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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 1-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.

KEYWORDS
electroconvulsive therapy, major depressive disorder, nortriptyline, randomized controlled trial, relapse

1 | 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 with 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]

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 because of 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.

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 1-year open-label study with nortriptyline in patients who recovered from depression during the RCT.

1.1 | 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.

2 | 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 1-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).

2.1 | 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.

2.2 | 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 1 week was part of the routine clinical practice and was used for diagnosing and screening for eligibility. It was routinely shortened to at least 5 days if ECT could not be delayed because of 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.

2.3 | RCT

Patients were withdrawn from all psychotropic medications, including benzodiazepines, at least 5 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 5 days prior to the first ECT treatment. All patients received an initial daily administration of two pills for 5 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 nonresponder.

2.4 | 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 4 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.

2.5 | 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.

2.6 | Assessments

2.6.1 | 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.

2.6.2 | Follow-up study

Weekly during the first month and then every 4 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 1 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.

2.7 | Outcome measures

2.7.1 | 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 1 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.

2.7.2 | Follow-up study

Our primary outcome measure was relapse, defined as a CGI score of at least 'much worse' compared with 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.

2.8 | 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] Because of 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 7 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).

2.9 | Statistical analyses

2.9.1 | 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 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 Chi-square 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.

2.9.2 | 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.

3 | RESULTS

3.1 | 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 because of 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.

After the completion of the RCT, 33 patients were eligible to participate in the follow-up study. Two patients declined to participate: one because of travel limitations and the other because of 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 because of travel limitations. A total of 31 patients were included in the analyses.

3.2 | Interventions

3.2.1 | 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) because of 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.

3.2.2 | 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.

3.3 | Outcomes

3.3.1 | 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.

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

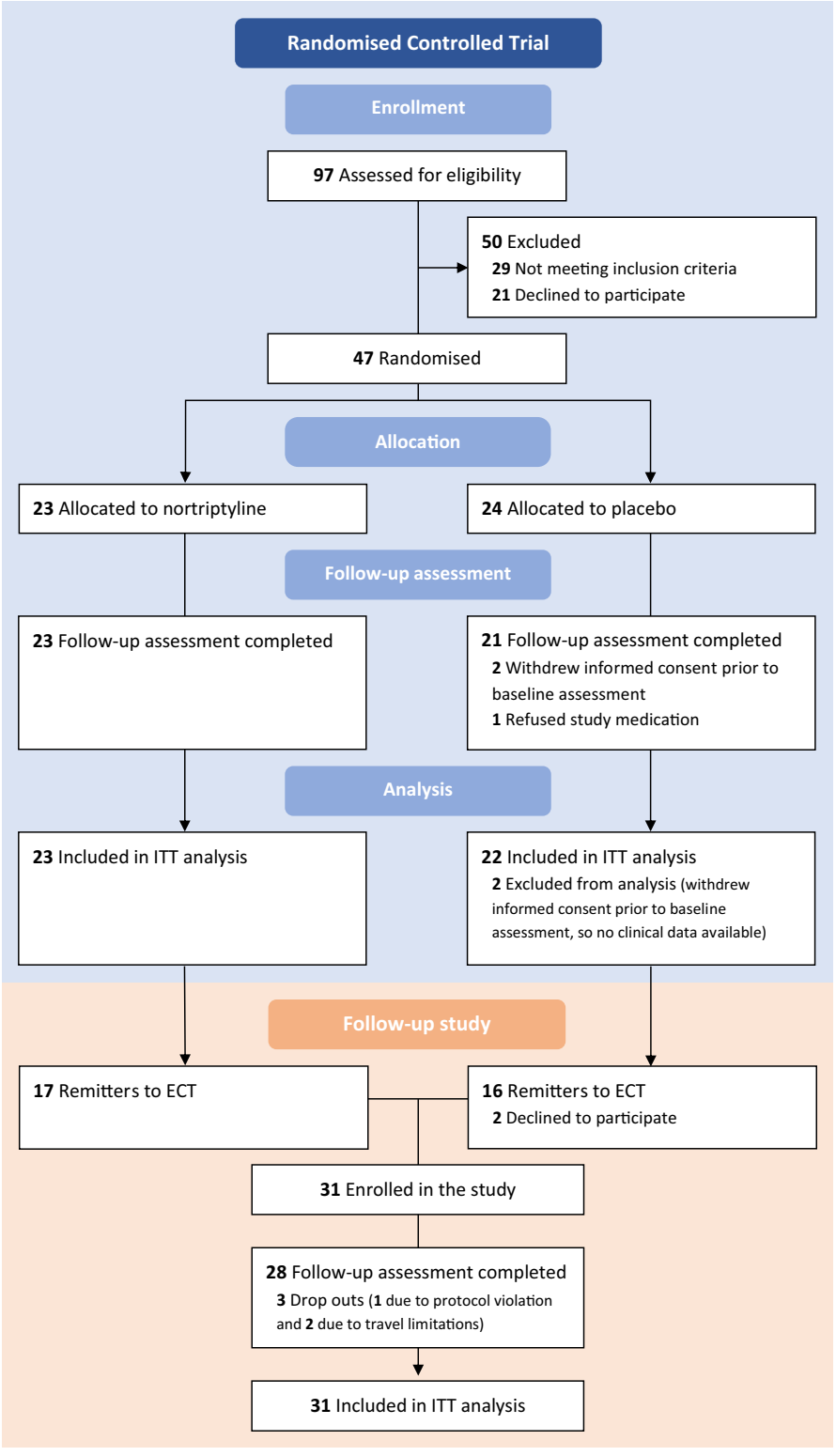

FIGURE 1 CONSORT flow diagram of the patient inclusion. CONSORT, Consolidated Standards of Reporting Trials; ECT, electroconvulsive therapy; ITT, intent-to-treat

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 with 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 $\chi^2(1) = 2.796$; $p = 0.094$).

3.3.2 | 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 per cent relapsed at a mean of 34.2 weeks after ECT

TABLE 1 Demographic and baseline clinical characteristics

	Nortriptyline ($n = 23$)	Placebo ($n = 24$)	Total sample ($n = 47$)	p-values
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.

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)	$\chi^2(1) = 0.005$; $p = 0.945$
Mean week to response (SE)	5.6 (1.01)	6.7 (0.96)	Log Rank $\chi^2(1) = 1.015$; $p = 0.314$
Remission, n (%)	17 (73.9)	16 (72.7)	$\chi^2(1) = 0.008$; $p = 0.928$
Mean week to remission (SE)	7.2 (0.89)	8.0 (0.92)	Log Rank $\chi^2(1) = 0.27$; $p = 0.602$

Abbreviations: HRSD, Hamilton Rating Scale for Depression.

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 Kaplan–Meier log rank $\chi^2(1) = 0.437$; $p = 0.509$). Figure 2 shows the Kaplan–Meier survival curve for the time to relapse.

4 | 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 numbers 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.

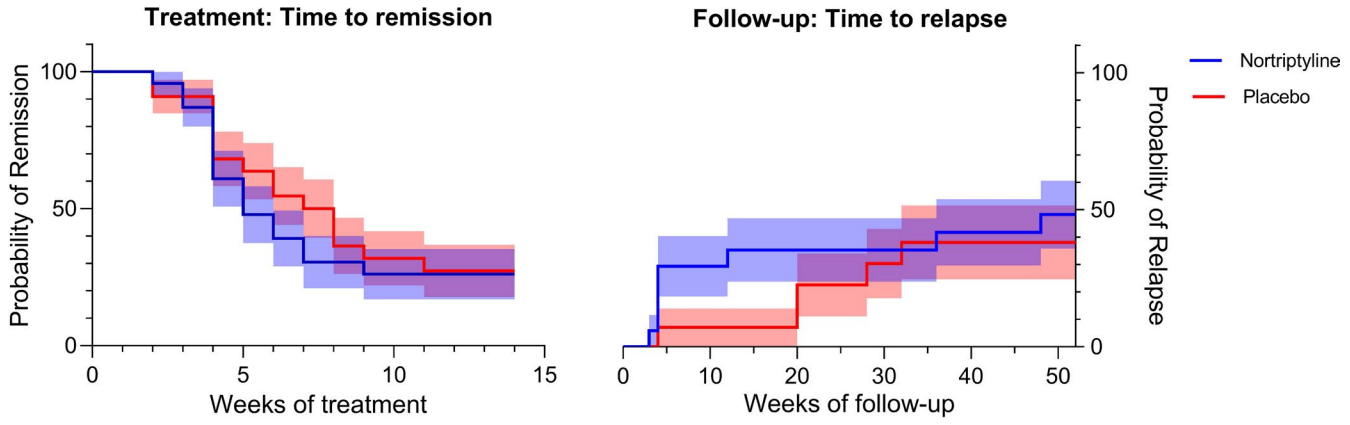

FIGURE 2 Kaplan–Meier survival curves for the RCT (left) and for the follow-up study (right)

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

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 with the study by Sackeim et al.,[7] our remission rates were considerably higher, possibly because of 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 because of 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 1-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 with 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 1 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 1 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. 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 because of 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.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

EP, WvdB and TB designed and conducted the study. AK was responsible for statistical analyses. EP, AK, WvdB and TB were involved in interpreting the data. EP wrote the manuscript and integrated the comments of all other authors. All authors participated in critical revision of the manuscript drafts and approved the final version.

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The data are not publicly available because of privacy or ethical restrictions.

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