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# Clinical characteristics associated with relapse 2 years after electroconvulsive therapy for major depression

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## Abstract

**Objective:** 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. We aimed to determine clinical characteristics that are associated with relapse within 2 years after successful ECT.

**Methods:** Patients who remitted to ECT in a randomised controlled trial comparing adjuvant nortriptyline and placebo during a course of bilateral ECT were followed-up prospectively for 1 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 2 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 2 years in patients with severe major depression who were treated with nortriptyline monotherapy after successful ECT is encouraging.

KEYWORDS

electroconvulsive therapy, major depressive disorder, predictors, relapse

Esther Pluijms and Poul Vinther contributed equally and share first authorship.

## 1 | 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 characteristics associated with relapse post-ECT. Some of them found that an older age[3–6] and the presence of psychotic features prior to ECT[2–8] are associated with a lower relapse rate and that medication resistance prior to ECT is associated with a higher risk of relapse.[5,9–11] However, other studies were not able to replicate these findings regarding older age,[12,13] psychotic features[9,12] and medication resistance.[3,4] Female sex,[11] a larger number of previous depressive episodes,[3,5,14] a longer duration of the index episode,[6,15] and achieving response but not remission to ECT[11] have also been identified as risk factors for relapse. In line with the results of one previous study,[6] our clinical impression is that a higher severity of depression prior to ECT might reduce the relapse rate, although this is still under debate.[5] Most previous studies on clinical characteristics associated with relapse after successful ECT had a short-term follow-up period of 3–12 months. Unfortunately, hardly any of them had a longer-term follow-up.

### 1.1 | Aim of the study

To add to the currently limited and inconclusive literature, we conducted a cohort study to determine clinical characteristics associated with relapse after successful ECT. We hypothesised 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 are associated with long-term, that is, 2 years, remission after successful ECT.

**Significant outcomes**

- Patients with psychotic features, with a higher severity of depression, and without medication resistance prior to ECT had a more favourable long-term prognosis after successful ECT.
- 50% of patients with severe major depression who were treated with nortriptyline monotherapy after successful ECT showed sustained remission over 2 years.
- Most relapses occurred within 6 months after successful ECT.

**Limitations**

- A relatively small sample size.
- The retrospective data collection for the second year follow-up.
- A limited generalizability of our findings, since all patients received bilateral ECT and were very severely depressed.

## 2 | METHODS

### 2.1 | Design

The current cohort study is embedded in a randomised controlled trial (RCT) comparing adjuvant nortriptyline and placebo during a course of bilateral ECT and a subsequent prospective 1-year follow-up study with open-label nortriptyline in patients who attained remission to ECT (Dutch Trial Register NTR5579).[16] We used prospective data from this follow-up study, that is, data up to 12 months post-ECT. In addition, we retrospectively collected data up to 2 years post-ECT. The RCT and subsequent 12-month prospective follow-up assessments were carried out from 2010 to 2018. The retrospective data collection took place from 2018 to 2019, that is, 2–8 years since initial treatment with ECT.

### 2.2 | 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.

### 2.3 | Patients

All patients included in the current study participated in an RCT comparing adjuvant nortriptyline and placebo

during a course of bilateral ECT and were in remission at the onset of the subsequent prospective 1-year follow-up study, which was 1 week after ECT cessation. Remission was defined as a score of ≤7 on the 17-item Hamilton Rating Scale for Depression (HRSD)[17] within 1 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 sixth session.

Patients were eligible to participate in the RCT if they were ≥18 years old; had a DSM-IV-TR[18] diagnosis of major depressive disorder as assessed with the schedule for affective disorders and schizophrenia (SADS)[19] during a routine drug-free observation period; had a score of ≥18 on the 17-item HRSD[17]; and had an indication for ECT. Indications for ECT were life-threatening situations and medication resistance, that is, 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.

## 2.4 | 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 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.

## 2.5 | 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. Patients with psychotic depression prior to ECT did not receive a combination of nortriptyline and an antipsychotic, since the optimal continuation pharmacotherapy following successful ECT in these patients has been studied scarcely and a combination treatment showed no advantage over antidepressant monotherapy in preventing post-ECT relapse in elderly patients with psychotic depression.[20] 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.

## 2.6 | Assessments and data collection

### 2.6.1 | 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[17] 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[19] 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)[21] was completed to assess medication resistance during the index episode; scores of ≥3 indicate medication resistance.

### 2.6.2 | Depressive symptoms

Depressive symptoms were collected prospectively for up to 12 months. The 17-item HRSD[17] and the Clinical Global Impression Scale (CGI)[22] were completed weekly

during the first month and then every 4 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,[23] the part concerning mood disorders, to determine the occurrence of depressive episodes.

## 2.7 | 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[22] or 17-item HRSD[17] assessment indicating relapse, that is, 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. In addition, 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. In addition, the worsening of depressive symptoms must have led to a change in the treatment regimen.

## 2.8 | Statistical analyses

Descriptive statistics were tested for normality using the Shapiro–Wilk test. For normally distributed continuous variables, means and standard deviations 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, that is, sex, psychotic features, and medication resistance, survival distributions were plotted using the Kaplan–Meier method to visually verify proportional hazard assumptions. For continuous variables, that is, 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.

# 3 | RESULTS

Thirty-three patients achieved remission to ECT and were still in remission at the onset of the prospective follow-up study. Two of them refused to participate in the prospective follow-up study. However, when approached some years later, they were willing to contribute to the retrospective data collection of the current study. In these two cases, we relied on retrospective data only. One patient responded to ECT, but did not reach remission until little over a week after ECT cessation. For this reason, he was not eligible to participate in the prospective follow-up study, but he was considered a remitter in the current study. Since we had collected follow-up data from both responders and remitters to ECT at the time, prospective data of the first year follow-up were available for this patient. In total, 34 patients were included in the current study.

Nineteen patients showed sustained remission over the first 12 months of prospective data collection. In these cases,

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

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 17 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 14 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 summarises the demographic and baseline clinical characteristics of the total sample. The mean age

**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** |

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

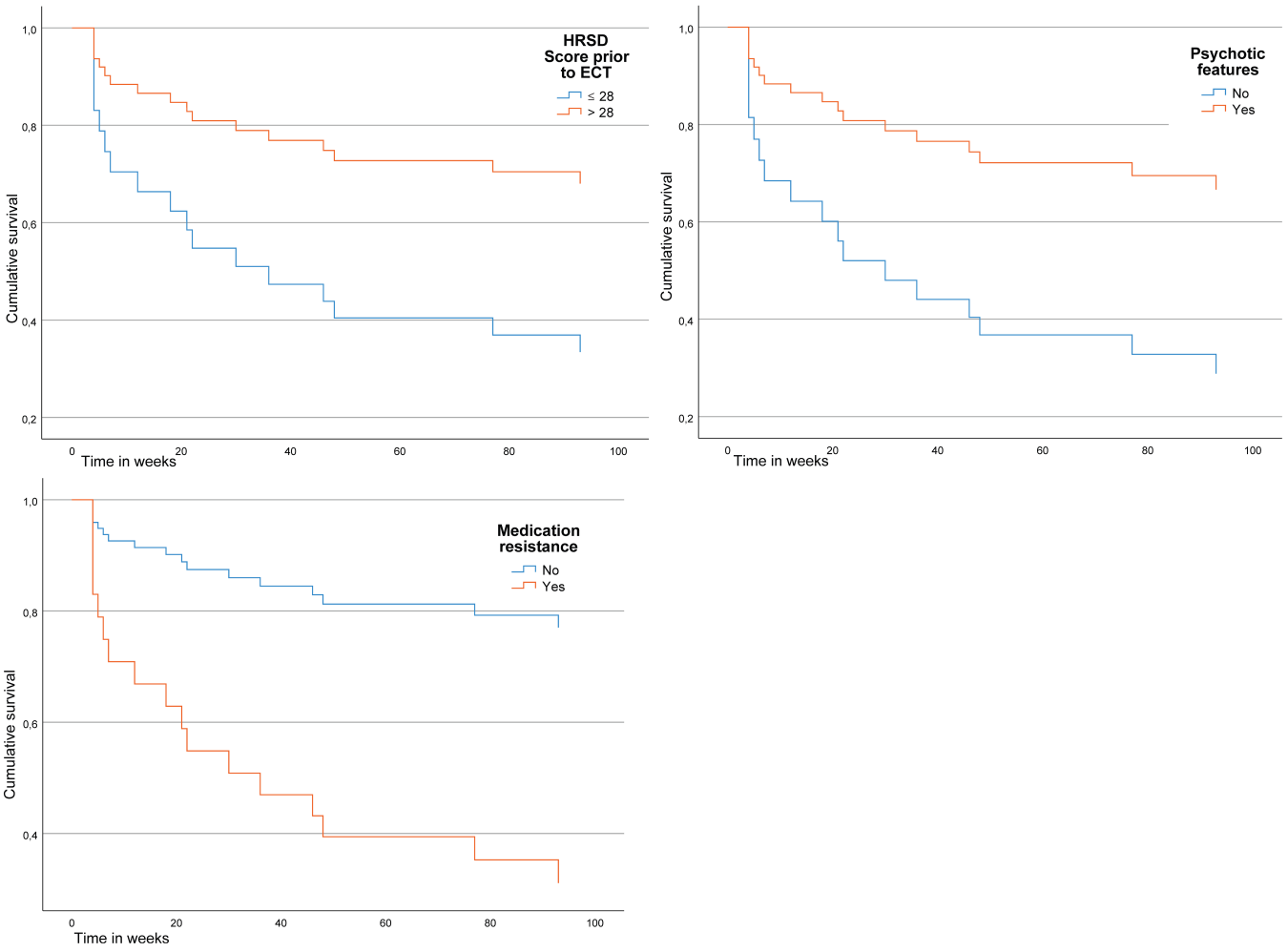


**FIGURE 1** Survival plots for the significant clinical characteristics. For the purpose of visualisation, the HRSD score prior to ECT (symptom severity) was dichotomized using a median split. ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression.

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.

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 1 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 summarises 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 HRs 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 are associated with long-term remission. Cox proportional hazards assumptions were met. Figure 1 shows the survival plots for the significant clinical characteristics.

## 4 | DISCUSSION

### 4.1 | Main findings

In patients with severe major depression who were treated with nortriptyline monotherapy after a successful course of bilateral ECT, the relapse rate at 2 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 2-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.

### 4.2 | Comparison with previous studies

A systematic review on relapse rates after ECT identified three prospective studies that followed patients for 2 years. A meta-analysis of these three studies showed a relapse rate of 50% at 2 years, which is similar to our relapse rate.[2]

Previous prospective studies on clinical characteristics associated with 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.,[11] remitters to ECT were randomised 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.,[14] 58% of remitters to ECT receiving treatment-as-usual relapsed. Compared with 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 1-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,[24] diagnosed in 23% of patients. Benzodiazepines and Z-hypnotics might mask relapse. Our relapse rate at 1 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.,[8] 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 associated with 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 three 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 1 year (44%). Heijnen et al.[25] 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[10–13,15] in the literature. Moreover, inconsistent findings most likely reflect small sample sizes and low numbers of relapses, especially after 1 year.

### 4.3 | 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 1-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 2 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 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. Another limitation is the limited generalizability of our findings, since all patients received bilateral ECT and were very severely depressed.

## 5 | TO CONCLUDE

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.[26,27] 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.[2–4,8,11,12] 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 2 years in patients with severe major depression who were treated with nortriptyline monotherapy after successful ECT is encouraging.

### AUTHOR CONTRIBUTIONS

Esther M. Pluijms, Poul T. Vinther, Astrid M. Kamperman, and Tom K. Birkenhäger formulated the research question. Poul T. Vinther and Astrid M. Kamperman were responsible for statistical analyses. Esther M. Pluijms and Poul T. Vinther wrote the manuscript and integrated the comments of all other authors. All authors approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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