Toward Targeted ECT:
The Interdependence of Predictors of Treatment Response in Depression Further Explained

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ABSTRACT

Objective: Several clinical variables assumed to be predictive of electroconvulsive therapy (ECT) outcome in major depressive disorder show substantial interrelations. The current study tries to disentangle this interdependence to distill the most important predictors of treatment success to help improve patient-treatment matching.

Methods: We constructed a conceptual framework of interdependence capturing age, episode duration, and treatment resistance, all variables associated with ECT outcome, and the clinical symptoms of what we coin *core depression*, ie, depression with psychomotor agitation, retardation, psychotic features, or a combination of the three. The model was validated in a sample of 73 patients with a major depressive episode according to *DSM-5* treated twice weekly with ECT (August 2015–January 2018) using path analyses, with the size and direction of all direct and indirect paths being estimated using structural equation modeling. Reduction in Montgomery-Asberg Depression Rating Scale (MADRS) scores during treatment was the ECT outcome measure.

Results: The baseline presence of psychomotor agitation, retardation, and/or psychotic symptoms strongly correlated with beneficial ECT outcome ($z = 0.84$ [SE = 0.17]; $P < .001$), and the association between age and the effect of ECT appears to be mediated by their presence ($z = 0.53$ [SE = 0.18]; $P = .004$). There was no direct correlation between age and ECT response ($P = .479$), but there was for episode duration and ECT outcome ($z = -0.38$ [SE = 0.08]; $P < .001$).

Conclusions: ECT is a very effective treatment option for severe depressive disorder, especially for patients suffering from severe depression characterized by the presence of psychomotor agitation, psychomotor retardation, psychotic symptoms, or a combination of these 3 features, with the chance of a beneficial outcome being reduced in patients with a longer episode duration. Age may heretofore have been given too much weight in ECT decision making.

Trial Registration: ClinicalTrials.gov Identifier: NCT02562846

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Electroconvulsive therapy (ECT) is a very effective treatment for severe major depressive disorder (MDD).[1,2] Given its effectiveness—especially in the most severe cases[3]—its relatively fast onset of action compared to antidepressants,[4] and the ease of monitoring adherence to treatment, ECT has become indispensable in today's clinical practice. Still, a more targeted use of ECT could further increase its efficacy and limit exposure to the treatment and its side effects for those less likely to fully benefit fully from it. In light of the demand for value-based health care delivery, this targeted use would improve the economic sustainability of our health-care systems.[5] The current study focused on easy-to-assess clinical variables associated with a positive outcome of ECT.

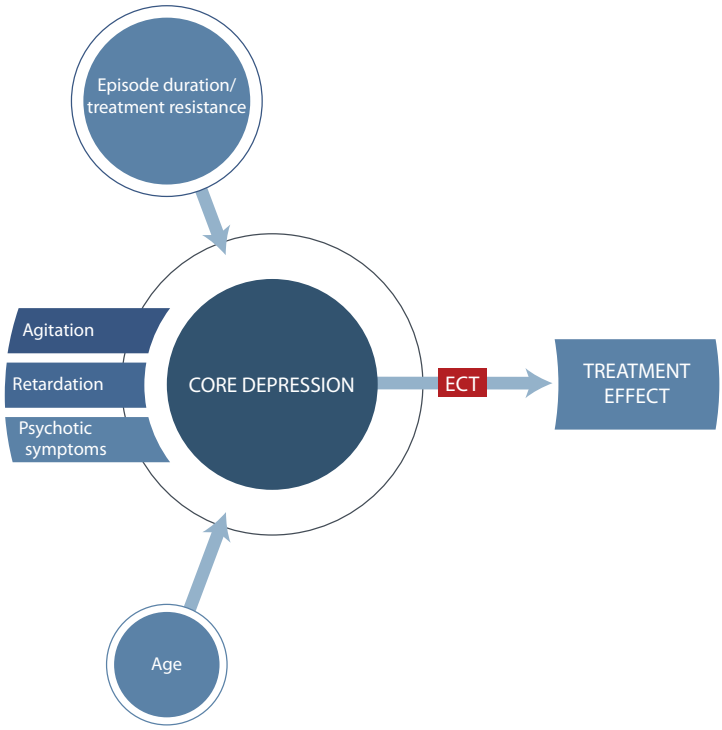
In a recent meta-analysis,[6] longer episode duration and medication failure were associated with reduced efficacy of ECT in patients with MDD. In our 2018 meta-analysis of clinical predictors,[3] we concluded that ECT was most successful in older patients and those with more severe depression and psychotic features. We recently reported[7] that the presence of psychomotor symptoms such as retardation (noticeable manifestations of slowing) and agitation (increased activity) also appears to be closely related to ECT outcome in depression: the patients with evident psychomotor symptoms were 4.9 times more likely to respond to ECT than those not presenting with such symptoms.

Psychomotor symptoms are a typical characteristic of melancholic depression,[8,9] with the symptoms often being more pronounced in depressed patients with psychotic features.[9,10] From a clinical point of view, patients with melancholic and/or psychotic depression are treated with ECT relatively early on in their disease, while patients without these symptoms have usually been treated with several antidepressants before ECT is considered, thereby prolonging the duration of the depression and increasing the risk of treatment resistance. Some of the clinical factors that have been linked to ECT outcome,—specifically, age, episode duration, and resistance to antidepressant treatment—may therefore have their predictive effects mediated by these psychomotor and psychotic symptoms. Recently, a path model

Clinical Points

- Several factors associated with electroconvulsive therapy (ECT) outcome in major depressive disorder show substantial entanglement, which makes it hard to distill the most relevant of these factors to improve patient-treatment matching.
- When a depressed patient presents with psychomotor or psychotic symptoms, ECT should be considered.
- Patient-treatment matching should not be based on the age of the patient.

Figure 1. Predicting ECT Outcome in Depression: Conceptual Framework of Predictor Interdependence



Abbreviation: ECT = electroconvulsive therapy

proposed by Heijnen et al[11] showed that age exerted its predictive effect on ECT outcome via other clinical variables, among which were psychomotor retardation and psychotic symptoms. It has remained unclear whether episode duration and treatment resistance are independent predictors or whether the predictive effect of either one is confounded by the presence of other factors. We consequently wondered how these predictors relate to each other and to ECT outcome.

We decided to extend the model proposed by Heijnen et al[11] by taking into account all of the clinical predictors that have been shown to be relevant in past meta-analyses. The proposed new model utilizes more precise evaluation scales to assess the two key elements, ie, psychomotor and psychotic symptoms. In our conceptual model (Figure 1), we suggest that ECT outcome is primarily related to the presence of depression with psychomotor retardation, agitation, psychotic features, or a combination of these symptoms. We propose to describe depression with these features as *core depression*. The other factors that have been linked to ECT outcome are hypothesized to be indirect predictors whose effects are mediated by the presence of elements of core depression.

METHODS

Study Group

We designed a single-site prospective observational study for patients with a depressive disorder that were treated with ECT. The study was registered at ClinicalTrials.gov (Identifier: NCT02562846). Patients were included between August 2015 and August 2017, and the study itself ran to January 2018. The study was approved by the Ethics Committee of the University Hospital of Antwerp. For a detailed description of the study methodology, we refer to several other articles describing our PROTECT cohort.[7,12,13]

To be eligible for study inclusion, patients had to meet the following criteria:

- Having been admitted to the University Psychiatric Hospital in Duffel (Belgium) or consulting for outpatient treatment with ECT.
- A diagnosis of major depressive disorder (MDD) or major depressive episode (MDE) in bipolar disorder (according to *DSM-5* criteria, as determined during the Mini-International Neuropsychiatric Interview [MINI][14] at screening) and a baseline 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[15] score ≥ 17 with an indication for ECT.
- Age between 18 and 85 years.

Patients meeting 1 or more of the following criteria were excluded from the study:

- Having drug or alcohol dependence (< 6 months before ECT), or a primary psychotic disorder as determined using the MINI[14] at screening.
- Being currently enrolled in a study with an investigational study drug.
- Any other condition that, in the opinion of the investigator, would compromise the well-being of the participant or prevent him/her from meeting or performing the study requirements.

All patients scheduled for treatment with ECT in our hospital were screened for inclusion in our study and, when eligible, asked for their informed consent.

Treatment

Electroconvulsive therapy. Patients were treated with ECT twice a week using a brief-pulse (0.5 ms) constant-current Thymatron System IV (Somatics LLC; Lake Bluff, Illinois). Electrodes were placed right unilaterally (RUL); bilateral electrode placement was used when a fast antidepressant effect was needed.[16] Patients initially treated with RUL ECT were switched to bitemporal ECT if response was inadequate after 6 treatments. Etomidate was the anesthetic of choice (0.15 mg/kg). Propofol (1 mg/kg) and ketamine (1–2 mg/kg) were used when etomidate was not tolerated or when clinical response was lacking after the first 12 sessions, respectively. Succinylcholine (0.5 mg/kg) was the muscle relaxant used. Lithium and benzodiazepines were withheld for at least 12 hours before each session given the negative influence of lithium on cognitive functioning[17] and benzodiazepines on seizure duration.[18] The stimulus dose was established prior to the first session by the age method for RUL electrode placement and half-age method for bilateral electrode placement.[19] After 2 sessions with insufficient seizure quality or duration despite adaptations for the potential influence of psychotropics and/or anesthetics, retitration was performed (dose increase of 50%).

The endpoint of the ECT course was determined by the treating psychiatrist based on improvement of mood as well as side effects of the treatment. ECT was continued until intolerable side effects or remission of depressive symptoms occurred. Treatment was also stopped when patients showed no further improvement during the last 3 sessions.

Pharmacologic treatment. Seven percent of patients did not use any antidepressant before ECT. Seventy-four percent were treated with antidepressant monotherapy (most often tricyclic antidepressants [n = 38] and selective serotonin reuptake inhibitors [n = 12]) and 19% with a combination of antidepressants. Almost 80 percent used additional antipsychotics for psychotic symptoms or agitation; 27% were receiving add-on mood stabilizers (mainly lithium), and benzodiazepines were used in 73% of patients (mean ± SD = 8.5 ± 5.9 mg diazepam equivalents per day). Patients continued pharmacologic treatment during the study period, with the drugs and doses preferably not being changed 4 weeks before and during the ECT course.

Predictors of ECT Outcome

We considered those variables that have been most consistently found to be associated with ECT outcome.[3,6,7] Age was considered as a continuous variable. Psychomotor functioning was assessed with the CORE Assessment of Psychomotor Functioning, and patients were classified as either melancholic or not melancholic based on a CORE cutoff score of 8.[20,21] To get an indication of the content of the psychomotor symptoms, the continuous scores on the CORE agitation and retardation subscales were used. Psychotic symptoms were classified as either present or absent; their severity was assessed using the psychosis subscale of the Psychotic Depression Assessment Scale (PDAS).[22,23] Episode duration was used as a continuous variable (in months), but also dichotomized (< 6 months or ≥ 6 months). Treatment resistance was also dichotomized based on whether patients had received either 0–2 or > 2 adequately dosed but failed antidepressant treatments of adequate duration for the current depressive episode.

Definition of Treatment Outcome

The reduction in MADRS scores during treatment was used to quantify the effect of the ECT intervention. The MADRS was used for assessment of change because this scale is rather sensitive to change[24] and independent of the presence and severity of psychomotor functioning. The primary outcome measure was the reduction in the actual MADRS score. In an attempt to isolate the effect on mood, change in MADRS dysphoria factor (consisting of the items reported sadness, pessimistic thought, and suicidal thought) score was computed[25,26] and used as a second outcome variable.

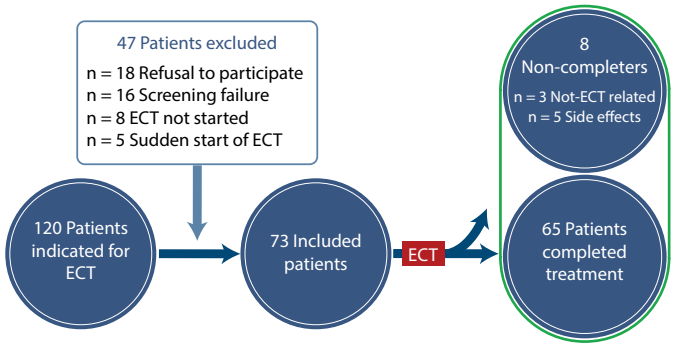
Statistical Analysis

Pearson or Spearman correlations were computed for variables coding for age and episode duration, treatment resistance, depressive symptomatology (ie, psychotic features, psychomotor agitation, and psychomotor retardation), and treatment outcome. To estimate the mediating role of depressive symptoms in the relationship between age/episode duration/treatment resistance and ECT treatment effect, we constructed a path model and estimated the size and direction of all direct and indirect paths using structural equation modeling. For this purpose, we used the presence of psychotic symptoms and the severity of psychomotor agitation and retardation to create a latent variable, which we termed *core depression*.

Finally, by means of sensitivity analysis, we re-estimated our path model, alternately using the dichotomized variable for episode duration instead of a continuous variable, treatment resistance instead of episode duration, a dichotomous variable to code for the presence or absence of CORE-defined melancholia instead of 2 continuous variables coding for agitation and retardation, the PDAS psychosis subscale score to code for the severity of psychotic symptoms instead of the presence or absence of psychotic symptoms, and the absolute change in MADRS dysphoria factor score instead of the change in total MADRS score, separately.

We used the following categories for our interpretation of the strength of the path coefficients: weak (< 0.2), moderate (0.2–0.5), or strong (> 0.5).[27] Since our model included both continuous and dichotomous variables, structural equation modeling analyses were conducted using robust weighted least squares estimation.[28] The fit of the path models is described using χ^2 test and P value (a nonsignificant χ^2 test indicates little difference between expected and the observed covariance matrices), the Comparative Fit Index (CFI; acceptable fit is indicated by a value ≥ 0.90[29]), and the Root Mean Square Error of Approximation (RMSEA; a value ≤ 0.08 indicates good fit[30]). Additionally, we report the R^2 of

Figure 2. Participant Flow



Abbreviation: ECT = electroconvulsive therapy

Table 1. Characteristics of the Study Population (N = 73)[a]

Characteristic	Value
Age, mean ± SD, y	58.8 ± 15.1
Female	56 (76.7)
Bipolar disorder	13 (17.8)
Psychotic features	33 (45.2)
CORE-defined melancholia	46 (63.0)
Episode duration, mo	
Mean ± SD	14.3 ± 18.1
Median (range)	6.5 (1–84)
Treatment resistant	46 (67.6)[b]
Baseline MADRS score, mean ± SD	32.8 ± 7.4
No. of ECT sessions, mean ± SD	11.2 ± 5.8
Endpoint MADRS score, mean ± SD	11.0 ± 7.4
MADRS decrease %, mean ± SD	65.2 ± 24.3
Responded to ECT	54 (74.0)
Remitted after ECT	41 (56.2)

[a]Values are shown as n (%) unless otherwise noted. Melancholia diagnosis is based on a score of ≥ 8 on the CORE Assessment of Psychomotor Functioning. Treatment resistance is defined as > 2 failed antidepressant treatments. Response is defined as ≥ 50% reduction in score on the MADRS, and remission is defined as a final MADRS score ≤ 10.
[b]Of the 73 patients, 46 were treatment resistant, and 22 did not have resistance, hence 46/68 (67.6%); resistance could not be determined with certainty for 5 patients.
Abbreviations: ECT = electroconvulsive therapy, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2. Path Model: Standardized Direct and Indirect Effects of Age, Episode Duration, and Clinical Features of Depression on ECT Outcome in 73 Patients Resulting From SEM Analyses[a]

	Reduction in Depressive Symptoms		
Variable	Z^b (Estimated)	SE	*P* Value
Age			
Direct effect	−0.14	0.19	.479
Indirect effect (age–core depression–treatment effect)	**0.53**	0.18	.004
Total effect	**0.39**	0.09	< .001
Episode duration			
Direct effect	**−0.38**	0.08	< .001
Indirect effect (episode duration–core depression–treatment effect)	0.11	0.11	.318
Total effect	**−0.27**	0.08	.001
Core depression			
Direct effect	**0.84**	0.17	< .001

[a]Significant effects are in boldface type. Model fit: $\chi^2_6 = 12.18$, $P = .058$; RMSEA = 0.12; CFI = 0.90. R^2 values are 69% (treatment effect) and 39% (core depression).
[b]Standardized coefficient.
Abbreviations: CFI = Comparative Fit Index, ECT = electroconvulsive therapy, RMSEA = Root Mean Square Error of Approximation, SEM = structural equation modeling.

the observed (treatment effect) and latent (core depression) outcome variables. The path analysis was conducted using MPlus, version 7.4.[31]

RESULTS

We screened 120 patients diagnosed with MDD or MDE scheduled for ECT between August 1, 2015, and September 1, 2017. Forty-seven patients were not included for different reasons (see Figure 2). The 73 patients participating in the study all gave their informed consent.

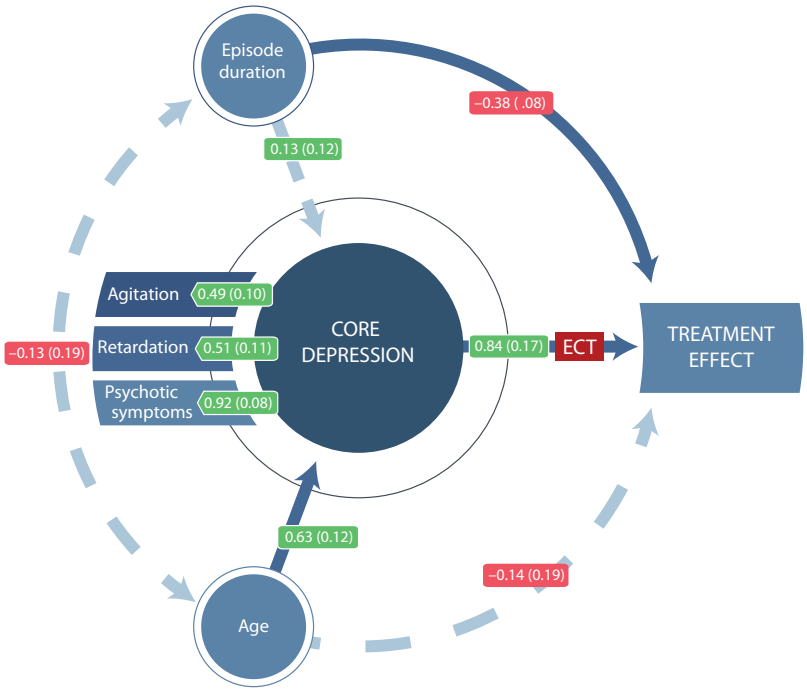
The reasons for screening failure (n = 16) were diverse. Three patients were too severely depressed to participate, mostly because of catatonic episodes during which they did not speak or interact with caregivers. One patient did not speak Dutch, and 2 were excluded because of recent (< 6 months) alcohol and/or cannabis dependency. The remaining 10 patients were excluded because of various diagnostic issues.

The clinical characteristics of the final patient sample can be found in Table 1. Our cohort was characterized by a relatively long mean episode duration and a clear predominance of female patients.

The results of the path analysis (Table 2 and Figure 3) show that the presence of core depression is strongly associated with change in depressive symptoms following an ECT course. The association between age and the effect of ECT appears to be mediated by the presence of core depression. There is no direct association between age and the effect of ECT. Only episode duration has a direct association with ECT outcome. The model fit is acceptable.

Correlations between the variables used in the path model can be found in Supplementary Table 1 and the results of the sensitivity analyses in Supplementary Tables 2–6. In most cases, the (dichotomous or continuous) variable changed in the analysis did not appear to greatly influence the size and significance of the associations. Because episode duration and treatment failure correlated strongly, they

Figure 3. Path Model of the Interactions Identified for Age/Episode Duration, Core Depression, and the Effect of ECT on Depressive Symptoms (N = 73)[a]



[a]Standardized coefficients and standard errors are reported. Significant paths ($P < .05$) are depicted as dark blue arrows and non-significant paths as light blue arrows. Negative associations are depicted in red, positive associations in green.
Abbreviation: ECT = electroconvulsive therapy

were not both incorporated in our original model. Having replaced episode duration by treatment resistance in one of the sensitivity analyses (Supplementary Table 3), we found that, unlike episode duration, treatment resistance was not directly associated with ECT outcome. In another sensitivity analysis (Supplementary Table 5), we used the dichotomous version of psychomotor symptoms in general (CORE score < or ≥ 8) instead of the clinically relevant split-up of agitation and retardation, but although the fit of this alternative model is better, this rather robust dichotomous variable did not markedly change the associations found in the path models. In our last sensitivity analysis (Supplementary Table 6), the outcome measure was changed from decrease in total MADRS score to the decrease of dysphoric or mood symptoms. Besides a disappearance of the association between episode duration and treatment outcome, associations found in this path model were somewhat less convincing but in general comparable to the ones in our original model.

DISCUSSION

In this study, we evaluated the interdependence of a literature-based selection of clinical predictors of ECT outcome in a Belgian cohort using a path model. Compared to the model recently proposed in a study conducted in The Netherlands,[11] we included an extra variable (episode duration) and grouped the psychomotor (retardation and agitation) and psychotic variables under the term *core depression* (Figure 1). We found a direct association between the presence of core depression and ECT response. Contrary to the results of previous meta-analyses, we did not find a direct predictive effect of age. Rather, the influence of age appeared to be mediated by the presence of symptoms of core depression.

Both psychomotor retardation and the presence of psychotic symptoms were associated with ECT outcome in both the Dutch and the Belgian cohort, while we, contrary to the Dutch study, also found presence of agitation to be associated with increased effectiveness of ECT. An explanation for this difference could be that, whereas Heijnen et al[11] used $HDRS_{17}$ item scores, the CORE agitation subscale we employed appears more sensitive in detecting the presence of agitation. Age was only indirectly associated with ECT outcome in both cohorts. We hence hypothesize that, rather than being a consequence of aging in and of itself, the favorable response ensues from clinical factors that distinguish older from younger patients.[32] A better response to ECT in an older population might then be related to a higher incidence of psychotic depression[33,34] and a higher severity of psychomotor agitation or retardation[35,36] relative to what is generally observed in younger patients, rather than to age per se.

This is a fundamental finding, putting results of other studies and our own meta-analysis summarizing these

studies[3] into perspective. Our meta-analysis of results obtained in over 2,800 patients confirmed the superior effect of ECT in older patients. The heterogeneity among the studies evaluated could not be explained by the presence of psychotic symptoms, but records of this potentially influential factor were not available for all studies. Contrary to what we then posed, ie, to have age as one of several elements guide the choice for ECT, the present, more detailed look at the interdependence of the outcome predictors leads us to reconsider that statement. We now venture that, in past decades, age has been given too much weight in the decision of whether or not to prescribe ECT.

It is unknown why psychomotor and psychotic symptoms are more frequently present in the older patients in our sample. Depression in older adults can be difficult to recognize because the symptoms are often attributed to aging itself, poor health, or dementia, and older people have a tendency to underreport depressive symptoms. In this way, a depressive disorder may not be recognized, eventually resulting in more severe depression with psychomotor and psychotic symptoms, and concomitant reduced intake, insomnia, and severe psychomotor disturbances. Because of limited physiologic reserves in frail older patients, this increase in depression severity may rather quickly be life-threatening. While patients in midlife will often be treated successfully with antidepressants in an ambulatory setting, the threshold for hospitalization seems to be and should be lower for older patients. They should more readily be treated with ECT because long delays could be life-threatening.

Episode duration, on the other hand, was directly associated with ECT response. Several factors can cause episodes to be prolonged, such as late help-seeking,[37] prior inadequate treatment,[38] or prior nonresponse to adequate treatment.[39] The fact that a patient with MDD or MDE does not respond to a sequence of adequate medication regimens might suggest the presence of treatment-resistant depression, although inadequate diagnostics,[38] the presence of comorbidity,[40] or other factors, such as familial, social, financial, or employment issues, may have prevented full recovery as well. When depressive symptoms persist, it is more likely that patients will encounter more of these additional problems, further delaying or reducing the chance of recovery. Accordingly, we speculate that the association between episode duration and ECT outcome could also be mediated by factors that we did not evaluate in our present investigations, such as the presence of a personality disorder.[41–43]

Our path model has a decent fit, and its validity is also confirmed by several sensitivity analyses. The model with CORE-defined melancholia as a dichotomous variable is a better fit to our data than our original model. We do, however, choose to retain and put forward the original model, based on theoretical and clinical grounds. Also, the original model gives us more information about how the variables relate to each other, which is the focus of these analyses.

The identification of reliable predictors of ECT response in depressive disorder can contribute to a more targeted patient selection, enhancing outcomes and remission rates and thereby limiting the burden of depression for both the patient and society. A more critical consideration of its application in patients not likely to respond would limit the burden of ECT.

In view of the demand for budget cuts in health care and the severity of the pathology in the patient populations typically treated with ECT, low-cost and quick assessment strategies are preferred over expensive and more invasive testing such as brain imaging. In our search for clinician- and patient-friendly assessment tools, we evaluated the predictive capacity of several relevant and easy-to-assess clinical variables, thereby offering a practical, cost-effective solution for more accurate patient-treatment matching.

Strengths and Limitations

This study is one of the first to look at the interdependence of several typical ECT outcome predictors rather than at the predictive effect of separate variables. Building on the first study to do so,[11] we extended the conceptual model proposed by our Dutch colleagues and used more sensitive scales to identify the presence and quantify the severity of the various predictors, which we believe are major strengths of our study. The use of sensitivity analyses enabled us to confirm our findings in our own cohort, while the naturalistic design of our study also is an advantage since, by testing it in a "real-world" population of severely depressed patients receiving treatment with ECT, it shows the potential of our model for use in clinical practice.

We have used the intention-to-treat sample (N = 73) in our analyses to limit the risk of overestimation of effect and path sizes. The true path sizes may therefore be even more pronounced than we calculated. Also, using the intention-to-treat sample makes our model better translatable to clinical practice. The relatively small sample size is a limitation of our study and requires replication of our findings in a larger sample. Such replication could be of great value to validate our findings and extend the evidence on what seems to be a rather commonsense finding—that the symptom profile of the depressed patient determines whether or not they will respond to ECT.

We opted for a conceptual model using a container construct of symptoms of clinical depression with a focus on psychotic and psychomotor symptoms because, theoretically, doing so seemed the most plausible approach to our query. This approach could lead to the misinterpretation that in order to consider ECT one should look for a specific subtype of depression, while based on our analyses we can conclude only that presence of the separate elements of the container construct is associated with ECT outcome. One could also argue that this model is not complete and that alternative models should also be tested. For example, we considered taking psychotic symptoms out of our container construct to gain further insight into the other variables' interdependence. We hope further data collection will shed more light on how all of the different elements determining ECT response in patients with severe depression interact.

Episode duration and treatment resistance were assessed retrospectively. When the patient was unable to provide the required data, or when the researcher questioned the reliability of the data provided, the family doctor or treating psychiatrist was consulted. Since both factors were assessed retrospectively, their exactness is inherently doubtful, which is a limitation of our study. Although we do not expect a major influence of the use of concomitant psychotropics, electrode positions,[44] or anesthetics used[45,46] or the length of the treatment course on ECT effectiveness, the heterogeneity in our treatment protocols should be taken into account when interpreting our results.

Future Research

It would be interesting for future research to delineate the role of comorbidity, particularly personality disorders,[41–43] which appear to have a negative impact on the outcome of all forms of depression treatment.[41,47] Among other instruments, the Standardized Assessment of Personality–Abbreviated Scale (SAPAS)[48,49] may then be used to screen for their presence, most preferably in large samples to create a valid prediction model that allows for all relevant clinical variables.

CONCLUSION

To conclude, on the basis of the results of our path analysis of the interdependence of predictors (assumed to be) associated with treatment response in depression, ECT can be said to be a very effective option for patients suffering from more severe forms of core depression, which are characterized by either psychomotor agitation or retardation, by psychotic symptoms, or by a combination of these three. However, the chance of a beneficial outcome is reduced in patients with a longer episode duration. In these patients, we suggest to first confirm the diagnosis of depression and to look for comorbidity that may interfere with the response to ECT. Our finding that age exerts merely an indirect influence on ECT outcome is interesting as it suggests that age alone is not a relevant factor when considering ECT.

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Supplementary Material

Article Title: Toward Targeted ECT: The Interdependence of Predictors of Treatment Response in Depression Further Explained

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary tables

Supplementary table 1 - Correlations and standard errors of correlations, mean scores, and standard deviations of the variables in the path-model, including variables used for sensitivity analyses.

	MADRS change	MADRS dysphoric symptoms change	Psychotic features (yes/no)	Psychotic features (PDAS - psychosis subscale score)	CORE-defined melancholic features (yes/no)	CORE retardation subscale score	CORE agitation subscale score	Age	Episode duration (months)	Episode duration (6 month split)	Therapy resistance (2 treatment split)
MADRS change	1.00										
MADRS dysphoric symptoms change	.80 (.07) ***	1.00									
Psychotic features (yes/no)	.58 (.10)***	.50 (.10)***	1.00								
Psychotic features (PDAS - psychosis subscale score)	.51 (.10)***	.41 (.11) **	.77 (.08)***	1.00							
CORE-defined melancholic features (yes/no)	.52 (.10)***	.55 (.10)***	.58 (.10)***	.66 (.09) ***	1.00						
CORE retardation subscale score	.42 (.11)***	.23 (.12)	.43 (.11)***	.59 (.10)**	.67 (.09)***	1.00					
CORE agitation subscale score	.36 (.11)**	.38 (.11)**	.39 (.11)**	.44 (.11)***	.45 (.11)***	-.02 (.12)	1.00				
Age	.43 (.11)***	.30 (.11)*	.34 (.11)**	.36 (.11)**	.40 (.11)**	.40 (.11)***	.33 (.11)**	1.00			
Episode duration (months)	-.32 (.11)**	-.05 (.12)	-.16 (.12)	-.04 (.12)	-.17 (.12)	-.35 (.11)**	.25 (.12)*	-.13 (.12)	1.00		
Episode duration (6 month split)	-.34 .(.12)**	-.23 (.12)	-.18 (.12)	-.24 (.12)*	-.23 (.12)	-.33 (.12)**	-.04 (.12)	-.24 (.12)	.87 (.06)***	1.00	
Therapy resistance (2 treatment split)	-.36 (.11)**	-.29 (.12)*	-.25 (.12)*	-.27 (.12)*	-.11 (.12)	-.25 (.12)*	-.04 (.12)	-.13 (.12)	.61 (.10)***	.50 (.11)***	1.00
M	21.8	7.0	Yes: 33/73	3.9	Yes: 46/73	5.4	2.4	58.8	14.3	<6: 33/68	<2: 22/68
SD	10.3	3.9	No: 40/73	3.0	No: 27/73	4.1	2.8	15.1	18.1	>6: 35/68	>2: 46/68

* $p < 0.05$, ** $p < 0.01$, *** $p<0.001$

Supplementary table 2 - Sensitivity analysis path model with episode duration (dichotomous variable – 6-month split) instead of episode duration (continuous variable – in months).

	Reduction in Depressive Symptoms		
	Estimated	SE	p-value
Age			
Direct effect	-.09	.10	.378
Indirect effect			
Age - Core depression - Treatment effect	**.49**	.12	<.001
Total effect	**.40**	.10	<.001
Episode duration (dichotomous)			
Direct effect	**-.30**	.09	<.001
Indirect effect			
Episode duration- Core depression– Treatment effect	.02	.06	.658
Total effect	**-.28**	.10	.011
Core depression			
Direct effect	**.59**	.16	<.001

Model fit: $\chi 2$ (6) = 14.09, p=0.029; RMSEA = 0.13; CFI =0.89.
R-squared values are 48% (Treatment effect) and 39% (Core depression)

Supplementary table 3 – Sensitivity analysis path model with treatment resistance (2-treatment split) instead of episode duration (continuous variable – in months).

	Reduction in Depressive Symptoms		
	Estimated	SE	p-value
Age			
Direct effect	-.04	.15	.782
Indirect effect			
Age- Core depression-Treatment effect	**.43**	.15	.003
Total effect	**.39**	.09	<.001
Treatment resistance			
Direct effect	-.13	.09	.146
Indirect effect			
Treatment resistance- Core depression - Treatment effect	-.18	.10	.060
Total effect	**-.31**	.10	.001
Core depression			
Direct effect	**.74**	.15	<.001

Model fit: $\chi 2$ (6) = 13.04, p=0.042; RMSEA = 0.13; CFI =0.90.
R-squared values are 59% (Treatment effect) and 44% (Core depression)

Supplementary table 4 - Sensitivity analysis path model with PDAS score (continuous variable) instead of presence/absence of psychotic symptoms (dichotomous variable) as a component of core depression.

	Reduction in Depressive Symptoms		
	Estimated	SE	p-value
Age			
Direct effect	.23	.12	.067
Indirect effect			
Age- Core depression-Treatment effect	.17	.10	.072
Total effect	**.40**	.10	<.001
Episode duration			
Direct effect	**-.27**	.10	.006
Indirect effect			
Episode duration- Core depression–Treatment effect	.01	.05	.924
Total effect	**-.28**	.10	.006
Core depression			
Direct effect	**.44**	.13	.001

Model fit: $\chi 2$ (6) = 47.70, p<0.001; RMSEA = 0.31; CFI =0.70.
R-squared values are 46% (Treatment effect) and 28% (Core depression)

Supplementary table 5 - Sensitivity analysis path model with presence/absence of melancholia (CORE-defined, dichotomous variable) instead of CORE agitation and retardation subscale scores as a component of core depression.

	Reduction in Depressive Symptoms		
	Estimated	SE	p-value
Age			
Direct effect	.07	.11	.517
Indirect effect			
Age- Core depression-Treatment effect	**.32**	.11	.003
Total effect	**.40**	.10	<.001
Episode duration			
Direct effect	**-.22**	.06	<.001
Indirect effect			
Episode duration-Core depression–Treatment effect	.05	.08	.510
Total effect	**-.27**	.08	.001
Core depression			
Direct effect	**.64**	.12	<.001

Model fit: $\chi 2$ (6) = 0.14, p=0.932; RMSEA = 0.00; CFI =1.00.
R-squared values are 55% (Treatment effect) and 27% (Core depression)

Supplementary table 6 - Sensitivity analysis path model with treatment effect expressed as absolute decrease of dysphoric symptoms of the MADRS at end-of-treatment compared to baseline instead of the total MADRS decrease.

	Reduction in Dysphoric Symptoms		
	Estimated	SE	p-value
Age			
Direct effect	-.10	.16	.528
Indirect effect			
Age- Core depression-Treatment effect	**.40**	.14	.004
Total effect	**.30**	.11	.005
Episode duration			
Direct effect	-.11	.07	.119
Indirect effect			
Episode duration-Coredepression–Treatment effect	.10	.08	.219
Total effect	-.01	.08	.918
Core depression			
Direct effect	**.66**	.15	<.001

Model fit: $\chi 2$ (6) = 28.03, p<0.001; RMSEA = 0.22; CFI =0.68.
R-squared values are 37% (Treatment effect regarding dysphoric symptoms) and 36% (Core depression)