Patterns of late-life depression: On the nature of depressive subtypes and the role of aging

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CHAPTER 5

5

Melancholia as predictor of electroconvulsive therapy outcome in later life

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Objectives: In clinical practice, particularly melancholic depression benefits from electroconvulsive therapy (ECT), albeit research using DSM-derived melancholia is not conclusive. We compared clinical characteristics and ECT-outcome of melancholic and non-melancholic depression, here defined by psychomotor symptoms.

Methods: 110 depressed older inpatients treated with ECT were included in the Mood Disorders in Elderly treated with ECT (MODECT) study. The CORE was used for the assessment of psychomotor symptoms, with a score of ≥ 8 defining melancholic depression. Depression severity was measured before, during and after ECT. Characteristics were compared across melancholic and non-melancholic patients. Regression analysis was used to assess the relation between psychomotor symptoms and remission/response, and survival analysis to examine the difference in time.

Results: Patients with melancholic depression had higher severity, lower cognitive and overall functioning and lower prevalence of cardiovascular disease. However, no significant relations were found between CORE scores and remission/response. Since psychotic symptoms are a positive predictor of ECT response and remission, we examined whether CORE score was a predictor of response in the non-psychotic group (N=49). In non-psychotic patients remission was 62%, and the association between CORE scores and remission almost reached significance (p=0.057).

Discussion: Although melancholically and non-melancholically depressed patients differed significantly on several clinical characteristics, ECT-outcome did not differ. Analyses may be hampered by a high prevalence of psychotic features. In non-psychotic patients CORE scores neared significance as predictor of remission, suggesting CORE scores might be a distinguishing characteristic of melancholia in non-psychotic patients, and a clinical useful predictor of ECT response.

Key words: late life depression; melancholic depression; psychomotor disturbances; predicting ECT response

Abstract

Introduction

Unipolar depressive disorders are among the most common psychiatric disorders in our society. Prevalence rates in older patients range from 1-16%, depending on setting (e.g. private households to institutions) and criteria used[1]. Electroconvulsive therapy (ECT) has been proven to be very effective in (older) patients with depression[2-4], especially with psychotic[5] or pronounced psychomotor disturbances, including catatonia[6] . Considering its distinct phenomenology and treatment response, it is suggested that depression characterised by profound psychomotor disturbances may delineate a distinct mood disorder called 'melancholic depression'[7].

The Diagnostic and Statistical Manual of Mental Disorder version IV Text Revision[8] and version 5[9] classifies melancholic depression as a depression subtype with psychomotor disturbances, decreased appetite and sleep, and diurnal symptomatology variation. In addition, it was recently demonstrated that patients with melancholic depression, either defined clinically[10] or data-driven[11,12] differed with respect to clinical characteristics and biological parameters from non-melancholic depression (e.g. higher mean age, higher age of onset, higher cortisol levels, and altered brain-connectivity in melancholic depression)[13-15] . However, previous studies using DSM-derived criteria for 'melancholic depression' failed to demonstrate favourable course trajectories during ECT[16] . A possible explanation is that a DSM diagnosis of melancholia does not require psychomotor disturbances, even though psychomotor symptoms are thought to be a core characteristic of melancholic depression and have also been identified as predictor of response to ECT [16]. Hence, the DSM criteria may lack content validity to identify melancholic depression[16] in depressed patients referred for ECT.

An observational instrument better suited for identifying melancholic depression by thorough assessment of psychomotor disturbances is the CORE[17]. Indeed, one study demonstrated that higher CORE scores predicted ECT response[18]. However, further CORE-based research is limited, especially in older adults, and a recent meta-analysis could not confirm the predictive value of psychomotor symptoms for ECT-outcome, since too few studies examined psychomotor disturbances[19,20]. To conclude, to date there is no consensus on the predictive value of presence of psychomotor disturbances on ECT outcome. Further insight into this predictive value could help clinicians to better identify patients who will probably benefit from ECT, facilitating personalised medicine.

In this study we examine differences in clinical characteristics and course trajectories during ECT across older depressed patients with and without psychomotor disturbances, defined by a cut-off CORE score of 8. We hypothesise that depressed patients with psychomotor disturbances (named 'melancholic') differ in several clinical characteristics from depressed patients without psychomotor disturbances (named non-melancholic), i.e. presence of psychotic symptoms, age, and depression severity[20], and cortisol measurements[21]. In addition, we hypothesise that melancholic depression is associated with a more favourable ECT-outcome compared to non-melancholic depression.

Methods

Data were derived from the Mood Disorders in Elderly treated with Electro Convulsive Therapy (MODECT) study, a two-site longitudinal study including older in-patients (55 years or older) with severe unipolar depression according to DSM-IV-TR criteria (American Psychiatric Association (APA), 2013), referred for ECT. Patients were recruited from tertiary psychiatric hospitals (GGZ inGeest, Amsterdam, the Netherlands and University Psychiatric Center, KU Leuven, Belgium). Patients with another major DSM-IV diagnosis or a major neurological illness (including Parkinson's disease, stroke and dementia) were excluded, thus retaining a data set of 110 patients. For a detailed description of the MODECT-study, we refer to Dols et al[5]. For the current study, patients with missing data on baseline CORE and/or MADRS scores were excluded (n=17). Attrition analysis showed that excluded patients more often started with bilateral treatment ($p = 0.002$), used alcohol more often ($p = 0.02$), and had more often missing baseline data of both MMSE ($p < 0.001$) and Apathy scale ($p = 0.03$). Attrition was non-differential with regard to sociodemographics (age, sex and education), presence of psychotic symptoms, ECT indication, response, remission, and physical comorbidities.

Melancholic depression

Psychomotor disturbances were assessed with the Dutch version of the CORE[17,22], an observational instrument proved to be reliable and valid in assessing psychomotor symptoms in depression[22-26]. The CORE consists of eighteen items, subdivided into three different subscales: retardation, agitation and non-interaction. Each item is scored from 0-3, with 0 defined as the 'absence or triviality' of a feature. In accordance with guidelines[17], a total CORE score of ≥ 8 served as the cut-off for melancholic depression. Hence, patients were divided into melancholic (CORE ≥ 8) and non-melancholic (CORE < 8) depressed patients.

Remission and response

The Dutch version of the MADRS was used to evaluate severity of depressive symptoms at baseline, weekly during ECT treatment, and the first week after treatment finished[27,28]. Remission was defined as a MADRS score ≤ 10 one week after ECT treatment finished. Response was defined as a decline in MADRS score of at least 50% one week after ECT treatment finished, compared to baseline MADRS score.

Characteristics

Sociodemographic, clinical and physical health characteristics as well as biological parameters were examined at baseline. Sociodemographics included sex, age, and education level (low, middle or high), and were obtained by interview. Clinical characteristics included age of onset of depression, severity of psychomotor symptoms, depression severity, psychotic features, cognitive functioning, apathy, daily functioning, treatment resistance, and ECT-characteristics. Age of onset of depression was dichotomized into early versus late onset of depression (age of first depressive episode < 55 years) and was obtained by interview. Severity of psychomotor disturbances was assessed by total CORE-scores. Depression severity was obtained by the MADRS[28]. Depression and the presence of psychotic features were based on the DSM-IVcriteria[8]. Cognitive functioning was

measured by the Mini Mental-State Examination (MMSE)[28]. Apathy was scored by the Apathy scale[30]. Daily functioning was assessed using the WHO Disability Assessment Schedule (WHO-DAS)[31,32]. The Antidepressant Treatment History Form (ATHF)[33] was used to assess previous antidepressant use for the current depressive episode, and treatment resistance. Through chart review we obtained use of psychotropic medication during ECT treatment (non-selective monoamine reuptake inhibitors (N06AA), selective serotonin reuptake inhibitors (N06AB), non-selective monoamine oxidase inhibitors (N06AF), monoamine oxidase A inhibitors (N06AG), other antidepressants (N06AX), lithium (N05AN01), haloperidol/ butyrophenone derivated antipsychotics (N05AD), atypical antipsychotics (N05AH) antiepileptics (N03A)), number of ECT treatments, percentage of patients receiving unilateral ECT, the amount of patients switching from unilateral to bilateral ECT, and ECT indication (medication resistance or urgent).

For cortisol measurements, salivary cortisol samples were obtained at several time points: at time of awakening, 30, 45 and 60 minutes after awakening and at 10 pm (e.g. T1; 07.00 am, T2; 07.30 am, T3; 07.45 am, T4; 08.00 am and T7; 22.00 pm). Patients received instructions concerning saliva sampling. Eating, drinking tea or coffee, and brushing teeth 15 minutes prior to sampling were not permitted. From the samples obtained within 2 hours after awakening (T1-T4), the area under the curve to the ground (AUCg) and to the increase (AUCi) was calculated, using Pruessner's formula[34]. For a more detailed description of the procedures, we refer to Suijk et al[35]. Finally, physical health characteristics included smoking status, alcohol use and physical comorbidity. Current versus former/ no smoking was obtained through interview. Alcohol use was obtained through the Alcohol Use Disorders Identification test (AUDIT)[36]. Physical comorbidity was assessed in a semi-structured interview, including the presence of chronic obstructive pulmonary disease/ asthma/ emphysema, cardiovascular disease, myocardial infarction, hypertension, diabetes, cerebrovascular disease, arthrosis, (rheumatoid) arthritis, malignant neoplasms, migraine, thyroid disease, consequences of an accident, permanent disability due to surgery, Parkinson disease, other disease of the central nervous system, or other diseases. Furthermore, we separately examined the prevalence of cardiovascular disease, hypertension and diabetes within groups.

ECT procedure

At least one week before starting ECT, patients were withdrawn from psychotropic medication, if clinical condition allowed. If this was deemed impossible, pharmacotherapy was kept stable 6 weeks before and during ECT. ECT therapy was administered twice weekly and conducted according to Dutch guidelines[37], starting right unilateral, unless there was an indication to start bilateral. All patients received brief-pulse ECT (0.5-1.0ms) with the Thymaton System IV, following dose titration protocol. A motor seizure of 20 seconds or more was considered adequate, otherwise the dose was raised according to Dutch guidelines. Switching to bilateral ECT occurred in case of clinical worsening or no clinical improvement after 6 unilateral sessions. Clinical worsening was defined as an increase in MADRS scores, increased suicidality, weight loss, dehydration or increase of psychotic features. See also Dols et al[5] for a more detailed description of ECT procedure.

Statistical analysis

Data were analysed using SPSS (Statistical Package of the Social Sciences, version 23, SPSS Inc., Chicago, IL). Statistical significance was defined as $p < 0.05$. Differences across groups for continuous variables were determined by independent t-tests for normally distributed data, and by Mann-Whitney tests for non-normally distributed data. Group differences for categorical variables were determined by chi-square tests.

Logistic regression analyses were conducted to analyse the association between melancholic depression and both remission and response as outcome measures, compared to non-melancholic depression, using total CORE scores and the retardation, agitation, and non-interaction subscales.

The analyses were adjusted for putative confounders, selected either on significant difference across melancholic and non-melancholic patients ($p < .05$), or based on previous findings[5,19].

Survival analyses (Cox regression) were performed in order to examine whether the melancholic and non-melancholic group differed in time (in days) to reach remission and response.

Results

Table 1 summarises demographic and clinical characteristics across melancholic and non-melancholic patients. The total population consisted of 89 patients, of whom 71 had melancholic depression. 66.7% were females, with a mean age of 73.0 years (SD=8.4). Sex and age did not differ significantly between groups. Patients with melancholic depression had higher baseline MADRS scores, lower MMSE scores, lower overall daily functioning, and lower prevalence of cardiovascular disease. No differences in cortisol measurements were found.

Next, the association between melancholic depression and ECT-outcome (remission and response) was examined (non-melancholic depression is reference) (see **table 2**: outcome defined as remission; and **table 3**: outcome defined as response). In model 1, the association between total CORE score and ECT-outcome was examined. In model 2, we additionally adjusted model 1 for demographics (age, sex and education). In model 3, analyses were further adjusted for psychotic symptoms, MMSE and cardiovascular diseases. Finally, in model 4, analyses were adjusted for all previous variables and MADRS scores. Note that there is considerable correlation between CORE and MADRS scores (Spearman's rho = 0.42, $p < 0.001$), reducing the reliability of model 4 due to possible multi-collinearity. Hence, these findings are presented in a separate model. In all models, melancholic depressionwas not associated with remission. Within melancholic patients, only psychotic symptoms were significantly associated with remission (model 4: OR: 3.61, CI: 1.02–12.71; **table 2**) and response (model 3: OR: 7.09, 95% CI: 1.41–35.73; model 4: OR: 6.16, CI: 1.21–31.29; **table 3**).

Subsequently, using logistic regression analyses the association between CORE subscales (respectively agitation, retardation and non-interaction) and ECT-outcome was examined. The results are shown in **table 4**. Again, scores on the three CORE subscales were not significantly associated with either remission or response; and within melancholic depression only psychotic symptoms were significantly associated with response.

Cox regression analysis was performed to examine potential differences in the time to achieve remission or response for the melancholic and non-melancholic patients. The survival distributions for two groups did not differ significantly (remission: OR(95%CI)=0.78(0.38-1.59), p=0.50, response: OR(95%CI)=0.95(0.51-1.77)).

With post-hoc sensitivity analyses, we examined whether characteristics and ECT outcome would differ if melancholic depression was defined as the median CORE score or higher (median CORE = 14.0). Using a higher threshold may exclude mild psychomotor disturbances due to other causes than melancholia, like medication or essential tremor. We also examined whether the outcome would differ when using the CORE as a continuous measure. However, both approaches did not change the results. (data available upon request). Furthermore, we examined whether there was an interaction effect between total CORE score and psychotic symptoms, which was not the case (p=0.80). Lastly, since psychotic symptoms are a positive predictor of ECT response and remission, we examined whether CORE score was a predictor of response in the non-psychotic group (N=49). 61% of non-psychotic subjects reached remission. For response, we found no significant difference (p=0.105), but the association between CORE score and remission nearly reached significance(p=0.057).

Discussion

In this study, we examined differences in clinical characteristics and course trajectories during ECT in older patients with melancholic depression compared to non-melancholic depression. Patients with melancholic depression, as defined by a cut-off CORE score of 8, had a higher depression severity, a lower MMSE score, lower overall daily functioning, and were less likely to have cardiovascular disease. Contrary to our hypothesis, response and remission rates did not differ between the two groups.

Previous findings suggested that melancholic depression has distinct characteristics[11,12,14] and a favourable ECT outcome[17], which is partly in line with the finding that our melancholic group showed several different characteristics compared to the non-melancholic group. Earlier studies defined a data-driven subtype of melancholia, and in line with our findings, this group was characterised by a higher severity, lower overall functioning, and a lower prevalence of cardiovascular disease[12,38]. However, we found no group differences for both number of patients and time to reach response or remission after ECT. Only psychotic features predicted a better ECT outcome. Using median CORE score (14.0) as cut-off did not alter results. However, since the ratio of melancholic versus

non-melancholic patients was rather askew (non-melancholic 19.4% (N=18)), the lack of a correlation with ECT outcome could be due to underpowering.

Previous studies suggested that people suffering from melancholic depression, have on average a higher age and age of onset of depression[39-41], although not all studies could replicate this[42]. We found limited differences in characteristics between melancholic and non-melancholic patients, with no difference in age, nor age of onset. Unfortunately, we could not examine the impact of age of onset on a continuous scale due to dichotomization of the data, with a cut-off of 55 years. The equal distribution of gender among groups is in line with earlier research[43], as is the significantly higher depression severity in the melancholic group[42,44,45], and the lower prevalence of cardiovascular disease in the melancholic group[12]. In our population, no significant difference in cortisol measures was found. This is in contrast with previous studies based on DSM-criteria reporting higher cortisol levels in melancholic versus non-melancholic depression[11,46], and with Parker et al[7] who argued that biological changes, such as hypercortisolemia, are distinct features of melancholic depression.

Next, we examined the impact of depression subtype on ECT outcome. In contrast to our hypothesis, response and remission did not differ significantly between both groups. Likewise, in multivariable regression analyses, melancholic depression was not associated with ECT-outcome, nor the CORE subscales, including agitation, retardation and non-interactiveness. An earlier study using the CORE demonstrated that higher CORE scores predict ECT response[18], as opposed to the non-predictive value of DSM-defined melancholia on ECT response[16]. These results have not been replicated yet as most studies to date did not use CORE measurement to define melancholic features, hampering comparisons. Psychotic features however did predict ECT outcome in our study within the melancholic group, in line with a recent meta-analysis, finding that psychotic features predict both response and remission in ECT treatment[20]. It is suggested that psychotic features are a symptom of a very severe (melancholic) depression rather than a distinct subtype[47]. In our study, post-hoc analyses showed a moderately high correlation between total CORE score and psychotic features (Spearman's rho = 0.42). This matches findings of Parker et al[7], who hypothesised that psychotic features within depression are a specific feature of melancholia, and therefore maybe even more distinguishing than psychomotor disturbances. In post-hoc analyses, we found the association between total CORE scores and remission within the non-psychotic group almost reached significance (p=0.057). This fits Parker's hypothesis, suggesting that CORE scores might be a distinguishing characteristic of melancholia, but that this effect has been 'overruled' in our study by the high prevalence of psychotic features in our sample.

To summarise, melancholic and non-melancholic depression only differed on a limited number of characteristics and were not associated with ECT-outcome. A possible explanation for our non-significant findings could be the high mean age of our cohort. CORE scores are found to increase with age[14,48,49], although the CORE is validated in the older population, too [50]. It is possible that higher CORE scores in older patients might be explained by various underlying pathophysiological pathways, such as neurodegenerative or vascular factors, and are therefore not clinically distinguishable from *true* melancholic

psychomotor disturbances. However, presence of psychotic features did predict ECT response, which may be indicative of a severe melancholic depression and thus a stronger predictor of response than the CORE.

The findings of this study should be interpreted in the context of the following strengths and limitations. Strengths of this study are the detailed observation of psychomotor disturbances, and the vast number of characteristics that were examined. However, selection bias may have hampered our findings. The number of non-melancholic patients was low (n = 18 (19.4%)), indicating a probable selection bias in ECT-referrals. Combined with a relatively small number of included participants (N=93) and a high response percentage, this study population may have been too homogenous to identify differences in outcome. In addition, it remains to be settled to what extent the CORE is a valid measure to assess psychomotor disturbances in older depressed patients. Psychomotor disturbances due to other clinical conditions, such as cerebral vascular damage, neurodegeneration, other somatic comorbidities or medication side effects , may artificially increase the CORE. Lastly, attrition differed with respect to type of ECT (more bilateral ECT), suggesting that attrition may differ with respect to severity and/or melancholic depression as well.

Conclusion

Patients with melancholic depression (defined as a CORE score ≥ 8) had higher depression severity, lower cognitive and overall daily functioning, and lower prevalence of cardiovascular disease than patients with non-melancholic depression. Total CORE score did not predict ECT outcome, but psychotic features did, and were moderately correlated to CORE scores. This suggests that psychotic features in combination with psychomotor disturbances may better characterize melancholic depression in older patients than psychomotor disturbances or psychotic features alone. Considering the significant correlation of CORE score with depression severity, our findings suggest that in this specific, rather homogeneous, sample of severely depressed in-patients, CORE-measurements may only have any additional value for prediction of treatment outcome in non-psychotic patients. However, replication studies are required to confirm our findings.

Conflict of interest
No conflict of interest is declared.

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Table 1. Baseline characteristics with melancholy defined as CORE >=8 (N=89)

	Total sample	Non-melancholic	Melancholic	X2, F, (df), overall P-value
Prevalence	89 (100%)	18(19.4%)	71(80.6%)	
Sociodemographics				
Sex, female, %	66.7	66.7	66.7	<.001(1), 1.00[1]
Age, mean (SD), years	73.0(8.4)	71.8(9.8)	73.3(8.1)	0.69(91), 0.49[2]
Education level, %				2.27(2), 0.32[1]
Low	15.9	11.8	16.9	
Middle	57.3	47.1	60.6	
High	26.8	41.2	23.1	
Clinical characteristics				
Age onset <55 years, %	54.8	50.0	56.0	0.21(2), 0.79[1]
CORE sumscore, median (IQR)	14.0(13.0)	5.0(3.0)	16.0(10.0)	<.001(-6.57), <.001[3]
MADRS sumscore, mean (SD)	33.7(8.7)	27.4(10.0)	35.2(7.7)	-3.62(91), <.001[2]
Psychotic features, %	47.3	50.0	46.7	0.07(1), 0.80[2]
MMSE sumscore, median (IQR)	26.0(6.0)	28.0(5.0)	25.0(7.0)	419.00(-2.03), 0.04[3]
Apathy, mean (SD)	24.8(7.2)	22.7(7.6)	25.3(7.1)	-1.31(75), 0.20[2]
WHO-DAS functioning, mean (SD)	43.6(15.0)	37.2(11.5)	45.6(15.4)	-2.01(65), 0.05[2]
No. antidepressant trials, median (IQR)	2.0(2.0)	2.0(1.0)	2.0(2.0)	3.26(5), 0.66[3]
Max. resistance score, median (IQR)	3.0(2.0)	2.5(3.0)	3.0(2.0)	5.32(4), 0.26[3]
Medication use during ECT, %	39.8	27.8	42.7	1.34(1), 0.25[1]
Electroconvulsive therapy				
No. ECT treatments, median (IQR)	11.0(7.0)	10.5(8.0)	12.0(7.0)	562(-1.10), 0.27[3]
Start unilateral, %	96.8	94.4	97.3	0.39(1), 0.53[1]
Switch unilateral to bilateral, %	31.2	38.9	29.3	11.98(2), <0.01[1]
ECT indication				0.97(1), 0.32[1]
Life threatening symptoms, %	25.8	16.7	28.0	
Pharmacotherapy resistance, %	62.4	66.7	61.3	
Other, %	11.8	15.7	10.7	
Response after ECT, %	77.4	72.2	78.7	0.35(1), 0.56[1]
Remission after ECT, %	68.8	55.6	72.0	1.83(1), 0.18[1]
Cortisol measurements				
AUCg, median (IQR)	6.9(4.6)	6.7(5.5)	7.4(5.2)	162(-1.69), 0.09[3]
AUCi, median (QR)	5.9(4.6)	5.7(4.9)	6.4(4.9)	163(-1.67), 0.09[3]
Evening cortisol, median (IQR)	3.2(2.2)	2.6(0.9)	3.5(2.2)	167.5(-1.76), 0.08[3]
Physical health				
Current smoking, %	25.6	29.4	24.6	1.16(2), 0.56[1]
Alcohol use, %	29.9	43.8	26.8	1.80(1), 0.18[1]
Alcohol units/ week, median (IQR)	0.0(1.0)	0.0(6.0)	0.0(1.0)	452.50(-1.57), 0.12[3]
No. physical comorbidities, median (IQR)	1.0(2.0)	2.0(2.0)	1.0(1.0)	6.54(5), 0.26[3]
Cardiovascular disease, %	23.7	50.0	17.3	8.58(1), 0.003[1]
Hypertension, %	30.1	27.8	30.7	0.06(1), 0.81[1]
Diabetes, %	7.5	0.0	9.33	1.62(1), 0.18[1]

Table 2. Logistic regression analysis of remission for total CORE score

Variable	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
Total CORE score	1.04 (0.98–1.09)	1.02 (0.96–1.09)	1.05 (0.97–1.14)	1.07 (0.98–1.16)
Sex (female)	-	0.47 (0.14–1.57)	0.41 (0.11–1.56)	0.40 (0.11–1.54)
Age	-	1.02 (0.96–1.09)	1.04 (0.97–1.11)	1.04 (0.97–1.11)
Education, low (high=ref) Education, middle (high=ref)	-	1.38 (0.29–6.39) 3.01 (0.87–10.46)	2.37 (0.41–13.72) 4.05 (0.98–16.69)	2.45 (0.41–14.72) 3.77 (0.89–15.87)
Psychotic symptoms	-	-	3.16 (0.95–10.48)	3.61 (1.02–12.71)
MMSE	-	-	1.13 (0.98–1.31)	1.14 (0.98–1.32)
Cardiovascular disease	-	-	0.61 (0.17–2.19)	0.57 (0.16–2.07)
MADRS	-	-	-	0.97 (0.89–1.05)

* Model 2 adjusted for demographics. ** Model 3 adjusted for demographics, psychotic symptoms, MMSE and cardiovascular diseases. *** Model 4 adjusted for variables in model 3, as well as MADRS score.

Table 3. Logistic regression analysis of response for total CORE score

Variable	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
Total CORE score	1.02 (0.96–1.08)	1.02 (0.95–1.09)	1.04 (0.95–1.13)	1.02 (0.93–1.12)
Sex (female)	-	0.70 (0.19–2.52)	0.67 (0.16–2.89)	0.69 (0.16–3.03)
Age	-	0.70 (0.19–2.52)	0.67 (0.16–2.89)	0.69 (0.16–3.03)
Education, low (high=ref) Education, middle (high=ref)	-	1.56 (0.28–8.78) 2.58 (0.68–9.73)	2.56 (0.36–18.39) 3.28 (0.69–15.53)	2.45 (0.34–17.67) 3.66 (0.75–17.80)
Psychotic symptoms	-	-	7.09 (1.41–35.73)	6.16 (1.21–31.29)
MMSE	-	-	1.14 (0.95–1.37)	1.13 (0.94–1.35)
Cardiovascular disease	-	-	0.63 (0.15–2.59)	0.70 (0.16–2.85)
MADRS	-	-	-	1.05 (0.96–1.13)

* Model 2 adjusted for demographics. ** Model 3 adjusted for demographics, psychotic symptoms, MMSE and cardiovascular diseases. *** Model 4 adjusted for variables in model 3, as well as MADRS score.

Table 4. Logistic regression analysis of remission and response with CORE subscales

Variable	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
		Outcome defined as remission		
CORE agitation	1.09 (0.91–1.29)	1.13 (0.92–1.39)	1.11 (0.89–1.39)	1.13 (0.89–1.42)
CORE retardation	1.05 (0.94–1.17)	1.01 (0.89–1.14)	1.04 (0.91–1.20)	1.06 (0.91–1.23)
CORE non-interaction	1.08 (0.96–1.21)	1.06 (0.93–1.21)	1.14 (0.96–1.35)	1.16 (0.97–1.39)
		Outcome defined as response		
CORE agitation	1.03 (0.86–1.24)	1.05 (0.84–1.31)	1.01 (0.80–1.28)	0.98 (0.77–1.25)
CORE retardation	1.03 (0.91–1.16)	1.01 (0.89–1.16)	1.06 (0.91–1.24)	1.03 (0.86–1.21)
CORE non-interaction	1.06 (0.94–1.21)	1.06 (0.91–1.23)	1.10 (0.91–1.34)	1.07 (0.88–1.31)

* Model 2 adjusted for demographics. ** Model 3 adjusted for demographics, psychotic symptoms, MMSE and cardiovascular diseases. *** Model 4 adjusted for variables in model 3, as well as MADRS score.