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# Remission Rates Following Electroconvulsive Therapy and Relation to Index Episode Duration in Patients With Psychotic Versus Nonpsychotic Late-Life Depression

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## ABSTRACT

**Objective:** Electroconvulsive therapy (ECT) is a safe and effective treatment, especially in psychotic late-life depression (LLD). However, it is not yet clear whether the greater efficacy seen in psychotic LLD is because of a shorter index episode duration. The first aim of this study was to substantiate the superior ECT remission rates in patients with psychotic LLD, as compared to patients with nonpsychotic LLD, and a second aim was to investigate whether this association is independent of the index duration.

**Methods:** 186 patients with LLD treated with ECT were included in the study: 76 from the Valerius cohort (data collection from 2001 to 2006) and 110 from the Mood Disorders Treated with Electroconvulsive Therapy (MODECT) cohort (data collection from 2011 to 2013). The Montgomery-Asberg Depression Rating Scale (MADRS) was used to evaluate depression severity, with remission defined as 2 consecutive MADRS scores < 10. Diagnosis of depression was based on *DSM-IV* (Valerius) and *DSM-IV-TR* (MODECT) criteria. A stepwise logistic regression model was built to assess the association between psychotic symptoms, index duration, and remission.

**Results:** Patients with psychotic LLD showed significantly higher remission rates compared to patients with nonpsychotic LLD (68.9% vs 51.0%), independent of index duration, additionally corrected for age, sex, and baseline depression severity (OR = 2.10 [95% CI, 1.07–4.10], *P* = .03).

**Conclusions:** Patients with psychotic LLD treated with ECT show higher remission rates compared to patients with nonpsychotic LLD. The high remission rates in patients with psychotic LLD are not explained by a shorter index duration. Future studies focusing on neurobiological differences in psychotic versus nonpsychotic depression may indicate why this subtype of depression is very responsive to ECT.

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Psychotic depression, characterized by mood-congruent delusions and/or hallucinations with depressive themes of guilt and worthlessness,<sup>1,2</sup> is the most severe form of depression, with severe cognitive impairment<sup>3,4</sup> and a high risk of suicide.<sup>5</sup> Psychotic symptoms are seen more commonly in late-life depression (LLD) than in younger patients<sup>2</sup> and in males than in females,<sup>2,6</sup> and patients with psychotic LLD more often experience their first depressive episode at a later age at onset.<sup>7</sup>

Patients with psychotic LLD show poor response to antidepressant or antipsychotic monotherapy but higher response to a combined treatment (ie, antidepressant plus an antipsychotic drug).<sup>8</sup> Still, patients frequently do not respond to or tolerate treatment with antidepressants,<sup>9,10</sup> while their symptoms are often life-threatening. Therefore, the current guidelines recommend electroconvulsive therapy (ECT) as a first-choice treatment option.<sup>9,10</sup> ECT has proven to be safe and effective in LLD,<sup>11–18</sup> with the highest effectiveness for patients with psychotic LLD.<sup>14,18–28</sup>

Although van Diermen et al<sup>14</sup> demonstrated in their large meta-analysis that ECT is particularly effective in LLD and in those with psychotic symptoms, Haq et al<sup>15</sup> concluded in their meta-analysis that a limited index episode duration is the most important predictor of response to ECT. Possibly, patients with psychotic LLD are referred for ECT faster, due to the severity of the illness and life-threatening symptoms resulting in a shorter index duration,<sup>29</sup> which may explain the superior ECT effectiveness for patients with psychotic LLD. Other studies suggest that the superior ECT effectiveness for patients with psychotic LLD might be explained by the fact that not all patients with psychotic LLD have been treated extensively with antidepressants, while most patients with nonpsychotic depression have failed to respond to 1 or more antidepressant trials before being referred to ECT.<sup>30–32</sup>

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## Clinical Points

- Electroconvulsive therapy (ECT) is a safe and effective treatment, especially in psychotic late-life depression (LLD). Duration of the index episode does not have an influence of the association between presence of psychotic symptoms and ECT remission.
- It is important to treat patients with psychotic LLD with ECT, no matter the length of the index episode.

In summary, ECT is highly effective in LLD, especially in those with psychotic symptoms. However, it is not yet clear whether patients with psychotic LLD show higher ECT effectiveness because they are referred for ECT with a shorter index duration or because of the clinical differences. The first aim of the current study was to investigate the difference in ECT remission between patients with psychotic LLD and nonpsychotic LLD. The second aim was to test whether the association between presence of psychotic symptoms and ECT remission can be explained by the duration of the index episode.

## METHOD

### Study Sample

This study combines data from 2 naturalistic observational cohort studies,<sup>19,33</sup> the Valerius cohort<sup>33</sup> and the MODECT cohort.<sup>19</sup>

**Valerius cohort.** This naturalistic study evaluated ECT efficacy in depressed older patients admitted to the clinic for Geriatric Psychiatry of the VU University Medical Centre/Stichting Buitenamstel Geestgronden, Amsterdam, The Netherlands.<sup>33</sup> Patients were included from 2001 until 2006. Inclusion criteria were age  $\geq 55$  years, referral for ECT, and a diagnosis of unipolar depression according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).<sup>34</sup> Patients with a clinical diagnosis of dementia were excluded. Over a period of 5 years, a total of 76 patients provided written informed consent to participate. A diagnosis of depression according to DSM-IV criteria was confirmed by 2 geriatric psychiatrists, who also examined all patients with respect to possible dementia.

**MODECT cohort.** This naturalistic prospective study investigated clinical characteristics, brain morphology, and responsiveness to ECT in patients with severe LLD.<sup>19</sup> Patients 55 years and older were included with a diagnosis of a severe unipolar depression according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR).<sup>1</sup> Exclusion criteria were a diagnosis of bipolar disorder, schizoaffective disorder, comorbid major DSM-IV-TR psychiatric illness, or neurologic illness (including stroke, dementia, and Parkinson's disease). Diagnoses were established by experienced psychiatrists and confirmed via the Mini-International Neuropsychiatric Interview Plus 5.0.0. (MINI-plus [MINI]).<sup>35</sup> Over a 3-year period (2011–2013), a total of 110 patients were included in the study. Patients were enlisted through 2 tertiary

psychiatric hospitals located in Amsterdam (GGZ inGeest, the Netherlands; N = 67) and Leuven (Psychiatric Center, KU Leuven, Belgium; N = 43).

### Clinical Characteristics and Assessments

**Demographics.** Demographic and clinical characteristics were obtained using a clinical interview and double-checked by chart review. Early onset depression was defined as having a first depressive episode before the cutoff age of 55 years.<sup>19</sup> The diagnosis of depression with or without psychotic symptoms was based on DSM-IV (Valerius cohort) and DSM-IV-TR (MODECT cohort) criteria and confirmed using the MINI in the MODECT cohort.<sup>1,34,35</sup> The duration of the index episode was defined as the period from the start of the depressive episode until the first ECT session in months.

**Depression severity.** To monitor the severity of depressive symptoms, the Montgomery-Asberg Depression Rating Scale (MADRS)<sup>36</sup> was administered before and after ECT and during ECT on a weekly basis. The total score for the MADRS ranges from 0 to 60, with higher scores being indicative of greater depression severity. To be classified as a responder to ECT, a MADRS score reduction of at least 50% was required. Remission after ECT is defined as a MADRS score lower than 10 for at least 2 successive weekly clinical evaluations.

**Cognitive functioning.** Global cognitive functioning was examined using the Mini-Mental State Examination (MMSE).<sup>35</sup> The MMSE consists of 11 categories aiming to assess the patient's cognitive functioning regarding attention, orientation, memory, registration, calculation, language, and visual-spatial skills. The total score for the MMSE ranges from 0 to 30, with scores of 24 and below being indicative of cognitive impairment. The MMSE was administered before and 1 week after the ECT course.

### ECT Procedure

Patients received ECT twice a week according to the Dutch and European guidelines for ECT.<sup>37,38</sup> ECT was conducted using the Thymatron System IV (Somatics, LLC, Lake Bluff, IL; maximum energy 200%, 1,008 mC). For the Valerius cohort, an age dosing protocol was used. Age determined the energy supplied; for example, a 75-year-old patient would receive right unilateral ECT at a dosage of 75%, corresponding with 378 mC. When treated bilaterally (bitemporal only), half of this dosage was considered adequate.<sup>39</sup> A motor seizure of a minimum of 25 seconds was considered adequate. A pulse width of 0.5–1 ms was provided. For the MODECT cohort, a titration protocol was used.<sup>19</sup> At the first treatment session, the subject's seizure threshold (ST) was established by empirical dose titration; for right unilateral electrode placement (RUL), 6 times the initial seizure threshold (ST), and for bilateral ECT, 1.5 times ST. All patients were treated with brief pulse ECT (0.5–1.0 ms). In both cohorts, patients were treated until remission, defined as a MADRS score of less than 10 on 2 consecutive ratings with a week interval or until patients showed no

**Table 1. Demographic and Baseline Clinical Differences Between Psychotic and Nonpsychotic Late-Life Depression and Full Sample<sup>a</sup>**

	Full sample (N = 186)	Nonpsychotic LLD N = 96 (51.6%)	Psychotic LLD N = 90 (48.4%)	Statistics <sup>b</sup>	
				F (df)/ OR + Wald (df)	P value
<b>Demographics</b>					
Age, y, mean (SD)	73.1 (8.2)	72.2 (7.8)	74.2 (8.6)	2.91 (1)	.090
Female, n (%)	122 (65.3)	58 (60.4)	64 (71.1)	0.62, 2.30 (1)	.13
Low education level, n (%)	20 (13.2)	11 (13.4)	9 (13.0)	0.84, 0.09 (1)	.77
<b>ECT characteristics</b>					
Unilateral treatment, n (%)	124 (66.7)	61 (63.5)	63 (70.0)	1.70, 2.45 (1)	.12
Number of ECT sessions, mean (SD)	12.2 (6.0)	12.0 (5.4)	12.5 (6.5)	0.41 (1)	.52
<b>Clinical characteristics</b>					
Late age at onset (> 55 y), n (%)	106 (57.9)	49 (52.1)	57 (64.0)	0.60, 2.82 (1)	.09
MADRS score before ECT, mean (SD)	33.5 (9.2)	33.0 (12)	35.0 (13)	2.39 (1)	.12
Index episode duration, mo, median (IQR)	6.0 (9)	7 (12)	6 (8)	2.42 (1)	.12
MMSE score before ECT, mean (SD)	24.8 (4.1)	25.9 (3.7)	23.5 (5.6)	10.32 (1)	<b>.002</b>
MMSE score post ECT, mean (SD)	26.2 (4.1)	26.5 (3.9)	25.8 (4.3)	1.33 (1)	.25

<sup>a</sup>Statistical tests are based on logistic regression analyses for dichotomous outcome variables and linear regression for continuous outcome variables.  $P < .05$  is considered as statistically significant (indicated by boldface). Education: low (no education, primary school) versus middle (high school, vocational training) and high (college, university). Depression severity is indicated by the MADRS. Cognitive functioning is indicated by the MMSE. Index episode duration: the period from the start of the depressive episode until the first ECT session in months.

<sup>b</sup>Corrected for cohort effect.

Abbreviations: ECT = electroconvulsive therapy, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination, OR = odds ratio, SD = standard deviation.

**Table 2. Demographics and Clinical Characteristics of Valerius and MODECT Cohorts<sup>a</sup>**

	Valerius cohort (n = 76)	MODECT cohort (n = 110)	Statistics	
			$\chi^2/t$ (df)/MW	P value
<b>Demographics</b>				
Age, y, mean (SD)	73.5 (7.8)	72.9 (8.5)	0.46 (184)	.46
Female, n (%)	49 (64.5)	73 (66.4)	0.07 (1)	.79
Low education level, n (%)	6 (10.2)	14 (15.2)	0.80 (1)	.37
<b>ECT characteristics</b>				
Unilateral treatment, n (%)	55 (72.4)	69 (62.7)	1.88 (1)	.17
Number of ECT sessions, mean (SD)	12.8 (6.5)	11.8 (5.6)	1.11 (179)	.27
<b>Clinical characteristics</b>				
Late age at onset (> 55 y), n (%)	45 (61.6)	61 (55.5)	0.69 (1)	.41
MADRS score before ECT, mean (SD)	33.6 (9.9)	33.4 (8.8)	0.16 (178)	.87
Remission after ECT, n (%)	38 (50.0)	73 (66.4)	5.0 (1)	<b>.03</b>
Episode duration, mo, median (IQR)	6.0 (9)	6.0 (9)		MW = .96
MMSE score before ECT, mean (SD)	25.4 (4.4)	24.3 (5.1)	1.39 (171)	.16
Psychotic symptoms, n (%)	34 (44.7)	56 (50.9)	0.69 (1)	.41

<sup>a</sup>Statistical tests are based on  $\chi^2$  statistics for categorical variables, t tests for continuous variables, Mann-Whitney (MW) as nonparametric alternative.  $P < .05$  is considered as statistically significant (indicated by boldface). Education: low (no education, primary school) versus middle (high school, vocational training) and high (college, university). Remission after ECT is defined as a MADRS score lower than 10 points after ECT. Index episode duration: the period from the start of the depressive episode until the first ECT session in months.

Abbreviations: ECT = electroconvulsive therapy, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination, MODECT = Mood Disorders Treated with Electroconvulsive Therapy.

further improvement in clinical condition during the last 2 weeks of ECT sessions after a minimum of 6 unilateral and 6 bilateral sessions. Switching to bilateral ECT was applied when after 6 unilateral treatments the clinical condition worsened (ie, an increase in total MADRS scores, presence of debilitating psychotic features, increased suicidality, dehydration, or weight loss or when after 6 unilateral treatments there was no clinical improvement according to the judgment of the treating psychiatrist). For the MODECT cohort, psychotropic medication was discontinued at least 1 week prior to ECT or, if this was deemed impossible, kept stable from 6 weeks before ECT and during the ECT course. In the Valerius cohort, psychotropic medication was tapered

off within 2 weeks before starting ECT. Antipsychotic medication was allowed when clinically indicated (agitation, anxiety, insomnia).

### Ethical Issues

Both protocols were approved by the Ethical Review Board of the VU University Medical Center, the MODECT protocol was also approved by the ethical review board of the Catholic University of Leuven and was conducted according to the Declaration of Helsinki and registered at ClinicalTrials.gov (identifier: NCT02667353). Written informed consent was obtained from all patients. The original data set of both cohorts is available by request from the first author.

**Table 3. Stepwise Logistic Regression Associations With Remission to Electroconvulsive Therapy in Late Life Depression<sup>a</sup>**

	OR (95% CI)	Wald $\chi^2$	P value
<b>Model 1</b>			
Psychotic depression Cohort	2.01 (1.07–3.79)	4.71	<b>.03</b>
	1.83 (0.97–3.44)	3.50	.06
<b>Model 2</b>			
Psychotic depression Cohort	1.89 (1.00–3.61)	3.79	.052
	1.92 (1.01–3.65)	4.00	.046
Index episode duration	0.98 (0.96–1.00)	2.85	.09
<b>Model 3</b>			
Psychotic depression Cohort	2.10 (1.07–4.10)	4.70	<b>.03</b>
	1.93 (1.10–3.69)	3.94	.047
Index episode duration	0.98 (0.96–1.00)	3.48	.06
Age	1.00 (0.96–1.04)	0.01	.94
Sex	1.31 (0.66–2.60)	0.59	.44
Baseline depression severity	0.97 (0.93–1.00)	2.98	.09

<sup>a</sup> $P < .05$  is considered as statistically significant (indicated by boldface). In all analyses, the degrees of freedom were 1. Depression severity is indicated by the Montgomery-Asberg Depression Rating Scale (MADRS); remission is defined as MADRS  $< 10$  for at least 2 successive clinical evaluations. Index episode duration: the period from the start of the depressive episode until the first electroconvulsive therapy session in months.

Abbreviation: OR = odds ratio.

**Table 4. Logistic Regression Associations With Remission to Electroconvulsive Therapy in Late Life Depression, Valerius Cohort<sup>a</sup>**

	OR (95% CI)	Wald $\chi^2$	P Value
<b>Model 1</b>			
Psychotic depression	1.99 (0.78–5.11)	2.05	.15
<b>Model 2</b>			
Psychotic depression	1.91 (0.74–4.95)	1.76	.18
Index duration	0.98 (0.94–1.02)	0.88	.35
<b>Model 3</b>			
Psychotic depression	1.97 (0.71–5.43)	1.72	.19
Index episode duration	0.98 (0.94–1.02)	0.93	.33
Age	1.00 (0.94–1.07)	0.00	.98
Sex	1.09 (0.39–3.08)	0.03	.87
Baseline depression severity	0.98 (0.94–1.03)	0.44	.51

<sup>a</sup> $P < .05$  is considered as statistically significant. In all analyses the degrees of freedom were 1. Depression severity is indicated by the Montgomery-Asberg Depression Rating Scale (MADRS); remission is defined as MADRS  $< 10$  for at least 2 successive clinical evaluations. Index episode duration: the period from the start of the depressive episode until the first electroconvulsive therapy session in months.

Abbreviation: OR = odds ratio.

## Statistical Analyses

Statistically significant differences between patients with and without psychotic LLD were estimated using linear regression models for continuous outcome variables and logistic regression models for dichotomous outcome variables and were corrected for cohort effect. A stepwise multiple logistic regression was built to first investigate the difference in ECT remission between patients with and without psychotic symptoms (model 1). In the second step, index episode duration was added to test whether the association between presence of psychotic symptoms and ECT remission is dependent on index duration (model 2). In the final step, we additionally corrected for age, gender, and baseline severity as these variables might also influence the

**Table 5. Logistic Regression Associations With Remission to Electroconvulsive Therapy in Late Life Depression, MODECT Cohort<sup>a</sup>**

	OR (95% CI)	Wald $\chi^2$	P value
<b>Model 1</b>			
Psychotic depression	2.03 (0.87–4.77)	2.65	.10
<b>Model 2</b>			
Psychotic depression	2.05 (0.75–5.60)	1.96	.16
Index duration	0.98 (0.96–1.01)	2.00	.16
<b>Model 3</b>			
Psychotic depression	2.26 (0.90–5.67)	3.04	.08
Index episode duration	0.98 (0.96–1.00)	2.90	.09
Age	1.00 (0.95–1.06)	0.02	.88
Sex	1.47 (0.57–3.81)	0.63	.43
Baseline depression severity	0.95 (0.89–1.01)	3.17	.08

<sup>a</sup> $P < .05$  is considered as statistically significant. In all analyses the degrees of freedom were 1. Depression severity is indicated by the Montgomery-Asberg Depression Rating Scale (MADRS); remission is defined as MADRS  $< 10$  for at least 2 successive clinical evaluations. Index episode duration: the period from the start of the depressive episode until the first ECT session in months.

Abbreviations: MODECT = Mood Disorders Treated with Electroconvulsive Therapy, OR = odds ratio.

association between psychotic symptoms and ECT remission (model 3). Every step was corrected for cohort effect (Valerius cohort vs MODECT cohort). In order to account for multicollinearity, correlation coefficients between all independent variables were computed. If a correlation coefficient between 2 variables was above 0.80 or if variance inflation factor (VIF)  $> 5$ , these variables were not added to the same model. Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 26, SPSS Inc., Chicago, IL). In all analyses, a  $P < .05$  was considered statistically significant.

## RESULTS

### Demographics and Clinical Characteristics

Patients ( $n = 186$ ) had a mean age of 73.1 years (standard deviation: 8.2) and were predominantly female ( $n = 122$ , 65.3%); see Table 1. The overall response rate was 74.2%, and the remission rate was 59.7%. In comparison to patients with nonpsychotic LLD, patients with psychotic LLD were numerically older, more often had a late age at onset, had a shorter index duration, and, lastly, showed more severe cognitive impairment at baseline (psychotic LLD mean MMSE = 23.5 [SD = 5.6], nonpsychotic LLD mean MMSE = 25.9 [3.7]); see Table 1. However, except for cognitive functioning before ECT, none of these differences reached statistical significance (Table 1). Post-ECT, both groups improved in cognitive functioning (psychotic LLD mean MMSE = 25.8 [SD = 4.3] versus nonpsychotic LLD mean MMSE = 26.5 [SD = 3.9]), and there were no statistical differences between both groups in cognitive functioning post-ECT. The MODECT cohort showed a significantly higher remission rate of 66.4% compared to 50% in the Valerius cohort ( $\chi^2_1 = 5.0$ ,  $P = .03$ ; Table 2); therefore, the stepwise logistic regression analyses were corrected for a cohort effect. In the Dutch part of the MODECT cohort,



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during ECT, antipsychotic medication was provided to 5 patients with psychotic LLD, of whom 2 remitted after ECT. In 5 patients with nonpsychotic depression, antipsychotic medication was provided during ECT, all of these patients remitted after ECT. No information on medication during ECT was available for the Belgian part of the MODECT cohort or for the Valerius cohort.

### ECT Remission in Psychotic LLD

Patients with psychotic LLD showed a significantly higher remission rate (68.9%) compared to patients with nonpsychotic LLD (51.0%) (OR = 2.01; 95% CI, 1.1–4.23, Wald  $\chi^2_1 = 4.71$ ,  $P = .03$ ); see Tables 1 and 3. After adding index duration, (see model 2, Table 3), the association between psychotic symptoms and remission just lost significance, albeit with a large effect size (OR = 1.92; 95% CI, 1.00–3.61; Wald  $\chi^2_1 = 3.79$ ,  $P = .05$ ). Index duration did not show a significant association with remission (OR = 0.98; 95% CI, 1.00–3.661; Wald  $\chi^2_1 = 2.82$ ;  $P = .09$ ). After additional correction for age, sex, and depression severity at baseline, psychotic symptoms were significantly associated with ECT remission (OR = 2.10; 95% CI, 1.07–4.10; Wald  $\chi^2 = 4.70$ ,  $P = .03$ ), with no significant association between index duration and ECT remission (OR = 0.97; 95% CI, 0.93–1.00; Wald  $\chi^2 = 2.98$ ,  $P = .09$ ).

### DISCUSSION

In the current study, we confirmed the superior remission rates for patients with psychotic LLD in comparison to patients with nonpsychotic LLD within a large combined clinical sample (remission, 68.9% vs 51.0%). To our knowledge, we are the first to demonstrate that the high ECT remission rates in psychotic LLD patients could not be explained by a shorter index episode duration.

Another explanation for the higher remission rates for patients with psychotic LLD might be that patients with psychotic LLD are often not treated extensively before they are referred to ECT, whereas patients with nonpsychotic LLD are often treatment-resistant before they were referred to ECT.<sup>30–32</sup> However, post hoc analyses in the present sample failed to demonstrate an association between treatment resistance and response to ECT in psychotic depression, which have been due to suboptimal assessment of treatment resistance in the Valerius cohort, since the assessment of treatment resistance was not based on the Antidepressant Treatment History Form.<sup>40</sup>

Psychotic LLD is often described as a more severe subtype of a depressive illness, with more cognitive impairment and higher suicide rates.<sup>3,5</sup> Indeed, we observed a higher depression severity at baseline, as measured with the MADRS questionnaire, for patients with psychotic LLD. Also, we observed that patients with psychotic LLD showed worse cognitive functioning before starting with ECT. This finding corroborates the results by Gomez et al,<sup>3</sup> showing a worse cognitive profile for patients with psychotic symptoms. Important to notice is that post-ECT, no difference was

observed between psychotic and nonpsychotic LLD patients; MMSE scores improved above the clinical cutoff of 24. The latter result supports findings of a randomized controlled trial (RCT) showing that improvement in depression was associated with improvement in cognition in psychotic LLD.<sup>41</sup> Also, we can confirm that in our sample, patients with psychotic LLD more often had a later age at onset of their first depressive episode (> 55 years).<sup>7</sup> Indeed, patients with LLD at a later onset of the first depressive episode have a greater vulnerability to developing psychotic symptoms, possibly due to elevated cortisol levels,<sup>42,43</sup> but, also, neuroimaging studies have shown differences between patients with LLD with and without psychotic symptoms on both structural and functional imaging.<sup>44,45</sup> However, a complete understanding of the neurobiological differences between psychotic and nonpsychotic patients that may clarify their superior ECT remission is still lacking.

### Strengths and Limitations

The strength of the current study is its naturalistic design with two cohorts providing a total sample size of  $N = 186$ , which represents clinical practice when treating severely depressed patients. Furthermore, to account for differences in clinical assessment and inclusion/exclusion criteria, we analyzed the cohorts separately; see Tables 4 and 5. Although actual significant effects differed per cohort, when looking at the odds ratios (effect size independent from sample size), psychotic symptoms showed a stable association with ECT remission, independent of the index duration. Therefore, we would argue that the association between psychotic symptoms and ECT efficacy is stable across protocols, which argues for generalizability of the results. It can be argued that the distinction between presence or absence of psychotic symptoms may be a more gradual process that evolves in a natural way from mood symptoms alone to a worse condition in which hallucinations and/or delusions may occur. Although some patients may experience psychotic symptoms from the start of the depressive symptoms, some patients do not. A second limitation might be the difference in ECT administration. The Valerius cohort was based on an age dose protocol,<sup>33</sup> whereas the MODECT cohort<sup>19</sup> was based on a titration protocol. This could have led to a higher voltage in the Valerius cohort and therefore more cognitive side effects and differences in remission rates, for which we have corrected in all analyses. However, it is of importance to notice that we did not observe a difference in cognitive functioning post-ECT. Another strength is the investigation of the index duration by clinical interview and clinical judgment of psychotic symptoms, although in the Valerius cohort the presence of psychotic symptoms was not confirmed by the MINI. While a clinical interview may be of great value, it also has its limitations; for example, there may be recall bias regarding the patient's recollection for establishing duration of the current episode. In our sample, dementia was considered as an exclusion criterion. It is still possible that patients were included with depression and an underlying neurodegenerative disease. However, we tried to diagnose

the patients as accurately as possible by administering robust neuropsychological testing before ECT, in addition to administration of the MMSE and a clinical judgment by neuropsychologists. So, a limitation might be that patients were included with an underlying neurodegenerative disease instead of depression alone. A final limitation to mention is that some patients did not taper off their psychotropic medication during ECT, which could have influenced their remission of depressive symptoms. However, information on prescribed psychotropic medication during ECT was not collected for all patients, so no firm conclusion can be drawn concerning this issue.

## CONCLUSION AND CLINICAL IMPLICATION

In conclusion, patients with psychotic LLD treated with ECT show higher remission rates compared to patients with

nonpsychotic LLD. The high remission rates in patients with psychotic depression could not be explained by a shorter index episode duration. These findings provide relevant information for clinicians as they confirm the importance of treating patients with psychotic LLD with ECT, no matter the length of the index episode. Future studies, with a randomized controlled design (ie, RCTs), could examine whether within patients with psychotic LLD a shorter index episode might cause even higher remission rates. Although we see some differences in clinical presentation and treatment outcome, a complete understanding of the underlying neurobiology is still lacking. So far, the superior response to ECT in psychotic LLD cannot be explained by their clinical profile. Future studies focusing on neurobiological differences in psychotic versus nonpsychotic depression may indicate why this is the case.

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## REFERENCES

- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Press; 2000.
- Gaudiano BA, Young D, Chelminski I, et al. Depressive symptom profiles and severity patterns in outpatients with psychotic vs nonpsychotic major depression. *Compr Psychiatry*. 2008;49(5):421–429.
- Gomez RG, Fleming SH, Keller J, et al. The neuropsychological profile of psychotic major depression and its relation to cortisol. *Biol Psychiatry*. 2006;60(5):472–478.
- Leinola H, Honkalampi K, Hänninen T, et al. Treatment-resistant major depressive disorder with psychotic features is associated with impaired processing speed. *Arch Clin Neuropsychol*. 2016;31(7):780–785.
- Dold M, Bartova L, Kautzky A, et al. Psychotic features in patients with major depressive disorder: a report from the European group for the study of resistant depression. *J Clin Psychiatry*. 2019;80(1):17m12090.
- Gaudiano BA, Weinstock LM, Epstein-Lubow G, et al. Clinical characteristics and medication use patterns among hospitalized patients admitted with psychotic vs nonpsychotic major depressive disorder. *Ann Clin Psychiatry*. 2016;28(1):56–63.
- Gournellis R, Lykouras L, Fortos A, et al. Psychotic (delusional) major depression in late life: a clinical study. *Int J Geriatr Psychiatry*. 2001;16(11):1085–1091.
- Wijkstra J, Lijmer J, Burger H, et al. Pharmacological treatment for psychotic depression. *Cochrane Database Syst Rev*. 2015;(7):CD004044.
- American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. American Psychiatric Association; 2010.
- Trimbos-instituut. *ADDENDUM Ouderen bij Multidisciplinaire depressie richtlijn. (ADDENDUM Late Life Depression Multidisciplinary Guideline)*. Utrecht; 2008.
- Socci C, Medda P, Toni C, et al. Electroconvulsive therapy and age: age-related clinical features and effectiveness in treatment resistant major depressive episode. *J Affect Disord*. 2018;227:627–632.
- Spaans HP, Sienaert P, Bouckaert F, et al. Speed of remission in elderly patients with depression: electroconvulsive therapy v. medication. *Br J Psychiatry*. 2015;206(1):67–71.
- Salzman C, Wong E, Wright BC. Drug and ECT treatment of depression in the elderly, 1996–2001: a literature review. *Biol Psychiatry*. 2002;52(3):265–284.
- van Diermen L, van den Amele S, Kamperman AM, et al. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis - corrigendum. *Br J Psychiatry*. 2018;212(5):322.
- Haq AU, Sitzmann AF, Goldman ML, et al. Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. *J Clin Psychiatry*. 2015;76(10):1374–1384.
- Rhebergen D, Huisman A, Bouckaert F, et al. Older age is associated with rapid remission of depression after electroconvulsive therapy: a latent class growth analysis. *Am J Geriatr Psychiatry*. 2015;23(3):274–282.
- Sackeim HA, Prudic J, Fuller R, et al. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology*. 2007;32(1):244–254.
- O'Connor MK, Knapp R, Husain M, et al. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. *Am J Geriatr Psychiatry*. 2001;9(4):382–390.
- Dols A, Bouckaert F, Sienaert P, et al. Early- and late-onset depression in late life: a prospective study on clinical and structural brain characteristics and response to electroconvulsive therapy. *Am J Geriatr Psychiatry*. 2017;25(2):178–189.
- Wagenmakers MJ, Oudega ML, Vansteelandt K, et al. Psychotic late-life depression less likely to relapse after electroconvulsive therapy. *J Affect Disord*. 2020;276:984–990.
- Atiku L, Gorst-Unsworth C, Khan BU, et al. Improving relapse prevention after successful electroconvulsive therapy for patients with severe depression: completed audit cycle involving 102 full electroconvulsive therapy courses in West Sussex, United Kingdom. *J ECT*. 2015;31(1):34–36.
- Birkenhäger TK, Renes JW, Pluijms EM. One-year follow-up after successful ECT: a naturalistic study in depressed inpatients. *J Clin Psychiatry*. 2004;65(1):87–91.
- Birkenhäger TK, van den Broek WW, Mulder PG, et al. One-year outcome of psychotic depression after successful electroconvulsive therapy. *J ECT*. 2005;21(4):221–226.
- Heijnen WTCJ, Kamperman AM, Tjokrodipio LD, et al. Influence of age on ECT efficacy in depression and the mediating role of psychomotor retardation and psychotic features. *J Psychiatr Res*. 2019;109:41–47.
- Spaans HP, Verwijk E, Stek ML, et al. Early complete remitters after electroconvulsive therapy: profile and prognosis. *J ECT*. 2016;32(2):82–87.
- Pinna M, Manchia M, Oppo R, et al. Clinical and biological predictors of response to electroconvulsive therapy (ECT): a review. *Neurosci Lett*. 2018;669:32–42.
- Petrides G, Fink M, Husain MM, et al. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J ECT*. 2001;17(4):244–253.
- van Diermen L, Poljac E, Van der Mast R, et al. Toward targeted ECT: the interdependence of predictors of treatment response in depression further explained. *J Clin Psychiatry*. 2020;82(1):20m13287.
- Tonna M, De Panfilis C, Provini C, et al. The effect of severity and personality on the psychotic presentation of major depression. *Psychiatry Res*. 2011;190(1):98–102.
- Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA*. 2001;285(10):1299–1307.
- Andresescu C, Mulsant BH, Peasley-Miklus C, et al; STOP-PD Study Group. Persisting low use of antipsychotics in the treatment of major depressive disorder with psychotic features.

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32. Blumberger DM, Mulsant BH, Emeremni C, et al. Impact of prior pharmacotherapy on remission of psychotic depression in a randomized controlled trial. *J Psychiatr Res*. 2011;45(7):896–901.
33. Oudega ML, van Exel E, Wattjes MP, et al. White matter hyperintensities, medial temporal lobe atrophy, cortical atrophy, and response to electroconvulsive therapy in severely depressed elderly patients. *J Clin Psychiatry*. 2011;72(1):104–112.
34. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition, *DSM-IV* Edition. Washington, DC: American Psychiatric Association; 1994.
35. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
36. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
37. Van den Broek WW, Birkenhager TK, De Boer D, et al. *Richtlijn Elektroconvulsietherapie*. Ned Ver voor Psychiatr; 2010:36.
38. National Institute for Health and Care Excellence. Guidance on the use of electroconvulsive therapy. NICE Technology Appraisal Guidance 59. London, National Institute for Clinical Excellence. NICE website. <https://www.nice.org.uk/guidance/ta59>. April 26, 2003.
39. Farah A, McCall WV. Electroconvulsive therapy stimulus dosing: a survey of contemporary practices. *Convuls Ther*. 1993;9(2):90–94.
40. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):10–17.
41. Victoria LW, Whyte EM, Butters MA, et al. Improvement in depression is associated with improvement in cognition in late-life psychotic depression. *Am J Geriatr Psychiatry*. 2017;25(6):672–679.
42. Keller J, Flores B, Gomez RG, et al. Cortisol circadian rhythm alterations in psychotic major depression. *Biol Psychiatry*. 2006;60(3):275–281.
43. Posener JA, DeBattista C, Williams GH, et al. 24-Hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Arch Gen Psychiatry*. 2000;57(8):755–760.
44. Oudega ML, van der Werf YD, Dols A, et al. Exploring resting state connectivity in patients with psychotic depression. *PLoS One*. 2019;14(1):e0209908.
45. O'Connor S, Agius M. A systematic review of structural and functional MRI differences between psychotic and nonpsychotic depression. *Psychiatr Danub*. 2015;27(suppl 1):S235–S239.

*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at [jkarp@psychiatrist.com](mailto:jkarp@psychiatrist.com), or Gary W. Small, MD, at [gsmall@psychiatrist.com](mailto:gsmall@psychiatrist.com).

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