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Research paper

Psychotic late-life depression less likely to relapse after electroconvulsive therapy

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ABSTRACT

Background: A substantial number of patients with late-life depression (LLD) that remitted after ECT experience relapse. Identifying risk factors for relapse may guide clinical management to devote attention to those at increased risk. Therefore the current study aims to evaluate which baseline clinical characteristics are related to relapse within six months after successful ECT in patients with severe LLD.

Methods: 110 patients with LLD from the prospective naturalistic follow-up Mood Disorders in Elderly treated with Electro-Convulsive Therapy (MODECT) study were included. A total of 73 patients (66.4%) remitted after ECT, six patients had missing information on relapse, rendering to a total sample size of 67 patients. Relapse within six months after ECT was defined as a Montgomery Åsberg Depression Scale (MADRS)-score > 15, readmission or restart of ECT. Logistic regression analyses were conducted to examine the association between baseline clinical characteristics and relapse.

Results: A total of 22 patients (32.8%) experienced a relapse. Patients with psychotic depression were less likely to relapse (odds ratio = 0.32, p = .047), corrected for prior admissions; 76.9% of patients with psychotic depression remained remitted.

Limitations: Due to its naturalistic design, no firm conclusions can be drawn on the effect of post-ECT treatment.

Conclusions: Patients with psychotic depression had a lower risk to experience relapse after successful ECT. This result strengthens the hypothesis that psychotic depression might be a specific depression subtype with a favorable ECT outcome up to six months after ECT.

1. Introduction

Electroconvulsive therapy (ECT) is a safe and effective treatment for late-life depression (LLD) (Dols et al., 2017; van der Wurff et al., 2003; van Diermen et al., 2018). ECT remission rates are high in LLD, ranging from 50% to 70% (Dols et al., 2017; Oudega et al., 2011; Tew et al., 1999).

Despite these impressive remission rates, patients and clinicians are confronted with relapse rates ranging from 37% to 51% within the first six months after ECT (Jelovac et al., 2013). Studies evaluating relapse have focused mainly on medication after the initial ECT-course to prevent relapse (Table 1) (Brakemeier et al., 2014; Itagaki et al., 2017; Kellner et al., 2016, 2006; Martiny et al., 2015; Nordenskjold et al., 2011, 2013; Tew et al., 2007; van Beusekom et al., 2007). In order to guide clinical management and devote specific attention to those at increased risk for relapse, studies exploring clinical characteristics

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Table 1
Summary of clinical studies investigating continuation therapy after an acute ECT-course in relation to relapse in late-life depression.

Reference	Patients (*N*)	Mean age ± SD	Diagnosis	Study design + intervention groups	Results
Kellner et al., 2006	184	57.2 ± 16.1	MDD	RCT m-ECT vs Lithium + Nortriptyline	m-ECT: 37.1% relapse; Lithium + Nortriptyline: 31.6% relapse No differences between groups, but lower relapse risk than placebo group.
Van Beusekom et al., 2007	26	Relapse: 57.7 ± 9.8 Non-relapse: 60.6 ± 7.4	MDD	Naturalistic follow-up Relapse vs non-relapse	Recurrence rate of depression: 42.3%, no difference between groups.
Tew et al., 2007	26	Protocolized: 56.1 ± 17.4 Usual care: 58.7 ± 18.5	MDD	Naturalistic / randomized CAU vs protocolized continuation treatment	Relapse rates within 6 months CAU: 51% Nortriptyline: 60% Nortriptyline + Lithium: 39% Placebo: 84% No difference CAU and protocolized, but different from placebo.
Nordenskjöld et al., 2011	486	55 ± 18	MDD	Population-based cohort study	Relapse within one year: 34% Risk factors: comorbid substance dependence, benzodiazepine treatment or antipsychotics. Protective factors: Lithium treatment.
Nordenskjöld et al., 2013	56	Medication only: 52 ± 17 Combination: 62 ± 13	MDD + BP	RCT m-ECT or m-ECT + pharmacotherapy	Medication only group: 61% relapse Combination group: 32% relapse.
Brakemeier et al., 2014	90	61.0 ± 14.3	MDD	Prospective RCT Medication only vs medication + CBT vs medication + *m*-ECT	Higher proportion of sustained response (no relapse or drop-out) in CBT-group (77%) vs ECT-group (40%) or medication group (44%).
Martiny et al., 2015	47	Escitolopram: 55.1 ± 14.9 Nortriptyline: 55.8 ± 13.8	MDD	RCT Escitolopram vs Nortriptyline	Overall relapse rate within 6 months: 33%. Lower risk for patients receiving Nortriptyline.
Kellner et al., 2016	120	70.5 ± 7.2	MDD + BP	RCT m-ECT plus medication (Venlafaxine plus Lithium) vs medication only	Additional ECT after remission was beneficial in sustaining mood improvement for most patients. Medication only: 20.3% relapse; Medication + ECT: 13.1% relapse.
Itagaki et al., 2017	100	UP: 64.9 ± 12.4 BP: 61.3 ± 17.1	MDD + BP	Naturalistic / Retrospective	Relapse after 1 year: 50% (UP and BP). Valproate potential maintenance therapy after ECT for UP.

Notes. Abbreviations: MDD: major depressive disorder; BP: Bipolar, CAU: care as usual; ECT: Electro-Convulsive Therapy, m-ECT = maintenance Electro-Convulsive Therapy, RCT = Randomized Controlled Trial.

associated with relapse are urgently needed.

To date, few studies investigated the association between baseline clinical characteristics and relapse after ECT in LLD. Studies on ECT effectiveness showed that response and remission rates are positively related with age (Haq et al., 2015; Pinna et al., 2018; Rhebergen et al., 2015; van Diermen et al., 2018). Despite the importance of higher age in predicting ECT effectiveness, most studies evaluating predictors of relapse after ECT have focused on adult patients with major depressive disorder (MDD), whilst studies among patients with LLD are underrepresented (Jelovac et al., 2013). In adult patients Sackeim et al. (2001) showed that medication resistance and more severe depressive symptoms are associated with a more rapid relapse after the acute ECT course. A longer illness duration (Medda et al., 2013; Verwijk et al., 2015) and an earlier age of onset (Medda et al., 2013; Prudic et al., 2013; Sackeim et al., 2001) have also been marked as a risk factor for relapse in adult patients.

While multiple studies have shown superior response after ECT for psychotic depression (Birkenhager et al., 2005; Dols et al., 2017; Haq et al., 2015; Heijnen et al., 2019; Pinna et al., 2018; Spaans et al., 2016), little is known about relapse rates of psychotic depression. Spaans et al. (2016) reported that patients with psychotic depression remit early during an ECT course (within 4 sessions) and are less likely to experience relapse within six months. These patients with psychotic depression were characterized by a shorter episode duration and cognitive slowing at baseline that re-established when ECT was completed (Spaans et al., 2016).

The primary aim of the present study is to evaluate which baseline clinical characteristics are related to relapse within six months after ECT in a cohort of remitted patients with LLD. We hypothesized that clinical characteristics associated with low response rates, increase the risk of relapse, including a longer index episode (Medda et al., 2013), early age at onset of first depression, a younger age (Dols et al., 2017; Haq et al., 2015; Medda et al., 2013; Pinna et al., 2018; Prudic et al., 2013; Sackeim et al., 2001; Spaans et al., 2016), more severe depression (Sackeim et al., 2001), worse baseline cognitive functioning (Spaans et al., 2016; Vasavada et al., 2017; Verwijk et al., 2014, 2015), and absence of psychotic symptoms (Atiku et al., 2015; Birkenhager et al., 2005; Heijnen et al., 2019; Spaans et al., 2016). A secondary aim is to evaluate which baseline clinical characteristics are association with remission.

2. Methods

2.1. Study sample

This naturalistic prospective study was part of the Mood Disorders in Elderly treated with Electro-Convulsive Therapy (MODECT) study, investigating clinical and structural brain characteristics and response to ECT (Dols et al., 2017). In the MODECT study, patients were aged 55 years and older with a diagnosis of a severe unipolar depression according DSM-IV-TR criteria (Association, 2000). Exclusion criteria were a diagnosis of bipolar disorder, a schizoaffective disorder, comorbid major DSM-IV psychiatric illness or neurological illness (including stroke, dementia, and Parkinson's disease). The diagnoses were established by experienced psychiatrists and confirmed via the Mini International Neuropsychiatric Interview Plus 5.0.0 (M.I.N.I.-plus (MINI) (Sheehan et al., 1998). Over a 3-year period (2011 till 2013) a total of 110 patients were included in the study. Patients were enlisted through two tertiary psychiatric hospitals located in Amsterdam (GGZ inGeest, the Netherlands; $N = 67$) and Leuven (Psychiatric Center, KU Leuven, Belgium; $N = 43$). During follow-up $N = 11$ patients dropped out. Out of the original sample of 110 patients, 73 patients remitted after the initial ECT-course of whom six patients had missing information on relapse, which rendered to a total sample size of $n = 67$ patients in the current study. Attrition was not associated with inclusion site, age, gender, level of education, cognitive functioning, depression severity, age of onset, or presence of psychotic symptoms. The study protocol of MODECT has been approved centrally by the Ethical Review Board of the VU Medical Center and by the ethical review board of the Catholic University of Leuven and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all the patients before testing.

2.2. Measurements

2.2.1. Relapse within six months after ECT

Remission after the acute ECT-course was defined by a Montgomery Åsberg Depression Scale (MADRS)-score (Montgomery and Asberg, 1979) of less than ten points. In remitted patients, relapse was determined by a psychiatrist and was based on a clinical interview with each patient six months after the initial ECT course. Relapse was defined as a MADRS-score > 15, re-admission or restart of ECT within the six-month period after ECT.

2.2.2. Baseline clinical characteristics

Demographic and clinical variables including age, gender, level of education, marital status, age at onset of first depression and information on post-ECT treatment were obtained by an interview and double-checked by chart review. Early onset depression (EOD) was defined as having a first depressive episode before the cut-off age of 55 years. The MADRS (Montgomery and Asberg, 1979) at baseline was used to measure depression severity. The diagnosis of depression with or without psychotic symptoms was based on DSM-IV-TR criteria and confirmed by use of the MINI (Sheehan et al., 1998). Global cognitive functioning was examined by the Mini-Mental State Examination (MMSE) at baseline (Folstein et al., 1975). The MADRS and MMSE were collected by research nurses well-trained on the protocol.

2.3. ECT procedure

Patients received ECT twice a week according to the Dutch guidelines for ECT (Van den Broek et al., 2010). The ECT system used in the study was the *Thymatron System IV* (Somatics, LLC, Lake Bluff, IL, USA; maximum energy 200%, 1008 C) using a titration protocol (Dols et al., 2017). Anesthesia was achieved with intravenous administration of etomidate (0.2 mg/kg) and succinylcholine (1 mg/kg). Patients started on a course with right unilateral ECT (d'Elia placement), some patients started with bilateral ECT based on indication (severity of clinical condition) (Kellner et al., 2010). At the first treatment, the subject's seizure threshold (ST) was established by empirical titration. Subsequent treatments were given at six times the ST for unilateral ECT and 1.5 times the ST for bilateral ECT. Patients were treated until remission, or until patients showed no further improvement during the last 2 weeks of ECT. Switching to bilateral ECT was applied when after six unilateral treatments, there was no clinical improvement. Psychotropic medication was discontinued at least one week prior to ECT, or if deemed impossible, kept stable during the ECT course.

2.4. Statistical analyses

Demographics and clinical characteristics of patients are reported as means with standard deviations (SD), medians with inter-quartile range (IQR) or absolute numbers with percentages of sub-groups.

Bivariate logistic regression analyses were performed in order to identify which baseline clinical variables would be associated with relapse within a period of six months after ECT. The same analyses was performed with remission as outcome variable.

A multiple logistic regression model was used to evaluate each unique predictor value. Variables showing $p < 0\ 0.05$ in the bivariate analyses were used as input variables in the multiple logistic regression model. In order to prevent multicollinearity, correlation coefficients between all independent variables were computed. If a correlation

coefficient between two variables was above 0.80 or if variance inflation factor (VIF) > 5, these variables were not added into the same model. Post-hoc analyses were performed to identify significant differences between psychotic and non-psychotic patients concerning baseline clinical characteristics, including age, depression severity, age of onset, index duration, cognitive functioning, prior antidepressants, prior admissions, or post-ECT treatment, e.g. use of antidepressants (TCA or SSRI), mood stabilizer (Lithium), combination pharmacotherapy (TCA + Lithium) or m-ECT. If a significant difference was observed on any of these variables, this was added into the multivariate model, controlling for multicollinearity. In all analyses $p < .05$ was considered as statistically significant. Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 24, SPSS Inc., Chicaco, IL).

3. Results

3.1. Demographic and clinical characteristics

The mean age was 73.8 years (SD 8.4) and the majority was female (64.2%). At baseline, patients had a mean MADRS-score of 33.1 (SD 8.3), which decreased to a mean MADRS-score of 4.3 (2.7) after the last ECT session. A total of 73 patients (66.3%) showed remission. Of the 67 patients with available six-months follow-up (FU) data, 45 patients remained in remission and 22 patients (32.8%) experienced a relapse (Table 2).

Table 2
Characteristics for total remitted patients and for relapse and non-relapse patients within six months after ECT remission.

Demographic and clinical characteristics	Total $N = 67$	Relapse† $N = 22$ (32.8)	Non-relapse $N = 45$ (67.2)
Mean age, yr., mean (SD)	73.8 (8.4)	73.8 7.9)	73.9 (8.8)
Gender, female, n (%)	43 (64.2)	14 (63.6)	29 (64.4)
Level of education, n (%) low, $N = 59$	29 (43.3)	9 (42.9)	20 (52.6)
Marital status, married, n (%)	51 (76,1)	14 (63.6)	23 (51.1)
MMSE-score at baseline, median (IQR), $N = 58$	26.0 (7.0)	27.5 (5.0)	24.0 (8.0)
Depression characteristics			
MADRS (depression severity)			
At baseline, mean (SD)	33.1 (8.3)	33.0 (6.3)	33.1 (9.2)
After last ECT, mean (SD)	4.3 (2.7)	4.7 (2.8)	4.2 (2.7)
Early onset of first depression (< 55 yr.), n (%)	25 (37.3)	9 (40.9)	16 (35.6)
Psychotic depression, n (%)	39 (58.2)	9 (40.9)	30 (66.7)
index episode in months, median (IQR), $N = 62$	6.0 (10.0)	6.0 (12.0)	5.5 ± (9.0)
ECT characteristics			
Number of ECT treatments, mean (SD)	10.4 (4.2)	10.7 (3.6)	10.2 (4.5)
Side of treatment, n (%)			
Unilateral treatment	55 (82.1)	18 (81.8)	37 (82.2)
Bilateral treatment	12 (17.9)	4 (18.2)	8 (17.8)
Treatment direct after ECT-course, n (%)	1 (1.5)	0 (0.0)	1 (2.2)
	20 (29.9)	6 (27.3)	14 (31.)
No treatment	1 (1.5)	0 (0.0)	1 (2.2)
Antidepressant	25 (37.3)	6 (27.3)	19 (42.2)
Mood-stabilizer	7 (10.4)	2 (9.1)	5 (11.1)
Combination pharmacotherapy			
m-ECT			

Notes. Education: low (no education, primary school) versus middle/high (high school, vocational training, college, university). Abbreviations: SD: standard deviation, IQR: interquartile range, MMSE: mini-mental state examination, MADRS: Montgomery Åsberg Depression Rating Scale, ECT: electro-convulsive therapy. †Relapse is defined as MADRS-score > 15, readmission or restarting the ECT. Treatment after ECT: Antidepressant = tricyclic antidepressant (TCA) or Selective Serotonin Reuptake Inhibitor (SSRI), mood-stabilizer = Lithium, combination pharmacotherapy = TCA + lithium, m-ECT = maintenance-ECT.

Table 3
Baseline clinical characteristics associated with relapse within six months after ECT based on bivariate logistic regression.

	Bivariate logistic regression		
	OR (95% CI)	Wald χ^2	*p*-value
Age	1.00 (0.94–1.06)	0.00	0.97
Depression severity	0.99 (0.94–1.06)	0.00	0.97
Early age at onset of first depression	1.26 (0.44–3.57)	0.18	0.67
(< 55 yr.)	0.35 (0.12–0.99)	3.91	**0.048**
Psychotic depression	1.00 (0.97–1.03)	0.07	0.80
Duration index episode	1.13 (0.99–1.29)	3.06	0.08
Cognitive functioning			

Notes. $P < .05$ is considered as statistically significant. In all analyses the degrees of freedom was 1. Depression severity is indicated by the Montgomery Åsberg Depression Rating Scale; cognitive functioning is indicated by the Mini-Mental-State Examination. Relapse is defined as MADRS-score > 15, readmission or restarting the ECT.

3.2. Clinical characteristics associated with remission and relapse after ECT

No clinical baseline characteristics were significantly associated with remission, including psychotic symptoms (odds ratio [OR]; 1.89, 95% confidence interval [CI]: 0.84–4.19; *Wald* $\chi^2 = 2.37$; df = 1, $p = .12$).

Of the remitted patients ($N = 73$), a total of 41 patients had a psychotic depression (56.2%). Patients with psychotic depression had a relapse rate of 23.1% (9 out of 39, missing FU: $n = 2$) within six months after ECT, whereas 46.1% (13 out of 28, missing FU: $n = 4$) of the non-psychotic patients experienced a relapse. Patients with psychotic depression had a decreased likelihood of developing a relapse (OR = 0.35, 95% CI: 0.12–0.99; *Wald* $\chi^2 = 3.91$; df = 1, $p = .048$), compared to those without psychotic symptoms at baseline (Table 3).

No significant association was observed between age, baseline depression severity, age at onset of first depression, duration index episode, or baseline cognitive functioning and relapse within six months. No significant differences were observed in baseline characteristics between psychotic and non-psychotic depression regarding their average age at treatment, gender, age at onset, depression severity, index-duration, number of previous antidepressants, or cognitive functioning. Also, these patients did not significantly differ in post-ECT treatment. A trend of significance was observed for prior admissions, such that patients with psychotic depression on average had less prior admissions ($M = 2.7$, SD = 2.4) compared to patients with non-psychotic depression ($M = 5.2$, SD = 7.7), t (df = 63) = 1.84, $p = .07$ (Table 4). Adding psychotic depression and prior admission in a multiple logistic regression model showed a significant effect of presence of psychotic symptoms (OR = 0.32, 95%CI: 0.11–0.98; *Wald* $\chi^2 = 3.96$; df = 1, $p = .047$), but not for prior admissions (OR = 1.06, 95%CI: 0.94–1.20; *Wald* $\chi^2 = 0.84$; df = 1; $p = .36$). In this analysis no multicollinearity was observed.

4. Discussion

The primary aim of this study was to evaluate which baseline clinical characteristics would be related to relapse within six months after ECT in a cohort of remitted patients with LLD. As a secondary aim, remission of this cohort was studied. In the current naturalistic prospective study, patients with LLD showed high remission rates of 66.3%, and a substantial amount of patients (67.3%) did not relapse after successful ECT. An important finding of the current study is that patients with psychotic depression at baseline were less likely to relapse after ECT compared to patients without psychotic symptoms;76.9% of the patients with psychotic depression remained remitted within six months after ECT. This result is in line with previous findings in the same cohort, showing that psychotic depression is positively associated

Table 4
Differences in post-ECT treatment between psychotic and non-psychotic patients.

	Non-psychotic depression(N = 28)	Psychotic depression(N = 39)	X^2, t(df)	p-value
Baseline clinical characteristics				
Age, mean (SD)	74.4 (7.9)	73.5 (8.9)	0.43 (65)	0.67
Depression severity, mean (SD)	31.2 (6.3)	33.9 (9.5)	−0.91 (65)	0.36
Age at onset first depression (< 55 yr), n (%)	12 (42.8)	13 (33.3)	0.63 (1)	0.43
Index duration, mean (SD)	9.1 (8.9)	10.4 (23.6)	−0.27 (60)	0.79
Cognitive functioning, mean (SD)	25.0 (3.9)	23.2 (5.8)	1.34 (56)	0.17
Nr of prior antidepressants current episode, mean (SD)	2.0 (1.1)	1.8 (1.02)	0.46 (63)	0.65
Prior admissions, mean (SD)	5.2 (7.7)	2.7 (2.4)	1.84 (63)	0.07
Treatment direct after ECT-course, n (%)				
Antidepressant	11 (39.2)	9 (23.1)	2.05 (1)	0.15
Mood-stabilizer	1 (3.6)	0 (0.0)	1.41 (1)	0.23
Combination pharmacotherapy	8 (28.6)	17 (43.6)	1.57 (1)	0.21
m-ECT	3 (10.7)	4 (10.3)	0.00 (1)	0.95

Notes. $P < .05$ is considered as statistically significant. Depression severity is indicated by the Montgomery Åsberg Depression Rating Scale; cognitive functioning is indicated by the Mini-Mental-State Examination.Treatment after ECT: Antidepressant = tricyclic antidepressant (TCA) or Selective Serotonin Reuptake Inhibitor (SSRI), mood-stabilizer = Lithium, combination pharmacotherapy = TCA + lithium, m-ECT = maintenance-ECT.

with better treatment response (Dols et al., 2017; Veltman et al., 2019) indicating that ECT is most effective in psychotic depression up to six months after ECT.

4.1. Comparison to previous literature

Contrary to our expectations, we did not find a significant association between duration of index episode, age at onset, age at treatment, depression severity or cognitive functioning at baseline and relapse. A possible explanation for this might be that ECT is extremely effective in severely depressed patients above the age of 65 (van der Wurff et al., 2003), independently from various baseline clinical characteristics that are of importance in adult populations. Patients in the current cohort had a mean age of 73.8 years and were severely depressed (mean MADRS at baseline = 33.1), while other studies included patients with a younger age, with bipolar depression, and they excluded patients with psychotic depression (Haq et al., 2015; Jelovac et al., 2013). Another possible explanation for this might be the lack of power in the current cohort. It is possible, that increasing the sample size might influence the results. For example, we did observe a trend in significance between baseline cognitive functioning and relapse (OR = 1.13, 95% CI = 0.99–1.29, p = .08), but with a small sample size caution must applied.

The finding that patients with psychotic depression were less likely to experience relapse, contributes to a growing body of literature on the association between psychotic depression and ECT effectiveness (Bingham et al., 2019; van Diermen et al., 2018; Brus et al., 2019). The presence of psychotic features based on clinical judgement was found to be a robust predictor of response to ECT in the MODECT-cohort as previously shown by Dols et al. (2017). In the current study, we did not observe a significant association between remission and psychotic depression, nor with age at onset. However, we did observe that patients with psychotic depression had a lower relapse risk within a period of six months after ECT. This is in line with the large population-based register study of Brus et al., 2019. Post-hoc we analyzed whether patients with psychotic depression differed from non-psychotic patients regarding various baseline characteristics, including age, depression severity, age of onset, index duration, cognitive functioning, prior antidepressants, prior admissions, or post-ECT treatment. No significant difference was observed for most variables, however prior admissions showed a trend. The latter is in line with other studies showing an important role of prior admissions in predicting relapse of depressive symptoms (Cearns et al., 2019; Donisi et al., 2016; Innes et al., 2015). After controlling for prior admissions, still patients with psychotic symptoms had a lower relapse risk after ECT. Hence, older depressed patients with psychotic features seem to have a better treatment prognosis. Our findings support the hypothesis that psychotic depression can be described as a specific depression subtype, with a more endogenous pathophysiology (Petrides et al., 2001; Schatzberg and Rothschild, 1992). Psychotic depression is characterized by mood-congruent delusions and/or hallucinations and is one of the most severe subtypes of major depression (Association, 2000; Gaudiano et al., 2008) with melancholic characteristics, a higher risk of suicide, greater depression severity, and more often treatment-resistance (Dold et al., 2019). Patients with psychotic depression may be referred for ECT more quickly, due to severity of the illness and life threatening symptoms. Therefore, the index duration of patients with psychotic depression is often shorter, which is related to a better ECT response (Haq et al., 2015; Kho et al., 2005; Prudic et al., 2013). Additionally, psychotic depression among patients with LLD has a later age of onset, which is also associated with a better ECT response (Dols et al., 2017; Haq et al., 2015; Medda et al., 2013; Pinna et al., 2018; Prudic et al., 2013; Sackeim et al., 2001). The current study could not confirm that age of onset and index episode are related to relapse after successful ECT. This may indicate that these characteristics predict initial ECT response as we have previously shown within the MODECT-study (Dols et al., 2017), but not treatment effect on the long term. Another explanation can be that all patients who remitted had short index episodes, i.e. median of 6 months (IQR = 10) and higher age, m = 73.8 (SD = 8.4). In a factor-analysis approach to characterize symptoms of psychotic depression, Gournellis et al. (2009) showed that *delusional strength* captures the essence of the depressive psychotic experience. This factor was strongly correlated with patient's overall severity of depression, lower age at index episode and shorter duration of illness. Next to this clinical distinct presentation of patients with psychotic LLD, Magnetic Resonance Imaging studies (MRI) studies also indicate a difference in resting-state functional connectivity. For example, studies have shown a decreased functional connectivity of the brain's fronto-parietal network for patients with psychotic depression (Neufeld et al., 2018; Oudega et al., 2019), and remission from psychotic depression was associated with an absence of increased default-mode network functional connectivity (Neufeld et al., 2018). In conclusion, different studies strongly suggest that psychotic depression is a distinct subtype of depression with better treatment prognosis on the short-term (response) and long-term (less relapse) and differences in pathophysiology.

4.2. Strengths and limitations

The strength of the current study is its naturalistic design, which represents clinical practice when treating the most severely depressed

patients. Another strength is that multiple clinical variables were evaluated, which provided an extensive overview of possible risk factors for developing relapse. These possible predictors were chosen carefully based on the current literature on remission and relapse after ECT in LLD. Still, due to the relatively small sample size, the amount of tested variables was limited. Due to its naturalistic design, we did not have strict protocols during the follow-up phase concerning pharmacotherapy and maintenance-ECT (m-ECT). Although we did not observe differences in post-ECT treatments between relapse and non-relapse patients, no causal conclusions can be drawn on the effectiveness of treatment post-ECT.

4.3. Future studies

Despite the interesting findings of the current study, replication studies in larger cohorts are recommended to validate the current findings. Another important issue for future research is long-term follow-up after ECT to evaluate relapse and cognitive functioning within 5 years after ECT. Additionally, it would be worthwhile to look into the differences in relapse prevention between psychotic and non-psychotic depression.

4.4. Conclusion and clinical implications

In conclusion, the majority of our patients with LLD remitted (66.4%), and of those the majority did not develop a relapse (67.3%) within a period of six months. Previously we showed patients with psychotic depression had a better ECT response (Dols et al., 2017; Veltman et al., 2019), now we confirmed that in these patients relapse rates are lower. Altogether, these findings strengthen the notion that psychotic depression is a distinct type of depression. Considering the higher response and lower relapse rates for patients with psychotic depression, this also means that patients without psychotic symptoms are less likely to respond well to ECT and have a higher risk to relapse. Therefore it is important to monitor these non-psychotic depressed patients more carefully after treatment completion and focus on relapse prevention, as their depression may have a more exogenic origin making them prone for relapse (Kellner et al., 2016, 2006; Nordenskjold et al., 2013).

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CRediT authorship contribution statement

Margot J. Wagenmakers: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Mardien L. Oudega:** Conceptualization, Writing - review & editing. **Kristof Vansteelandt:** Writing - review & editing. **Harm-Pieter Spaans:** Writing - review & editing. **Esmée Verwijk:** Writing - review & editing. **Jasmien Obbels:** Writing - review & editing. **Didi Rhebergen:** Writing - review & editing. **Eric van Exel:** Writing - review & editing. **Filip Bouckaert:** Writing - review & editing. **Max L. Stek:** Writing - review & editing. **Pascal Sienaert:** Conceptualization, Writing - review & editing. **Annemieke Dols:** Conceptualization, Writing - review & editing.

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