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Differences in Speed of Response of Depressive Symptom Dimensions in Older Persons During Electroconvulsive Therapy

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Introduction: Electroconvulsive therapy (ECT) is an important and effective treatment for depression. However, research on course trajectories of depressive symptoms during ECT is limited. Insight into putative differences in speed of response of depressive symptom dimensions may enable clinicians to optimally inform patients and their relatives. Therefore, we aim to examine course trajectories of depressive symptom dimensions in depressed older persons during ECT.

Methods: Data were derived from the Mood Disorders in Elderly treated with Electro Convulsive Therapy study, including 110 persons, aged 55 years or more, with a current diagnosis of major depressive disorder and referred for ECT. Exploratory factor analysis was used to identify symptom dimensions, using the 10 depression items of the Montgomery-Åsberg Depression Rating Scale (MADRS). Differences in course trajectories of symptom dimension during 2 weeks were examined by multilevel analyses.

Results: Three symptom dimensions were identified: a "mood," "melancholic," and "suicidal" dimension. Mood showed a significantly greater severity decline as compared with melancholic and suicidal at the 1-week follow-up. At the 2-week follow-up, both mood and melancholic demonstrated a significantly greater decline as compared with suicidal. However, because scores on the suicidality item of the Montgomery-Asberg Depression Rating Scale were already lower at baseline compared with the other items, a floor effect cannot be ruled out.

Discussion: All symptom dimensions of depression showed a rapid response to ECT. Our findings did not support the general assumption that suicidal symptoms may be the first to improve. However, a floor effect on the suicidality item cannot be ruled out.

Key Words: course trajectories, factor analysis, major depressive disorder, late life depression

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Depressive disorders among older persons are highly common and frequently of a chronic nature. They cause a high burden for both patients[1] and their caregivers,[2] with high societal costs.[3,4] Considering this great personal and societal impact, adequate treatment is of paramount importance. In addition to pharmacotherapy, electroconvulsive therapy (ECT) is an important treatment option for severe depressive disorders in older persons. It was demonstrated that older age is a positive predictor for ECT outcome,[5,6] with remission rates from 73% to 90% in patients more than 65 years of age.[7,8] In addition, the speed of remission is high[9,10] and significantly higher for ECT compared with pharmacotherapy.[11]

When treating depression, not all symptoms resolve at the same pace or to the same magnitude.[12–14] Both pharmacotherapy and psychotherapy are known to ameliorate not all symptoms to the same extent,[15,16] and, on average, remission occurs after several weeks to months. On the other hand, studies on ECT in both depressed older and younger adults have found that depressive symptoms show a very rapid response to ECT,[9,10] and within younger adults response has been found especially rapid for psychomotor symptoms, such as inhibition, agitation, or inner tension.[17–19] In a recent study on early remission in ECT, the early remitters [requiring 4 or less ECT sessions, accounting for 14% of the study population] had a significantly higher age than the other subjects.[20] However, insight into response trajectories of different symptom dimension within depressed older persons is lacking.

To gain a better insight into the dimensions of depressive symptoms and their course trajectories during ECT in depressed older persons, we explored the speed of response of different depressive symptom dimensions in an elderly cohort receiving ECT.

MATERIALS AND METHODS

Study Population

Data were derived from the Mood Disorders in Elderly treated with Electro Convulsive Therapy (MODECT) study, a 2-site longitudinal study including older in-patients (55 years or older) with severe unipolar depression according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*)[21] referred for ECT. Patients were recruited from tertiary psychiatric hospitals (GGZ inGeest, Amsterdam, the Netherlands, and the University Psychiatric Center, KU Leuven, Belgium). Patients with another major *DSM-IV* diagnosis or major neurological illness (including Parkinson disease, stroke, and dementia) were excluded, thus retaining a data set of 110 persons. Diagnosis was made at admittance to the ward by a psychiatrist and confirmed by the Mini International Neuropsychiatric Interview 5.0.0, Dutch version.[22] The study protocol of MODECT has been approved centrally by the ethical review board of the VU University Medical Center, Amsterdam, the Netherlands, and subsequently by the ethical review board of the Leuven University, Leuven, Belgium. Before participating in the study, all patients were provided with oral and written information. Written informed consent was obtained from

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all patients or—in case of inability consent—a legal representative. For a detailed description of the MODECT study, we refer to Dols et al.[23]

Depressive Symptoms

Depressive symptoms were measured by the Dutch version of the 10-item Montgomery-Åsberg Depression Rating Scale (MADRS[24,25]), a validated questionnaire for investigating 10 symptoms of major depressive disorder (MDD), including apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, anhedonia, pessimistic thoughts, and suicidal thoughts. For each item, a minimum of 0 points and a maximum of 6 points can be scored according to symptom intensity. The cumulative score of the MADRS can be used as an indicator for the severity of a depression. In MODECT, MADRS was assessed at baseline (before ECT), and weekly during ECT by raters trained to administer the MADRS. For the current study, baseline measurements and MADRS scores during the first 2 weeks were used, because significant improvement to complete remission is often seen within 2 weeks already.[11,20] Patients were excluded if baseline MADRS, 1-week follow-up, or 2-week follow-up MADRS was missing (n = 21).

Attrition analysis showed that persons with missing MADRS scores did not differ with respect to total MADRS score for baseline, week 1 and week 2, sex, age, and education from persons included in the study.

Characteristics

To characterize the study population and to enable comparison to other similar studies, sociodemographics and clinical variables were examined. For a detailed description of measurement of characteristics and clinical variables, we refer to Dols et al.[23] In short, sociodemographics included sex, age, and years of education. Clinical variables included early onset of depression (<55 years) versus late onset, assessed by interview. Number of prior depressive episodes and prevalence of psychotic features were assessed at baseline by the Mini International Neuropsychiatric Interview and clinical interview. Current medication use was assessed by interview and double-checked by chart review. Previous antidepressant treatment and treatment resistance were scored with the Antidepressant Treatment History Form.[26,27] Depression severity was defined as the MADRS total score.[24] Number of somatic disorders was assessed in a semistructured interview (Dols et al[23]). Prevalence of cardiovascular disease was being defined as presence of hypertension or a history of myocardial infarct or stroke and obtained through semistructured interview. Current smoking was assessed by semistructured interview. Alcohol use was measured by 2 questions based on the Alcohol Use Disorders Identification Test[28] on frequency and amount of alcohol consumption.

Electroconvulsive Therapy Procedures

A course of twice weekly ECT along Dutch standards was given to all patients.[29,30] A course started with right unilateral stimuli. For ECT, the Thymatron System IV (Somatics LLC, Lake Bluff, Ill) (maximum energy, 200%, 1008 mCoulomb) was used, according to a titration dosing protocol. All patients were treated with brief-pulse ECT (0.5–1.0 ms) twice a week. The stimulus intensity was determined by empirical dose titration at the first treatment, for right unilateral ECT 6 times the initial seizure threshold, and for bilateral ECT 1.5 times the initial seizure threshold. A motor seizure of less than 20 seconds or a seizure on electroencephalogram recordings of less than 25 seconds was considered inadequate, upon which the dose was raised according to Dutch guidelines.[29,30] If the clinical condition worsened or if no clinical improvement was seen after 6 unilateral treatments, a switch to bilateral ECT was applied. Electroconvulsive therapy was continued until the patient reached a MADRS score of less than 10 at 2 consecutive ratings with a week interval. In addition, if no further improvement was seen for 2 weeks, after a minimum of 6 unilateral and 6 bilateral sessions, ECT was stopped. Psychotropics such as benzodiazepines, antidepressants, and mood stabilizers were tapered off within 2 weeks before starting ECT, if clinically possible. Antipsychotics were allowed if clinically indicated.

Statistical Analyses

Because the MADRS consists of 10 items, examination of course trajectories of all items within depressed persons during the 2-week follow-up would entail multiple comparisons, prone to type I error. Therefore, a factor analysis on baseline data incorporating the 10 items of the MADRS was conducted to reduce the number of items into a limited number of dimensions. Previously, several studies have addressed factor analysis of the MADRS, with factor structures ranging from 2 to 4 dimensions.[31] However, because the number of dimensions across studies differed, and because earlier studies used populations ranging from younger to older persons, we decided to perform an exploratory factor analysis (EFA) instead of a confirmatory factor analysis. Oblique rotation (promax) was used because the final dimensions were expected to be intercorrelated. Dimensions were extracted, based on preferential loading on 1 dimension, differences between loadings of at least 0.20, and eigenvalues (>1.0),[32] observation of the scree plot, and interpretability of the dimensions. Next, course trajectories of the identified dimensions within depressed persons during the 1-week follow-up and 2-week follow-up were compared using multivariate, multilevel analyses (multivariate with respect to both the different groups, and follow-up in time). For that purpose, depression dimensions were standardized over the entire measurement period, and multilevel analyses were performed on 3 levels. The dimensions were clustered within time points, and time points were clustered within patients. In multilevel analyses, time, different dimensions (both represented by 2 dummy variables), and the interaction between time and dimension were added to the model. The EFA was performed with SPSS version 21 (IBM Corp Released 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp), and the multilevel analyses were performed with MLwiN version 2.31 (Multilevel Modelling for Windows, Centre for Multilevel Modelling, University of Bristol).

RESULTS

The total sample consisted of 89 depressed older people, of whom 66.4% were women, with age ranging from 55 to 92 years and a mean age of 73.1 years (SD ± 8.3). Almost half of the sample (46.4%) had psychotic symptoms, and the mean number of prior depressive episodes was 3.7 (SD ± 3.3). MADRS scores at baseline ranged from 20 to 49, with a mean score of 32.6 (SD ± 7.6), and 78.7% had physical comorbidity, with a prevalence of cardiovascular disease of 43.8% (Table 1).

Exploratory factor analysis identified 3 symptom dimensions (Table 2), including a dimension consisting of apparent and reported sadness, concentration difficulties, and anhedonia (MADRS items 1,2,6,8), henceforth called mood dimension; a second dimension consisting of inner tension, reduced sleep, reduced appetite, lassitude, and pessimistic thoughts (MADRS items 3,4,5,7,9), henceforth called "melancholic" dimension; and a third, separate dimension consisting of suicidality only (MADRS item 10), henceforth called "suicidality" dimension. Factor loadings are presented in Table 2.

Next, the course trajectories of the 3 symptom dimensions during the first 2 weeks of ECT were compared. Figure 1 shows the observed development over time in the 3 depression symptom

TABLE 1. Characteristics of Study Population (N = 89)

Sociodemographics	
Sex, female, %	66.7
Age, mean (SD)	73.4 (9.8)
Education level, mean (SD), y	6.4 (2.7)
Clinical characteristics	
Age onset, early, %	42.9
No. prior depressive episodes, median (IQR)	3 (2)
Psychotic features, %	46.4
Current medication use, %	39.8
ATHF (resistance sum score), mean (SD)	6.3 (4.9)
MADRS, mean (SD)	32.6 (7.6)
Physical health	
Physical comorbidity, present, %	78.7
Cardiovascular disease, %	43.8
Smoking, %	18.2
Alcohol # daily, mean (SD)	2.2 (0.7)

ATHF indicates Antidepressant Treatment History Form.

dimensions. Within depressed persons, all symptom dimensions rapidly declined in severity after the start of ECT. Table 3 shows the results of the multivariate multilevel analyses. The mood dimension showed a significantly greater decline than the melancholic and suicidal dimensions during the first week of ECT (ie, the mood dimension decreased with 0.31 SD units more than the melancholic dimension between baseline and follow-up). However, during the 2-week follow-up, the speed of response in the mood dimension did not differ significantly from the melancholic symptom dimension. Notably, although the decline of the suicidality dimension after 1 week was comparable to the decline of the melancholy dimension, after 2 weeks the suicidal dimension declined significantly less than the other 2 dimensions (ie, the mood dimension decreased with 0.76 SD units more than the suicidal dimension). Post hoc analyses revealed that the median baseline score on the suicidality item was 2 (interquartile range (IQR), 3), which was significantly lower than scores on most of the other MADRS items, and decreased to 1 (IQR, 3) after 1 week (Table 4).

Post hoc, we also performed analyses of the decline over time for each individual MADRS item, to see whether this would generate new insights (supplement 1, http://links.lww.com/JECT/A74). All items (apart from lassitude and suicidality) declined significantly each week. In addition, the individual mood items showed greater coefficients of decline in week 1 as compared with week 2, except for reported sadness (coefficient = 0.88 in week 1 versus 0.89 in week 2), and all individual melancholic items showed greater coefficients of decline in week 2 as compared with week 1 (results available upon request). This is in line with findings on speed of response of the aggregated domains, in which the mood dimension shows a significantly higher speed of improvement as compared with melancholic dimension in week 1. Improvement of lassitude seemed to lag behind, because there was only significant improvement in week 2. Suicidality only showed significant improvement in week 1 (as compared with baseline). To conclude, findings are largely in line with findings on aggregated items.

TABLE 2. Factor Loadings of MADRS Items After Oblique Rotation (N = 89)

	Dimension		
MADRS items	**Mood**	**Melancholic**	**Suicidality**
Apparent sadness	0.275	−0.047	0.007
Reported sadness	0.212	0.143	0.070
Inner tension	0.161	0.197	−0.145
Reduced sleep	−0.093	0.497	−0.071
Reduced appetite	0.094	0.165	0.147
Concentration difficulties	0.274	0.022	−0.208
Lassitude	0.030	0.403	−0.213
Anhedonia	0.290	−0.156	0.203
Pessimistic thoughts	−0.036	0.217	0.198
Suicidality	0.008	−0.014	0.781

Gray marked cells indicate highest factor loading.

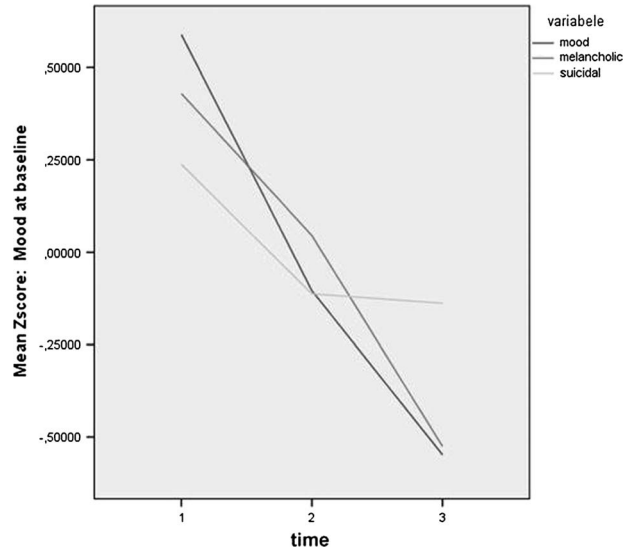

FIGURE 1. Speed of response of symptom dimensions within depressed persons during first 2 weeks of ECT (1 = baseline, 2 = after 1 week, 3 = after 2 weeks). Speed of response of mood (upper line at time point 1), melancholic (middle line at time point 1), and suicidal (lower line at time point 1), measured at baseline, 1 week, and 2 weeks. Note that although all symptoms improve rapidly, the decline of the yellow line stalls after 1 week. This might be due to a floor effect, because baseline scores on the suicidal cluster were lower than those of both other clusters.

DISCUSSION

The aims of our study were to identify dimensions of depressive symptoms within an older population and to examine differences in speed of response of symptom dimensions within depressed older persons during the first 2 weeks of ECT. Three depressive symptom dimensions were identified, including a mood, melancholic, and suicidal dimensions. All dimensions showed rapid and significant improvement during the follow-up, but the mood dimension demonstrated the highest speed of improvement during the first week of ECT, as compared with the melancholic and suicidal dimensions. Likewise, both mood and melancholic dimensions improved at a significantly faster speed than the suicidal dimension during the 2-week follow-up.

Through EFA, 3 dimensions were identified, similar to an earlier study by Parker et al.[33] This study used MADRS items in a population of 225 in- and outpatients aged 59 years and more with MDD. They identified 3 distinct dimensions: a "dysphoric apathy/retardation" dimension, similar to our mood dimension; a

TABLE 3. Comparison of Course of 3 Symptom Dimensions

	Mood vs Melancholic, Score Difference, *P* (95% CI)	Mood vs Suicidal, Score Difference, *P* (95% CI)	Melancholic vs Suicidal, Score Difference, *P* (95%CI)
Baseline–1-week follow-up	**0.31, *P* = 0.03 (0.42–0.96)**	**0.35, *P* = 0.01 (0.38–0.92)**	0.05, *P* = 0.73 (0.91–1.24)
Baseline–2-week follow-up	0.18, *P* = 0.23 (0.53–1.11)	**0.76, *P* < 0.01 (0.54–0.96)**	**0.55, *P* < 0.01 (0.16–0.74)**

Bold values indicate significance.
CI indicates confidence interval.

"psychic anxiety" dimension; and a dimension with vegetative symptoms. Our melancholic dimension corresponds to their psychic anxiety and vegetative dimension combined. However, whereas our EFA supports a separate suicidal dimension, Parker et al[33] included suicidal symptoms in the vegetative dimension. Our finding of a distinct suicidal dimension can be explained by the fact that our study sample contains solely inpatients, whereas Parker et al[33] used a mixture of in- and outpatients. Severely suicidal depressed older persons are more likely to be admitted and treated with ECT, which means that suicidality is probably a more prominent symptom in our inpatient sample compared with other studies including outpatients too, even though our population had a moderately high score on suicidality. Unfortunately, the study of Parker et al[30] does not provide mean MADRS scores on the suicidal item, thereby hampering comparison. Other studies analyzing the factor structure of the MADRS also identified 3 dimensions, but great differences between theirs and our study population hamper comparisons with our study findings.[34]

Our main study aim was to examine differences in course trajectories of the identified dimensions. All dimensions improved significantly during the first 2 weeks, which is an advantage of ECT over other antidepressant treatments, because the latter usually requires several weeks to reach improvement,[11] with studies also finding lagging on different symptoms or symptom dimensions.[12–16] We found that the suicidal dimension significantly lagged behind the mood dimension after the first week of ECT, but a floor effect causing that delay could not be ruled out. In post hoc analyses, we examined the decline of each individual MADRS item in week 1 compared with baseline, and week 2 to week 1. We found that all items, apart from lassitude and suicidality, decline significantly each week, with a greater improvement of mood items as compared with melancholic items in week 1. To conclude, findings are largely in line with findings on aggregated items. Because the suicidal dimension was composed of only 1 item, the responsiveness of this domain may be limited and a floor effect may be present.

Because ECT is known to strongly enhance dopamine,[35] the fast improvement of the mood dimension may be caused by the inclusion of anhedonia in this dimension, a symptom linked to disturbances in the dopamine pathways.[36–38]

The findings of our study should be interpreted in the context of the following strengths and limitations. The design of this study provided the opportunity to examine course trajectories of depressive symptoms in detail, with weekly assessment of the MADRS. The MADRS, however, does not fully correspond to the *DSM-IV-TR* criteria for MDD.[21] The MADRS only addresses loss of sleep and weight/appetite, whereas the *DSM-IV-TR* includes change of sleep and both gain and loss in weight/appetite. Likewise the *DSM-IV-TR* criterion of psychomotor changes (both agitation and retardation) is not properly addressed by the MADRS. This may be of particular importance to our study, because psychomotor symptoms are considered to be a predictor of ECT response.[19] Earlier studies found a correlation between the MADRS item "inner tension" and total CORE score (an instrument to assess psychomotor symptoms in depression), but being a single item measure, this item may not be sufficiently valid to measure the full construct of psychomotor disturbances.[39]

Next, our results show that, although suicidality improved rapidly, the speed of response significantly lagged behind the mood dimension in week 1 and behind both dimension in week 2. Post hoc analyses revealed that the median baseline score on the suicidality item was 2 (IQR, 3), which was significantly lower than scores on most other MADRS items (Table 4), and decreased to 1 (IQR, 3) after 1 week. These findings suggest that a floor effect probably hampered any further decrease after week 1, because the median baseline value was, of all items, closest to zero.

To conclude, our findings show that ECT induces a rapid decline of all symptom dimensions in depressed older persons, with primacy of the mood dimension. Because anhedonia was included in this dimension, these findings suggest that ECT may rapidly restore dopamine-related symptomatology. To what extent

TABLE 4. Scores on Separate MADRS Items (N = 89) [Mean (SD); Median (IQR)]

	Baseline	After 1 Week	After 2 Weeks
1. Apparent sadness	4.2 (1.2); 4.0 (1)	3.1 (1.5); 3.0(2)	2.5 (1.4); 3.0 (1)
2. Reported sadness	4.4 (1.4); 5.0 (1)	3.5 (1.4); 4.0 (1)	2.7 (1.5); 3.0 (3)
3. Inner tension	3.7 (1.2); 4.0 (1)	3.0 (1.3); 3.0 (2)	2.3 (1.3); 3.0 (2)
4. Reduced sleep	2.7 (1.6); 3.0 (2)	2.3 (1.7); 2.0 (3)	1.6 (1.5); 2.0 (3)
5. Reduced appetite	2.8 (1.8); 3.0 (3)	2.5 (1.8); 2.5 (3)	1.9 (1.6); 2.0 (3)
6. Concentration difficulties	3.8 (1.3); 4.0 (2)	3.2 (1.4); 4.0 (2)	2.7 (1.4); 3.0 (2)
7. Lassitude	3.3 (1.6); 4.0 (3)	3.0 (1.6); 3.0 (2)	2.3 (1.6); 2.0 (3)
8. Inability to feel	3.8 (1.4); 4.0 (2)	2.8 (1.3); 3.0 (2)	2.3 (1.5); 2.0 (2)
9. Pessimistic thoughts	3.1 (1.7); 3.0 (2)	2.8 (1.4); 3.0 (2)	2.1 (1.6); 2.0 (2)
10. Suicidal thoughts	1.8 (1.6); 2.0 (3)	1.4 (1.4); 1.0 (3)	1.1 (1.2); 1.0 (2)

the (relatively) lagging behind of suicidal symptoms is related to clinometric properties of the MADRS (eg, a floor effect) needs to be settled. Above all, because all depressive symptom dimensions already improved during the first week after ECT, this study underlines the potency of ECT to rapidly ameliorate depressive symptoms, a great benefit for clinical practice.

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