; $p=0.945$) and 73% ($\chi^2(1) = 0.008$; $p=0.928$), respectively. Additionally, in the nortriptyline group, the time to response and time to remission were 5.6 and 7.2 weeks, respectively. In the placebo group, these figures were 6.7 (log rank $\chi^2(1) = 1.015$; $p=0.314$) and 8.0 (log rank $\chi^2(1) = 0.27$; $p=0.602$) weeks, respectively.

Our findings suggest that the addition of nortriptyline to ECT for severe major depression does not enhance its efficacy. Against expectations, our findings did not support the study hypotheses and were not in line with either the results of our meta-analysis or the results of the study by Sackeim et al. (19). Sackeim et al. conducted an RCT that assigned 319 patients with major depression to right unilateral or bilateral ECT and to adjuvant nortriptyline, venlafaxine, or placebo. ECT was administered with an optimal stimulus dose in only 10% of patients who received right unilateral ECT. The remission rates were more favourable in patients who received nortriptyline (63%) or venlafaxine (60%) compared with placebo (49%), with a statistically significant difference only

between nortriptyline and placebo. Compared with those in the study by Sackeim et al., our remission rates of 74% in the nortriptyline group and 73% in the placebo group were considerably higher, possibly due to a larger proportion of patients with psychotic features (44% in our study versus 20% in the study by Sackeim et al.). Moreover, in our study, all patients were treated with bilateral ECT with an optimal stimulus dose. Additionally, our patient sample consisted of a high proportion of medication-resistant patients (58%). This figure is possibly higher than that in the study by Sackeim et al. and probably higher than those in the studies included in our meta-analysis, since five of the nine studies in the meta-analysis were conducted in the sixties. At that time, ECT was a first-line treatment.

We assume that our highly effective ECT and the relatively large percentage of medication-resistant patients might have prevented us from identifying an add-on effect of nortriptyline to ECT. Further increasing the proportion of responders and remitters by applying any additional treatment is exceptionally difficult due to high response and remission rates (ceiling effect) (24), and medication-resistant patients with severe major depression will show a weak response to any subsequent treatment, including an adjuvant antidepressant during the course of ECT (3). Post hoc analyses of the results of our RCT showed that the remission rate and time to remission in medication-resistant patients (69% and 8.6 weeks) were lower and longer than those in patients without medication resistance (79% and 6.2 weeks, respectively). However, these differences were not statistically significant. Notably, despite a high proportion of patients with medication resistance, which is a well-known predictor of a poor ECT outcome, the response and remission rates in our RCT were very high. Our favourable findings might be explained by diagnosing patients during a routine medication-free period; refraining from giving patients benzodiazepines during the course of ECT (25, 26); the use of bilateral ECT; the use of empirical dose titration and subsequent use of an adequate stimulus dose; adjusting the stimulus dose setting during the course of ECT to maintain a motor seizure duration of at least 25 s, if necessary, up to the device maximum of 1008 mC; and continuing ECT as long as the patient improves, aiming for full remission (27).

Concerning studies on the influence of an adjuvant TCA during a course of ECT, in only two studies, the study by Sackeim et al. (19) and our RCT (28), a TCA was adequately dosed, i.e., a dosage based on plasma levels. Both studies used nortriptyline. Sackeim et al. (19) also used venlafaxine as an add-on medication to ECT. However, at the dosage used (mean 187 mg/day), venlafaxine was comparable to an SSRI instead of a TCA.

In conclusion, adding an antidepressant to ECT aiming to increase its efficacy is only reasonable in less severely depressed patients without medication resistance. Nortriptyline has the best evidence and is safe to use with ECT (2, 19, 29). In severely

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depressed patients with psychotic features and medication resistance, ECT is a highly effective treatment to which combination with an antidepressant has no added value. The key to successful ECT is optimal indication and administration. If, for whatever reason, ECT cannot be performed optimally, we suggest adding an antidepressant to ECT.

Does an adjuvant antidepressant during a course of ECT for severe major depression prevent relapse after successful treatment?

High relapse rates after successful ECT prompted our one-year open-label follow-up study with nortriptyline in patients who recovered from depression during the RCT described in the previous paragraph. We aimed to test the hypotheses that starting nortriptyline at the onset of ECT, rather than after ECT completion, would result in (I) a decrease in the relapse rate and (II) a slower time to relapse. We included 31 patients and present the data in **Chapter 6**. The dosage of nortriptyline was adjusted to maintain therapeutic plasma levels of 50-150 µg/L. Patients were kept free from all psychotropic medications aside from nortriptyline. In patients who had received nortriptyline during the RCT, 47% relapsed at a mean of 34 weeks after successful ECT. In patients who had received placebo, these figures were 36% ($\chi^2(1) = 0.408$; $p=0.524$) and 40 weeks (log rank $\chi^2(1) = 0.437$; $p=0.509$).

Our findings suggest that an adjuvant antidepressant during the course of ECT neither prevents relapse nor affects the time to relapse after ECT completion. Unfortunately, our findings did not support the study hypotheses. However, they are in line with previous studies. Only a few RCTs have tried to demonstrate a reduction in the relapse rate by starting an antidepressant at the onset of ECT and continuing that medication after ECT completion. These studies showed that a 6-month continuation of paroxetine (30); a 6-month continuation of nortriptyline or venlafaxine, both with lithium added (31); and a 12-week continuation of agomelatine (32) did not significantly affect the relapse rates.

In conclusion, continuation pharmacotherapy undoubtedly reduces the relapse rate after successful ECT (4, 33, 34). However, despite continuation pharmacotherapy or continuation ECT, 50% of patients in remission will relapse within one year (4). Combining ECT with an antidepressant and subsequently continuing the antidepressant after ECT completion has no prognostic benefits. To prevent relapse, we suggest implementing at least the following two strategies: applying ECT only in patients who are likely to respond to ECT and continuing the course of ECT as long as the patient improves, aiming for full remission (27). Additionally, other strategies must be considered, such as tapering ECT instead of abruptly stopping treatment and more intensive continuation pharmacotherapy, continuation ECT, or both after successful ECT (35).

Which clinical factors predict long-term remission after successful ECT for severe major depression?

To ensure an effective, individually tailored continuation treatment, more evidence on predictors for relapse after successful ECT is needed. In **Chapter 7,** we performed a follow-up study to determine clinical predictors for relapse or sustained remission two years after ECT for severe major depression. This study is embedded in the RCT and subsequent prospective one-year follow-up study, which are both described in the previous two paragraphs. For the first year post-ECT, we used data from this prospective follow-up study. Additionally, for the second year post-ECT, we conducted a retrospective observational cohort study. We included 34 patients. The relapse rate at two years was 50%. Among patients who relapsed, 64.7% did so within the first six months, another 23.5% relapsed during the following 6 months, and only two patients (11.8%) relapsed during the second-year follow-up. In patients with psychotic features prior to ECT, in patients with a higher symptom severity prior to ECT, and in patients who were medication-resistant prior to ECT, the hazard ratios for relapse two years post-ECT were 0.33 (p=0.029), 0.88 (p=0.014), and 4.48 (p=0.019), respectively.

Our findings suggest that the presence of psychotic features, more severe depression, and the absence of medication resistance prior to ECT predict long-term remission. We found no association between relapse rate and age, sex or episode duration. Remarkably, patients with psychotic depression prior to ECT have the most favourable prognosis after ECT completion, which is a well-replicated (34, 36-38) and important finding given the severity of this subtype of depression. Previous studies show conflicting results concerning prior medication resistance as a predictor for relapse after ECT completion. Similar to our study, some studies (18, 39, 40), but not others (8, 15), found an association between prior medication resistance and a higher risk of relapse. In a recent study by Jelovac et al. (38), medication resistance had no impact on relapse. However, this finding might be confounded, since medication-resistant patients were significantly younger and significantly more likely to have nonpsychotic depression, both of which are predictors for relapse.

All studies used the Antidepressant Treatment History Form (ATHF) (41) to determine medication resistance. This instrument labels an inadequate response to a 4-week treatment with an adequate dosage of an SSRI as 'medication-resistant'. Most psychiatrists would not consider this a strong antidepressant medication trial. Perhaps our patients were more treatment resistant than patients in other studies, since they had participated in an RCT in which an indication for ECT was medication resistance, i.e., at least an inadequate response to a plasma level targeted dosage of TCA for ≥ 4 weeks or venlafaxine > 225 mg/day for ≥ 4 weeks.

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Contrary to previous studies (4, 31, 38), we found no association between relapse and either age or episode duration. Our patient sample consisted of relatively old patients, with a mean age of 63 years, and only 3 patients were younger than 50 years. Furthermore, most patients in our sample had an episode duration of at least 6 months (68%), and in 44% of patients, the index episode lasted for at least one year. Concerning age and episode duration, our rather homogeneous patient sample might have prevented us from finding an association between these clinical factors and relapse after successful ECT.

In conclusion, most relapses after successful ECT for severe major depression occur in the first 6 months. Therefore, this period warrants close and careful patient follow-ups. Perhaps counterintuitive, patients (I) with lower symptom severity and/or (II) without psychotic features and/or (III) with medication resistance prior to ECT require equal or even more attention than patients with psychotic depression prior to ECT, since the risk of relapse is much higher in the former group. To prevent relapse, at-risk patients require a more intensive continuation treatment.

CONSIDERATIONS ABOUT RELAPSE PREVENTION AFTER SUCCESSFUL ECT

Since almost all patients will relapse if no continuation treatment is used (34), patients usually receive antidepressant medication after ECT. Although equally effective in preventing relapse (42), continuation ECT is used less frequently.

A study by Sackeim et al. (34) is the most convincing study on relapse prevention by means of continuation pharmacotherapy. In this 6-month RCT, patients were randomized to receive placebo, nortriptyline or nortriptyline + lithium after successful ECT. The relapse rates were 84%, 60%, and 39%, respectively, with a statistically significant difference between nortriptyline + lithium and placebo. Although this study showed a clear benefit of continuation pharmacotherapy and the addition of lithium in particular, the absolute relapse rates were still high. A meta-analysis by Jelovac et al. (12) found relapse rates of 37% at 6 months and 51% at one year post-ECT, despite continuation pharmacotherapy.

A study by Kellner et al. (42) and a meta-analysis by Elias et al. (43) are the most convincing studies on relapse prevention by means of continuation ECT. In the 6-month RCT by Kellner et al., patients were randomized to continuation pharmacotherapy with nortriptyline + lithium or continuation ECT after successful ECT. The relapse rates were 32% and 37%, respectively, with no statistically significant difference between the two groups. The meta-analysis by Elias et al. (43) showed that continuation ECT + pharmacotherapy

was associated with significantly fewer relapses than pharmacotherapy alone at 6 months and one year after successful ECT. Since ECT was combined with antidepressant medication in four of five included RCTs, they were not able to perform a meta-analysis of continuation ECT alone.

In 2019, Gill and Kellner published recommendations for the use of continuation ECT after successful ECT for major depression (35). Their recommendations based on both published evidence and clinical consensus are thorough and useful for clinical practice. They outline the following general principles: (I) some form of treatment against relapse of depression is required after every successful course of ECT, (II) this treatment should include antidepressant medication ± lithium ± continuation ECT, and (III) this treatment should also include psychosocial interventions and psychotherapy (cognitive behavioural therapy) as indicated, but psychological therapies should rarely be used without con-comitant biological prophylaxis.

Regarding the choice between antidepressant medication ± lithium ± continuation ECT, Gill and Kellner argue that continuation ECT is usually not indicated after a patient's first course of ECT but should be considered after a second or consequent course of ECT. They suggest that antidepressant medication ± lithium should be the first-line prophylaxis after the first course of ECT.

Based on the findings from the research in this thesis, we would like to suggest some adjustments to Gill and Kellner's recommendations. First, concerning continuation pharmacotherapy, Gill and Kellner prefer venlafaxine over nortriptyline if a patient has not been on any antidepressant in the past. However, in the study by Prudic et al. (31), venlafaxine and nortriptyline, both combined with lithium, were equally effective in preventing relapse, suggesting that nortriptyline is an equivalent alternative. We prefer nortriptyline, since an advantage of nortriptyline over venlafaxine is the ability to monitor therapeutic plasma levels, which facilitate treatment. Moreover, nortriptyline has been studied the most, and in our prospective follow-up study, relapse rates were more favourable compared to those in other studies, including the study by Prudic et al. (31), while patients were treated with nortriptyline monotherapy. Second, Gill and Kellner recommend considering the addition of lithium to an antidepressant if a patient suffered from psychotic depression prior to ECT. However, this recommendation is based on only one study, a narrative review of the literature (44). Based on the findings from our follow-up study in which patients received nortriptyline monotherapy, we would rather recommend the combination of an antidepressant and lithium in patients without psychotic features, since these patients were much more likely to relapse after successful ECT. Therefore, patients without psy-chotic features probably need more intensive continuation treatment to prevent relapse,

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while patients with psychotic depression prior to ECT appeared to remain well with nortriptyline monotherapy. Third, after a patient's second or subsequent course of ECT, Gill and Kellner recommend adding continuation ECT to antidepressant medication, among others, if a patient had a history of psychotic depression. However, this recommendation is based on only one study with a design that might have caused continuation ECT to have a more favourable outcome than continuation pharmacotherapy, since all patients attained remission following ECT + nortriptyline and were then assigned to continuation of ECT + nortriptyline or nortriptyline alone (45). Moreover, all patients were diagnosed with psychotic depression. Again, based on our findings, we would rather recommend a combination of continuation ECT and antidepressant medication in patients without psychotic features. These patients were more likely to relapse after successful ECT and therefore probably need more intensive continuation treatment to prevent relapse.

Furthermore, patients with lower symptom severity prior to ECT and patients who were medication resistant prior to ECT relapsed more often than severely depressed patients and nonmedication-resistant patients. The former group probably also needs a more intensive continuation treatment after successful ECT to prevent relapse.

RECOMMENDATIONS FOR CLINICAL PRACTICE

General recommendations about the place of ECT in the treatment algorithm
- Patients with severe major depression, especially those with psychomotor symptoms, should be referred for ECT within 6 months of the onset of depression. These patients respond well to ECT, with the beneficial outcome being reduced in patients with a longer episode duration.
- If patients with severe major depression suffer from psychotic features, ECT should be the first step in the treatment algorithm. These patients respond well to ECT and have a favourable long-term prognosis after successful ECT.

Recommendations to increase the remission rate to ECT
- Ensure optimal indication for and administration of ECT
  - Establish a proper diagnosis during a routine medication-free period.
  - Consider the use of bilateral ECT in patients with severe major depression.
  - Use empirical dose titration and a subsequent adequate stimulus dose of at least 1.5 times the seizure threshold in bilateral ECT.

- Adjust the stimulus dose setting during the course of ECT to maintain a motor seizure duration of at least 25 s, if necessary, up to the device maximum of 1008 mC.
- Refrain from giving patients benzodiazepines during the course of ECT.
- In less severely depressed patients without psychotic features and/or without medication resistance prior to ECT, consider combining ECT with an adequately dosed TCA from the start of ECT. Nortriptyline has the best evidence.
- In patients with psychotic depression prior to ECT, a TCA should be started during the course of ECT to ensure an adequate plasma level at ECT completion. Consider combining ECT with an adequately dosed TCA from the start of ECT. Nortriptyline has the best evidence.

Recommendations to reduce the relapse rate after successful ECT
- Continue the course of ECT as long as the patient improves, aiming for full remission.
- Be especially alert to early symptoms of relapse in the first 6 months post-ECT, since most patients relapse during this period. Consider a follow-up, at least the first 6 months post-ECT, at an outpatient clinic specialized in care for patients who have received ECT.
- Counterintuitively, during follow-up, patients with lower symptom severity and/or without psychotic features prior to ECT require at least equal or even closer attention than patients with psychotic depression prior to ECT, since the risk of relapse is much higher in the former group of patients. The same applies to patients who are medication-resistant prior to ECT.
- In patients with major depression (I) with psychotic features and/or (II) with a higher severity of depression*, and/or (III) without medication resistance prior to ECT, consider TCA monotherapy as continuation treatment after successful ECT. Nortriptyline has the best evidence.
- In patients with major depressive disorder (I) without psychotic features and/or (II) with a lower severity of depression* and/or (III) with medication resistance, consider TCA + lithium as continuation treatment after the first course of successful ECT and continuation ECT after the second and consequent courses of successful ECT. Nortriptyline has the best evidence.

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*82.4% of patients in our sample suffered from severe depression (17-item HRSD score ≥ 24 (46)). The remaining six patients had a score of 20 (n=2), 22 (n=2) or 23 (n=2). The median HRSD score was 28, with 25th and 75th percentiles of 25 and 35, respectively. With regard to the severity of depression, the terms 'higher' and 'lower' should be considered in this context.

RECOMMENDATIONS FOR FUTURE RESEARCH

Improving remission rates to ECT

Patients who receive ECT often suffer from medication-resistant, severe major depression. Approximately 50% of these patients achieve remission following ECT, and increasing this remission rate would be of considerable clinical significance. Only two RCTs, i.e., the study by Sackeim et al. (16) and our own study (27), aiming to determine whether the addition of a TCA during a course of ECT enhances its efficacy have recently been published. These studies, which compared adequately dosed nortriptyline with placebo during a course of ECT, showed opposite results. Sackeim et al. (19) also used a relatively low dose of venlafaxine as an add-on medication to ECT, which was not significantly more effective than placebo. The use of imipramine and high-dose venlafaxine may not necessarily show the same results as the use of nortriptyline since these antidepressants have different pharmacodynamic profiles. For future research, an RCT comparing imipramine (dosage based on plasma levels) and/or venlafaxine (dosage of 300-375 mg/day) with a placebo during a course of ECT would be relevant.

Reducing relapse rates after successful ECT

Despite continuation pharmacotherapy (4) or continuation ECT (42) after successful ECT, almost 40% of patients will relapse within 6 months, and 50% will relapse within a year. Thus, even with continuation treatment, relapse rates are high. Along with the skewing of relapse to the first several weeks after ECT completion (31), future research on other strategies to maintain remission is needed. Evidence indicates that tapering ECT over a few weeks instead of the usual abrupt cessation of ECT might reduce the relapse rate. However, data are limited, and information regarding the optimal tapering schedule is lacking. Lisanby et al. (47) developed an algorithm to individualize the continuation ECT schedule aiming to adapt the frequency of ECT to symptom fluctuations to prevent overtreatment of those who do not need it and undertreatment of those who might have relapsed with a rigid dosing schedule. They tested their symptom-titrated, algorithm-based longitudinal ECT (STABLE) schedule, which included tapering ECT over 24 days (fixed ECT frequency: two ECTs in week 1, one ECT in week 2, and one ECT 10 days later), followed by continuation ECT over a period of 5 months (flexible ECT frequency). The algorithm identified 100% of patients who ultimately relapsed as requiring additional ECT at an average of 2.2 weeks before relapse while exposing 20% of sustained remitters to additional ECT. Since this was a retrospective study, whether an RCT would support the superior efficacy of this algorithm compared to a fixed dosing schedule for continuation

ECT would be interesting to explore. Additionally, studies on the optimal tapering schedule would be useful.

For adequately powered RCTs, multiple centres are needed. In the Netherlands, the indications for and administration of ECT may differ between centres but should be aligned in collaborative research. Although multicentre studies on improving remission rates with ECT and reducing relapse rates post-ECT are needed, this might be difficult to realize. Therefore, our recommendations for future research are challenging.

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APPENDICES

S U M M A R Y

Major depressive disorder (major depression) is a common, sometimes life-threatening mental illness that often has a major impact on daily life. Therefore, an effective treatment is essential. One treatment option is electroconvulsive therapy (ECT). Although ECT is the most effective treatment for patients with severe major depression, only 50-65% of them attain full remission following ECT. After successful ECT, approximately 50% of those in remission will relapse within a year. The aim of this thesis was to contribute to improving these results. We determined predictors of efficacy of ECT and predictors of relapse after successful ECT to better tailor treatment to the patient and thereby improve the remission and relapse rates. Furthermore, we investigated whether the addition of nortriptyline to a course of ECT enhances its efficacy and prevents relapse after successful ECT.

Predictors of efficacy of ECT

ECT is currently mainly used to treat medication-resistant patients with severe major depression. Medication resistance and a longer episode duration are often related. We investigated the influence of both factors on the efficacy of ECT. **Chapter 2** describes the results of a retrospective chart study (n=56) on the influence of episode duration. The odds of response (decrease in Hamilton Rating Scale for Depression (HRSD) score of ≥ 50%) and remission (HRSD score post-ECT of ≤ 7) increased by a factor of 1.019 and 1.003, respectively, for each additional month in an episode. Episode duration did not appear to affect ECT outcomes. **Chapter 3** describes the results of a retrospective chart study (n=41) on the influence of medication resistance. The response rates in patients with (72%) and without (67%) medication resistance were not significantly different. Patients without medication resistance were almost twice as likely to attain remission (50%) than medication-resistant patients (28%). Again, this difference was not significant. Medication resistance did not appear to affect the efficacy of ECT, certainly not the response rate. At the time when we conducted our two retrospective chart studies, the literature on the influence of episode duration and medication resistance on the efficacy of ECT was limited and inconclusive. Since then, evidence has increased, and both a longer episode duration and medication resistance are generally accepted to predict poor ECT outcomes. We were not able to identify these associations, probably due to homogenous patient samples in both studies and a relatively small patient sample in the second study.

Influence of an adjuvant antidepressant during a course of ECT on the efficacy of ECT

Chapter 4 is a case report in which we describe the outcome of two consecutive treatments with ECT in a patient with major depression with psychotic features: the first treatment was ECT monotherapy and the second treatment included ECT in combination with imipramine. The patient showed a faster and more complete response to the second course of ECT, which suggested a synergy between ECT and imipramine. Seeking evidence to support the findings from our case report, we performed a systematic literature search and a meta-analysis **(Chapter 5)**. The systematic search yielded an overview of all (n=12) studies published to date regarding the influence of an adjuvant antidepressant on the efficacy of ECT. Only randomized controlled trials (RCTs) (n=9) were included in the meta-analysis. Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors/ serotonin norepinephrine reuptake inhibitors (SSRIs/SNRIs) and monoamine oxidase inhibitors (MAOIs) showed the same small to moderate effect sizes, which are clinically relevant since they reflect an add-on effect to ECT. The effect sizes of TCAs and MAOIs were most likely underestimated due to suboptimal doses in most of the included studies. An adjuvant antidepressant appeared to have a beneficial effect on ECT outcomes. Since only one RCT included in our meta-analysis was of good quality, we designed an RCT to complement the limited amount of existing research. In **Chapter 6,** we present the results of this double-blind RCT, in which patients (n=47) received either nortriptyline or placebo during a course of bilateral ECT. The response and remission rates were not significantly different between the nortriptyline group (83% and 74%, respectively) and the placebo group (81% and 73%, respectively). In the nortriptyline group, the time to response and time to remission were 5.6 and 7.2 weeks, respectively, and in the placebo group, these figures were 6.7 and 8.0 weeks, respectively. Again, these differences were not significant. In our patient sample, which consisted of severely depressed patients who were often medication resistant (58%) and suffering from psychotic depression (44%), ECT was shown to be a highly effective treatment to which an antidepressant had no added value. Against expectations, our findings did not support the study hypotheses and were not in line with the results of our meta-analysis. We assume that our highly effective ECT and the relatively large percentage of medication-resistant patients might have prevented us from identifying an add-on effect of nortriptyline to ECT.

Influence of an adjuvant antidepressant during a course of ECT on relapse after successful ECT

High relapse rates after successful ECT prompted our one-year prospective follow-up study with open-label nortriptyline in patients (n=31) who fully recovered from depression

during the RCT described in the previous paragraph **(Chapter 6)**. In patients who had received nortriptyline during the RCT, 47% relapsed at a mean of 34 weeks after successful ECT. In patients who had received placebo, these figures were comparable (36% and 40 weeks). Starting nortriptyline at the onset of ECT, rather than after ECT completion, did not appear to prevent relapse after successful ECT and did not appear to affect the time to relapse. Although these findings did not support the study hypotheses, they were in line with the results from previous studies. Thus, to prevent relapse other strategies must be considered.

Predictors of relapse after successful ECT

The risk of relapse after successful ECT varies among patients. Identifying patients who are at increased risk for relapse to intensify their treatment regimen after successful ECT might prevent relapse. A limited number of studies have focused on predictors of relapse. These studies had relatively short follow-up periods and sometimes showed conflicting results. This prompted our follow-up study to determine clinical predictors of relapse two years after successful ECT for severe major depression **(Chapter 7)**. We used the data from the prospective follow-up study described in the previous paragraph. Second-year follow-up data were collected retrospectively. We included 34 patients in the follow-up cohort. The relapse rate at two years post-ECT was 50%, with most relapses occurring within the first 6 months. Patients with psychotic features, with a higher symptom severity, and without medication resistance prior to ECT appeared to have a more favorable long-term prognosis. No effect was found for age, sex or episode duration on the relapse rate.

In **Chapter 8,** we present a general discussion of the main findings of this thesis. We provide recommendations for clinical practice and for future research.

We conclude that a longer episode duration and medication resistance are generally accepted to predict decreased efficacy of ECT for severe major depression. Therefore, we recommend to refer patients with severe major depression for ECT within six months of the onset of depression. An exception is the presence of psychotic features; in patients with psychotic depression, ECT should be the first step in the treatment algorithm, since these patients respond well to ECT and have a favorable long-term prognosis after successful ECT. Additionally, we conclude that adding an antidepressant to ECT aiming to increase its efficacy is only reasonable in less severely depressed patients without medication resistance. Nortriptyline has the best evidence and is safe to use with ECT. In severely depressed patients with psychotic features and medication resistance, ECT is a highly effective treatment to which combination with nortriptyline has no added value.

Nevertheless, combining ECT with nortriptyline should still be considered to ensure an adequate plasma level at ECT completion. Finally, we conclude that starting nortriptyline at the onset of ECT, rather than at ECT completion, has no prognostic benefits. Among severely depressed patients who attained remission to ECT, those who were least severely depressed, nonpsychotic and medication-resistant prior to ECT are at increased risk of relapse after successful ECT. To prevent relapse, these patients need more intensive continuation treatment with, for example, nortriptyline in combination with lithium or continuation ECT, while in patients with psychotic depression prior to ECT nortriptyline monotherapy is sufficient. Since most relapses occur within the first six months after successful ECT, we emphasize the relevance of close and careful patient follow-up in this period. Counterintuitively, during follow-up, patients with lower symptom severity and/or without psychotic features prior to ECT require at least equal or even closer attention than patients with psychotic depression prior to ECT. The same applies to patients who are medication-resistant prior to ECT.

For future research, an RCT aiming to determine whether the addition of imipramine and/or venlafaxine to ECT enhances its efficacy and prevents relapse after successful ECT would be relevant. Additionally, studies on the optimal tapering schedule for ECT and studies exploring the superior efficacy of an individualized continuation ECT schedule compared to a fixed dosing schedule would be useful.

SAMENVATTING

Een depressieve stoornis (depressie) is een veelvoorkomende, soms levensbedreigende ziekte, die vaak een grote impact heeft op het dagelijks leven. Een effectieve behandeling is daarom essentieel. Eén van de behandelmogelijkheden is elektroconvulsietherapie (ECT). Hoewel ECT de meest effectieve behandeling is voor patiënten met een ernstige depressie, bereikt slechts 50-65% van hen een volledige remissie en valt na succesvolle ECT ongeveer 50% binnen een jaar terug. Het doel van dit proefschrift was een bijdrage leveren aan het verbeteren van deze cijfers. Om ECT en vervolgbehandeling na succesvolle ECT beter af te kunnen stemmen op de patiënt en daarmee de remissie- en terugvalpercentages te verbeteren, onderzochten wij voorspellers van de effectiviteit van ECT en van terugval na succesvolle ECT. Daarnaast hebben wij onderzocht of het toevoegen van nortriptyline aan een ECT kuur de effectiviteit van ECT verhoogt en terugval na succesvolle ECT voorkomt.

Voorspellers van effectiviteit van ECT

Een ernstige depressie met medicatieresistentie is tegenwoordig de belangrijkste indicatie voor ECT. Medicatieresistentie en een langere episodeduur zijn vaak aan elkaar gerelateerd. Wij onderzochten de invloed van beide factoren op de uitkomst van ECT. In **hoofdstuk 2** wordt een retrospectief status onderzoek (n=56) beschreven naar de invloed van episodeduur. Voor elke maand langere episodeduur nam de kans op respons (afname Hamilton Rating Scale for Depression (HRSD) score ≥ 50%) en remissie (HRSD score post-ECT ≤ 7) toe met respectievelijk een factor 1.019 en 1.003. Episodeduur leek niet van invloed te zijn op de effectiviteit van ECT. In **hoofdstuk 3** wordt een retrospectief status onderzoek (n=41) beschreven naar de invloed van medicatieresistentie. De kans op respons bij patiënten met (72%) en zonder (67%) medicatieresistentie was niet significant verschillend. Patiënten zonder medicatieresistentie hadden een bijna twee keer zo grote kans op remissie (50%) dan medicatieresistente patiënten (28%), echter dit verschil was niet significant. Medicatieresistentie leek niet van invloed te zijn op de effectiviteit van ECT, zeker niet op de uitkomstmaat respons. Ten tijde van onze twee retrospectieve status onderzoeken was de literatuur over de invloed van episodeduur en medicatieresistentie op de effectiviteit van ECT beperkt en verdeeld. Sindsdien zijn er meer studies verschenen en op basis daarvan wordt tegenwoordig algemeen aangenomen dat een langere episodeduur en medicatieresistentie duidelijke voorspellers zijn van een slechte uitkomst van ECT. Wij hebben deze associaties waarschijnlijk niet kunnen aantonen door homogene patiëntengroepen in beide studies en een relatief kleine patiëntengroep in de tweede studie.

Invloed van het toevoegen van een antidepressivum aan ECT op het effect van ECT

Hoofdstuk 4 is een casusbeschrijving over een patiënt met een recidiverende psychotische depressie. Wij beschrijven het beloop van twee opeenvolgende ECT kuren; de eerste met ECT monotherapie en de tweede met ECT in combinatie met imipramine. De patiënt herstelde sneller en vollediger op de tweede ECT kuur, wat een synergistisch effect van een combinatiebehandeling suggereerde. Om deze bevinding met bewijs te onderbouwen, voerden wij een systematisch literatuuronderzoek en een meta-analyse uit **(hoofdstuk 5)**. De systematische zoekopdracht leverde een overzicht op van alle (n=12) tot dan toe gepubliceerde onderzoeken naar de invloed van het toevoegen van een antidepressivum aan ECT op de effectiviteit daarvan. Alleen de gerandomiseerde gecontroleerde onderzoeken (RCTs) (n=9) werden geïncludeerd in de meta-analyse. Tricyclische antidepressiva (TCAs), selectieve serotonine heropname remmers/serotonine noradrenaline heropname remmers (SSRIs/SNRIs) en mono-amine oxidase remmers (MAOIs) hadden een vergelijkbare, kleine tot matige effectgrootte, wat klinisch relevant is omdat het een add-on effect bij ECT betreft. In de meeste studies werden suboptimale doseringen van TCAs en MAOIs gebruikt, waardoor het effect van deze antidepressiva waarschijnlijk is onderschat. Het toevoegen van een antidepressivum aan ECT leek een gunstige invloed op de uitkomst van ECT te hebben. Omdat slechts één RCT in onze meta-analyse een goede kwaliteit had, hebben wij als aanvulling op de beperkte hoeveelheid bestaand onderzoek een RCT opzet.

In **hoofdstuk 6** presenteren wij de uitkomsten van dit dubbelblinde onderzoek, waarin patiënten nortriptyline of placebo kregen tijdens een bilaterale ECT kuur. De respons- en remissiepercentages waren niet significant verschillend tussen de nortriptyline groep (respectievelijk 83% en 74%) en de placebogroep (respectievelijk 81% en 73%). De tijd tot respons en remissie was in de nortriptyline groep respectievelijk 5.6 en 7.2 weken en in de placebogroep 6.7 en 8.0 weken. Ook deze verschillen waren niet significant. In onze patiëntengroep, die bestond uit patiënten met een ernstige depressie, veelal met psychotische kenmerken (44%) en medicatieresistentie (58%), bleek ECT een zeer effectieve behandeling te zijn, waarbij toevoeging van nortriptyline geen meerwaarde leek te hebben voor uitkomst van ECT. Tegen de verwachting in ondersteunden onze bevindingen de studiehypothesen niet en waren zij niet in overeenstemming met de resultaten van onze meta-analyse. Waarschijnlijk hebben de zeer effectieve ECT en een relatief hoog percentage medicatieresistente patiënten ervoor gezorgd dat wij geen add-on effect van nortriptyline konden aantonen.

Invloed van het toevoegen van nortriptyline aan ECT op terugval na succesvolle ECT

Hoge terugvalpercentages na succesvolle ECT waren de aanleiding voor ons prospectief follow-up onderzoek van één jaar met open-label nortriptyline bij patiënten (n=31) die volledig herstelden van hun depressie tijdens de in de vorige paragraaf beschreven RCT **(hoofdstuk 6)**. Van de patiënten die tijdens de RCT nortriptyline hadden gekregen, viel 47% terug na gemiddeld 34 weken. Bij patiënten die placebo hadden gekregen, waren deze cijfers vergelijkbaar (36% en 40 weken). Het starten van nortriptyline bij aanvang van ECT, in plaats van na het staken van ECT, leek terugval na succesvolle ECT niet te voorkomen en de snelheid van terugval niet te beïnvloeden. Hoewel deze bevindingen de studiehypothesen niet ondersteunden, kwamen zij wel overeen met resultaten uit eerdere studies. Er zijn dus andere strategieën nodig om terugval na succesvolle ECT te voorkomen.

Voorspellers van terugval na succesvolle ECT

Het risico op terugval na succesvolle ECT verschilt tussen patiënten. Een mogelijke strategie om terugval te voorkomen, is het identificeren van hoogrisicopatiënten om hen een intensievere vervolgbehandeling te kunnen bieden. Er zijn een beperkt aantal studies naar voorspellers van terugval gedaan. Deze studies hadden een relatief korte follow-up periode en lieten soms tegenstrijdige resultaten zien. Dit was de aanleiding voor een follow-up studie naar klinische factoren die terugval tot twee jaar na succesvolle ECT voorspellen (**hoofdstuk 7**). Wij gebruikten de data uit het prospectieve follow-up onderzoek, beschreven in de vorige paragraaf. Data over het tweede jaar follow-up werden retrospectief verzameld. Er werden 34 patiënten geïncludeerd in het cohort, waarvan twee jaar na succesvolle ECT 50% was teruggevallen. Terugval vond vooral in de eerste zes maanden plaats. Patiënten met een psychotische depressie, met ernstiger symptomen, en zonder medicatieresistentie voorafgaand aan ECT bleken een gunstiger lange termijn prognose te hebben. Leeftijd, geslacht en episodeduur leken geen invloed te hebben op terugval.

In **hoofdstuk 8** presenteren wij de discussie over de bevindingen van dit proefschrift. Wij doen aanbevelingen voor de praktijk en geven suggesties voor vervolgonderzoek.

Wij concluderen dat algemeen wordt aangenomen dat een langere episodeduur en medicatieresistentie de uitkomst van ECT verslechteren. Om die reden raden wij aan om patiënten met een ernstige depressie binnen zes maanden na het ontstaan van de depressie te verwijzen voor ECT. Een uitzondering is de aanwezigheid van psychotische kenmerken; bij patiënten met een psychotische depressie adviseren wij ECT als eerste

behandelstap toe te passen, omdat ECT zeer effectief is bij deze patiënten en zij bovendien een relatief gunstige prognose na succesvolle ECT hebben. Wij concluderen ook dat het toevoegen van een antidepressivum aan ECT om de effectiviteit ervan te vergroten alleen zinvol is bij minder ernstig depressieve patiënten zonder medicatieresistentie. Nortriptyline is in dit kader het best onderzochte antidepressivum en kan veilig tijdens ECT gebruikt worden. Bij patiënten met een ernstige depressie met psychotische kenmerken en medicatieresistentie is ECT een zeer effectieve behandeling waarbij het toevoegen van nortriptyline geen meerwaarde voor de uitkomst heeft. Een combinatiebehandeling van ECT met nortriptyline moet toch overwogen worden, om een adequate bloedspiegel aan het eind van de ECT kuur te garanderen. Tot slot concluderen wij dat het starten van nortriptyline bij aanvang van ECT, in plaats van na het staken van ECT, prognostisch geen voordelen heeft. Onder ernstig depressieve patiënten die remissie bereikten met ECT, lopen patiënten die voorafgaand aan ECT het minst ernstig ziek, niet-psychotisch en medicatieresistent waren het grootste risico op terugval. Om terugval te voorkomen, hebben deze patiënten een intensievere vervolgbehandeling nodig met bijvoorbeeld nortriptyline in combinatie met lithium of vervolg ECT, terwijl nortriptyline monotherapie afdoende is voor patiënten met een psychotische depressie voorafgaand aan ECT. Omdat terugval na succesvolle ECT vooral in de eerste zes maanden plaatsvindt, benadrukken wij het belang van een intensieve en zorgvuldige follow-up in deze periode. Tegen de intuïtie in, moeten patiënten die voorafgaand aan ECT het minst ziek en niet-psychotisch waren even intensief of wellicht intensiever vervolgd worden dan patiënten met een psychotische depressie voorafgaand aan ECT. Ditzelfde geldt ook voor medicatieresistente patiënten.

Voor verder onderzoek zou een RCT relevant zijn om te bepalen of het toevoegen van imipramine en/of venlafaxine aan ECT de effectiviteit ervan kan verhogen en terugval na succesvolle ECT kan voorkomen. Daarnaast zou onderzoek naar het optimale afbouwschema voor ECT en naar de effectiviteit van een geïndividualiseerde, flexibele frequentie in plaats van een vaste frequentie van vervolg ECT waardevol zijn voor terugvalpreventie na succesvolle ECT.

CURRICULUM VITAE

Esther Pluijms werd geboren op 28 juni 1968 in Leiden. Zij groeide op in Katwijk en Leiderdorp. In 1986 behaalde zij haar VWO diploma aan het Visser 't Hooft Lyceum in Leiden. Omdat zij in datzelfde jaar werd uitgeloot voor de studie Geneeskunde begon zij een opleiding tot radiodiagnostisch laborant in het Leids Universitair Medisch Centrum in Leiden. In 1987 kon zij alsnog beginnen aan de studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Tijdens haar studie zette zij met medestudenten een studenten waterpolo- en zwemvereniging op en was enkele jaren bestuurslid. In 1994 behaalde zij haar artsexamen en ging als arts niet in opleiding tot specialist eerst aan het werk bij de Robert Fleury Stichting in Leidschendam en later bij het Psychiatrisch Centrum Bloemendaal in Den Haag. Op de Biologisch Psychiatrische Afdeling van deze laatste instelling maakte zij onder supervisie van dr. Tom Birkenhäger kennis met het doen van onderzoek. Over dit onderzoek schreef zij later twee publicaties. Van 1996 tot 2001 volgde zij de opleiding tot psychiater aan het Haags Leids Opleidingsconsortium Psychiatrie. Na afronding van deze opleiding werkte zij twee jaar als psychiater bij de Robert Fleury Stichting in Gouda. In 2003 maakte zij de overstap naar het Erasmus MC, waar zij nu nog steeds werkzaam is als psychiater binnen de zorglijn stemmingsstoornissen. In 2009 zette zij samen met dr. Tom Birkenhäger en prof. dr. Walter van den Broek een klinische trial op, wat de aanzet was tot haar promotietraject. Naast onderzoek houdt zij zich bezig met patiëntenzorg en onderwijs. Zij heeft veel ervaring in onderwijs, training en supervisie van bachelor- en masterstudenten Geneeskunde en artsen in opleiding tot psychiater. Als onderwijscoördinator van de afdeling psychiatrie is zij nauw betrokken de ontwikkeling van toetsprogramma- en curriculumonderdelen van de opleiding Geneeskunde aan de Erasmus Universiteit in Rotterdam. Van 2012-2018 was zij lid van de Opleidingscommissie Erasmus MC. Op dit moment is zij lid van de Examencommissie Erasmus MC, kamer Geneeskunde, mastersectie (sinds 2018), het Platform Coördinatoren Psychiatrieonderwijs van de Nederlandse Vereniging voor Psychiatrie (sinds 2015) en de Werkgroep ECT Nederland (sinds 2003).

Zij woont samen met haar partner Maarten en hun dochter Eva, die een master Earth Sciences – Geology and Geochemistry doet in Amsterdam. Hun dochter Noortje woont op kamers in Leiden en volgt daar een bachelor Biologie.

PHD PORTFOLIO

Name PhD student:	Esther Pluijms
PhD period:	2009-2022
Erasmus MC department:	Psychiatry
Promotors:	Prof. dr. Witte J.G. Hoogendijk Prof. dr. Walter W. van den Broek
Co-promotor:	Dr. Tom K. Birkenhäger

Courses	Year	Workload (EC)
Scientific Integrity	2022	0.3
Presenteren met impact	2017	0.6
Academic Writing	2017	0.2
Endnote	2015	0.1
Systematic Literature Retrieval	2015	0.1
Werken met tutorgroepen	2015	0.2
Senior Kwalificatie Onderwijs (SKO)	2014	8.0
Basis Kwalificatie Onderwijs (BKO)	2013	8.0
Teach the Teacher III	2013	0.4
Onderwijs en Techniek van Theater	2010	0.6
Teach the Teacher II	2009	0.4
Corsendonkcursus	1997	2.2

Presentations	Year	Workload (EC)
Symposium afdeling Psychiatrie Erasmus MC	2015	0.5
Symposium Werkgroep ECT Nederland (WEN)	2014	0.5
Symposium afdeling Anesthesiologie Erasmus MC	2012	0.5
Bijdrage aan meerdere ECT-trainingen voor psychiaters	2009 – 2014	2.0
Symposium Voorjaarscongres NVvP	2009	0.5

Conferences, seminars and workshops	Year	Workload (EC)
Geaccrediteerde nascholing	2009 – 2022	23.4

- Shared Care jaarsymposium (2021)

- Symposium Digitaal leren en innoveren: adaptief leren en blended learning (2021)

- Congres wet- en regelgeving in het hoger onderwijs (2019)

- Examinatorenbijeenkomst Erasmus MC (2019, 2021)

- Training Wet Verplichte GGZ (2019)

- Training Ontwikkelen van een e-learning module (2018)
- Actualiteitendag examencommissies (2017)
- AMEE (Association for Medical Education in Europe) conference (2017, 2019-2021)
- ECT symposium (2016, 2019, 2021)
- Nationaal congres farmacotherapie in de psychiatrie (2015, 2020, 2022)
- NVMO (Nederlandse Vereniging voor Medisch Onderwijs) congres (2015-2018, 2021)
- Invitational conference ECT (2014)
- APA (American Psychiatric Association) conference (2014)
- Onderwijsmiddag Erasmus MC (2013-2019, 2022)
- Training Bouwen aan een nieuw curriculum (2012)
- Bunnik symposium (2012)
- Student-docent dagen Erasmus MC (2012, 2013, 2015, 2016-2018, 2022)
- Diverse onderwijsworkshops Erasmus MC: tentamenvragen maken, digitaal toetsen van klinisch redeneren, stemsystemen, flipping the classroom, onderwijs van klinisch redeneren, gebruik van video in het onderwijs, geavanceerde mogelijkheden van Canvas, interactieve werkvormen, FeedbackFruits, casusgestuurd onderwijs en projectonderwijs (2012-2022)
- NVvP (Nederlandse Vereniging voor Psychiatrie) voorjaarscongres (2009, 2012-2018)
- Psyfar Praktijkgerichte nascholing over psychofarmacologie (2009-2022)

Supervision and Teaching	Year	Workload (EC)
Onderwijs geneeskundestudenten, bachelor en master (colleges, patiëntdemonstraties, vaardigheidsonderwijs)	2011 – heden	60.0
Supervisie geneeskundestudenten, bachelor en master (systematische review, coschappen)	2009 – 2020	28.0
Supervisie artsen in opleiding tot psychiater (klinische stage en onderwijsstage)	2009 – heden	28.0

Other Activities	Year	Workload (EC)
Lid mastersectie Examencommissie Erasmus MC	2018 – heden	74.0
Lid Platform coördinatoren medisch onderwijs NVvP	2015 – heden	6.0
Coördinator onderwijsstage artsen in opleiding tot psychiater	2015 – heden	25
Lid Commissie organisatie student-docent dagen Erasmus MC	2015, 2016	2.0
Lid Opleidingscommissie Erasmus MC	2012 – 2018	44.0
Onderwijscoördinator afdeling Psychiatrie, bachelor en master Geneeskunde Erasmus MC	2011 – heden	112.0
Tentamencoördinator en examinator afdeling Psychiatrie, bachelor en master Geneeskunde Erasmus MC	2011 – heden	113.0
Disciplinecoördinator Psychiatrie Erasmus MC	2011 – heden	80.0
Auteur drie casus in Leerboek Psychiatrie	2005, 2009	4.3

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