

Depressive Symptom Dimensions in Treatment-Resistant Major Depression and Their Modulation With Electroconvulsive Therapy

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Objective: Symptom heterogeneity in major depressive disorder obscures diagnostic and treatment-responsive biomarker identification. Whether symptom constellations are differentially changed by electroconvulsive therapy (ECT) remains unknown. We investigate the clustering of depressive symptoms over the ECT index and whether ECT differentially influences symptom clusters.

Methods: The 17-item Hamilton Depression Rating Scale (HDRS-17) was collected from 111 patients with current depressive episode before and after ECT from 4 independent participating sites of the Global ECT-MRI Research Collaboration. Exploratory factor analysis of HDRS-17 items pre- and post-ECT treatment identified depressive symptom dimensions before and after ECT. A 2-way analysis of covariance was used to determine whether baseline symptom clusters were differentially changed by ECT between treatment remitters (defined as patients with posttreatment HDRS-17 total score ≤ 8) and nonremitters while controlling for pulse width, titration method, concurrent antidepressant treatment, use of benzodiazepine, and demographic variables.

Results: A 3-factor solution grouped pretreatment HDRS-17 items into core mood/anhedonia, somatic, and insomnia dimensions. A 2-factor

solution best described the symptoms at posttreatment despite poorer separation of items. Among remitters, core mood/anhedonia symptoms were significantly more reduced than somatic and insomnia dimensions. No differences in symptom dimension trajectories were observed among nonremitting patients.

Conclusions: Electroconvulsive therapy targets the underlying source of depressive symptomatology and may confer differential degrees of improvement in certain core depressive symptoms. Our findings of differential trajectories of symptom clusters over the ECT index might help related predictive biomarker studies to refine their approaches by identifying predictors of change along each latent symptom dimension.

Key Words: major depressive disorder, symptom heterogeneity, electroconvulsive therapy, Hamilton Depression Rating Scale, factor analysis

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Major depressive disorder (MDD) is among the most common and debilitating psychiatric disorders¹ and is a leading cause of disability worldwide.² Antidepressants and psychotherapy are typical first-line interventions; however, up to a third of patients remain unresponsive to pharmacotherapeutic treatments.³ Contributing to this failure rate is depressive symptom heterogeneity. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnosis of MDD requires the presence of 1 of 2 core symptoms and an additional 3 or 4 of 7 other symptoms (or a minimum of 5 of 9 symptoms), which amounts to 227 potential depressive symptom constellations.⁴ Consequently, patients with the same diagnosis can experience different symptomatic burdens. In addition, antidepressant treatments (eg, monoamine oxidase inhibitors, *N*-methyl-D-aspartate receptor antagonists, atypical antipsychotic augmentation, different modes of neurostimulation⁵) available to unresponsive patients have different mechanisms and targets. Major depressive disorder heterogeneity and the manifold mechanisms by which different treatments act on the central nervous system call into question whether certain antidepressant interventions are more effective at targeting particular MDD features and can be tailored for patients with particular symptom profiles.

Electroconvulsive therapy (ECT), considered the most effective treatment for severe or treatment-resistant MDD, is typically prescribed when patients have failed to respond to multiple interventions or need a rapid response.⁶ Compared with most interventions, ECT elicits fast-acting (patients typically respond in 2–4 weeks) and prominent antidepressant effects.⁷ However, although the general efficacy of ECT is well established, it remains unknown whether particular symptoms, or sets of symptoms, are most effectively targeted.

Although several validated depression rating scales are available,⁸ the Hamilton Depression Rating Scale (HDRS⁹) remains among the most frequently used for determining treatment

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efficacy. The psychometric validity and factor structure of the HDRS have been addressed previously.¹⁰ The HDRS is reportedly more sensitive to treatment-related symptom changes than the Beck Depression Inventory¹¹ and the Zung Self-Rating Depression Scale¹² and has been validated in cross-cultural cohorts.^{13,14} However, the HDRS is criticized for its multidimensional factorial structure and inability to define unidimensional depressive symptoms,¹⁵ and the relatively low interrater and internal reliability for some items.¹⁰ Recognition of these limitations has spurred efforts to modify the HDRS for better classifying depression symptom severity. Bech et al¹⁶ used the Rasch analysis¹⁷ and identified a unidimensional subset of 6 HDRS items (HDRS-6).^{18–20} Using factor analysis and item response theory techniques, others identified unidimensional HDRS subscales composed of partially overlapping core items.^{21,22} Notably, not all HDRS items are equally sensitive for detecting antidepressant treatment response.^{21–24} Meta-analyses have shown that unidimensional subscales, including the HDRS-6,¹⁶ are more sensitive to treatment effects of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants compared with placebo than the total HDRS score.^{21,25,26}

Given the varied MDD symptoms, different modes of antidepressant treatments (ie, pharmacological, behavioral, and neurostimulation) may distinctly influence different symptom dimensions tied to overlapping and unique neurobiological mechanisms of response. Furthermore, specific symptomatic profiles or depression biotypes²⁷ might benefit from select antidepressant interventions. Addressing how changes in HDRS items covary over distinct treatments could inform the mechanisms of therapeutic response and inform more effective personalized treatments. Previously, Okazaki et al²⁸ evaluated ECT-related changes along the 3 factors of the Montgomery-Asberg Depression Rating Scale, dysphoria, retardation, and vegetative symptoms, in a cohort of 24 Japanese patients with MDD. Okazaki et al reported that pretreatment dysphoric symptoms were significantly more elevated among patients who subsequently responded to ECT compared with those who did not. As with most ECT studies however, this previous study is limited by its modest sample size.

Using the 17-item HDRS (HDRS-17),⁹ we investigated how symptomatic dimensions of depression vary with ECT in a multi-site cohort of 111 patients participating in the Global ECT-MRI Research Collaboration (GEMRIC).²⁹ Specifically, we evaluated the effects of ECT on multidimensional features of depression symptom severity. Exploratory factor analysis (EFA) and hierarchical clustering were used to identify covarying HDRS-17 items before and after the ECT index series (ECT-IS). Given the prevalence of somatic symptoms in treatment-resistant MDD,³⁰ the expected overlap with antidepressant drug therapies that show predictive effects with regard to the presence and severity of psychic and somatic anxiety symptom subscales,³¹ and the previous HDRS factor analyses, we hypothesized that HDRS-17 items would segregate into psychic and somatic clusters. We further hypothesized that HDRS-17 factor(s) identified with EFA with prominent weightings from more unidimensional constructs found in the HDRS-6 (depressed mood, feelings of guilt, work and interests, retardation, psychic anxiety, and somatic symptoms) would be most reduced by ECT.

MATERIALS AND METHODS

Patients

Among the GEMRIC participants,²⁹ 111 patients with a current major depressive episode (N = 68 female; age, 52.16 ± 14.67)

from 4 independent sites had complete item-level HDRS-17 scores available before and after ECT treatment for analysis. Data for 28 participants were acquired from site 1, 39 from site 2, 16 from site 3, and 28 from site 4. Also included were 9 patients with bipolar disorder, 19 patients with psychotic features, and 6 patients with a single major depressive episode. Ninety-six patients were diagnosed with recurrent MDD. Patient clinical and demographic information is summarized in Table 1.

All ECT protocols were naturalistic (stimulus parameters were not manipulated for research purposes). Individual need for ECT was clinically determined at each site. Site 1 used a MECTA Spectrum 5000Q device (Oswego, Oregon), whereas all other sites used Thymatron IV devices (Somatics Inc, USA). Barbiturate (methohexital or thiopental) induction was used at all sites. Treatment resistance was defined as failure to respond to at least 2 prior adequate medication trials for sites 1 and 2; at least 1 unsuccessful psychotherapy for site 4; and there were no strict criteria for treatment resistance for site 3. Patients completed clinical assessments before and less than 2 weeks after ECT-IS, where ECT was administered 2 to 3 times weekly for site 4 and 3 times weekly for sites 1, 2, and 3. Electroconvulsive therapy index series duration was clinically determined based on response speed and magnitude, ending when maximal response was achieved or lack of appreciable and sustained benefit. Within and across sites, modes of ECT administration included bitemporal, left anterior right temporal, and right unilateral electrode placement. Suicidal ideation was not exclusionary at any site. Patients at site 1 were tapered off antidepressant medication before treatment, but at the other study sites, participant's antidepressant medications continued.

All participants provided written informed consent as approved by their local ethical committees or institutional review boards, and centralized analysis of pooled data was approved by the Regional Ethic Committee South-East in Norway (2013/1032 ECT and Neuroradiology, June 1, 2015).

Depression Symptom Severity Measure

Trained psychiatrists administered the HDRS-17 at each site immediately before and within 2 weeks after ECT-IS. As previously outlined, the HDRS-17 is among the most commonly used depression rating scales and has been validated in cross-cultural cohorts.^{13,14} However, its psychometric properties are criticized as it is a multidimensional scale and items have variety of ranges; some range between 0 and 4, whereas others range from 0 to 2.

Statistical Methods

We conducted EFAs of HDRS-17 items independently at each time point, with oblique, oblimin rotations³² to allow for between-factor correlations, to identify latent symptom dimensions. A range of factor numbers was considered. For each solution, we assessed item cross loadings and average weighting onto each factor as goodness-of-fit criteria, favoring solutions with minimal cross loadings and higher average item weightings. Only items with loadings of 0.3 or greater were included for each factor, and we required a minimum of 3 items loaded onto each factor. Subject-level factor loadings were then computed by a unit-weighting approach, that is, each factor was an unweighted sum of all HDRS items meeting the loading ≥ 0.3 criterion. Hierarchical clustering of HDRS-17 items was used to corroborate factor structures. This proceeded by defining the pairwise Euclidean distances between each item across all subject's scores. All items were scaled to a range of ± 1 . We applied the Ward hierarchical

TABLE 1. Demographic and Clinical Features

	Overall	Site 1	Site 2	Site 3	Site 4
n	111	28	39	16	28
Age, mean (SD), y	52.16 (14.67)	41.07 (14.45)	64.43 (9.08)	52.12 (10.82)	46.17 (10.22)
Male/female	43/68	14/14	13/26	5/11	11/17
Clinical info					
RUL	91	26	37	0	28
BT	21	1	2	15	3
Others	1 LART	1 LART			
RUL number, mean (SD)	9.22 (5.26)	8.0 (3.63)	10.32 (3.06)	—	13.46 (4.46)
BT number, mean (SD)	6.69 (6.50)	—	7.28 (3.54)	14.20 (4.98)	6.33 (1.52)
ECT device	—	MECTA	Thymatron	Thymatron	Thymatron
Titration Method	—	Seizure threshold (n = 28)	Seizure threshold (n = 39)	Seizure threshold (n = 2) ½ age (n = 14)	½ age (n = 28)
ECT pulse width, ms	—	0.3 (n = 26) 0.5 (n = 2)	0.25 (n = 36) 1 (n = 3)	0.5 (n = 15) NA (n = 1)	0.5 (n = 28)
ECT pulse amplitude, mA	—	800 (n = 28)	900 (n = 39)	900 (n = 15) NA (n = 1)	900 (n = 28)
Antidepressant medication	—	None (n = 28)	None (n = 2) SSRI (n = 17) SNRI (n = 16) TCA (n = 4)	None (n = 3) SSRI (n = 4) SNRI (n = 3) TCA (n = 6)	None (n = 5) SSRI (n = 4) SNRI (n = 15) TCA (n = 4)
Antipsychotic medication, yes/no/NA	—	0/28/0	20/19/0	8/7/1	19/0/9
Benzodiazepines, yes/no/NA	—	0/28/0	16/22/1	8/8/0	0/28/0
Lithium, yes/no/NA	—	0/28/0	0/39/0	1/15/0	4/0/24
Bipolar	9	4	0	5	0
Psychotic features	19	0	16	3	0
Single episode	6	0	2	2	2
Treatment resistant, yes/no, count	105/3	28/0	36/3	13/0	28/0
HDRS 17 baseline score, mean (SD)	24.42 (6.31)	23.89 (6.82)	25.28 (6.70)	28.0 (4.87)	21.71 (4.80)
HDRS 17 follow-up score, mean (SD)	12.0 (9.11)	20.0 (9.41)	6.64 (7.16)	13.00 (6.71)	10.92 (6.57)

BT indicates bitemporal stimulation; LART, left anterior right temporal stimulation; NA, not available; TCA, tricyclic antidepressants.

agglomerative clustering method³³ to the Euclidean distance matrices to identify separable clusters.

We used an analysis of covariance model to determine whether ECT conferred differential degrees of change on baseline symptom dimensions as a function of remission status. Here, remission was defined as a posttreatment HDRS-17 total score of 8 or less. Because unit-weighted symptom dimensions had differing scales due to loadings from variable numbers of HDRS items with differing ranges, we *z*-transformed the baseline factor scores and *z*-transformed the factor scores at follow-up by scaling them relative to the baseline scores. Thus, the degree of change along each symptom dimension over ECT-IS was calculated as the difference between the *z*-transformed follow-up and baseline scores (follow-up – baseline). Symptom dimension change was then predicted from main effects of dimension number (categorical), remission status (categorical), and an interaction of dimension number and remission status. The model further included covariates for ECT parameters [pulse width, titration method (seizure threshold or ½ age), and number of right unilateral stimulation (RUL) treatments], concurrent antidepressant treatment and antidepressant class, use of benzodiazepine, patient age, sex, and site. We adjusted for multiple

comparisons in post hoc tests using the Tukey range test. All analyses were conducted in R 3.4.0 (<https://www.r-project.org/>).

RESULTS

Demographic and Clinical Effects

Age differed significantly between the majority sites. Only sites 1 and 4 as well as sites 3 and 4 did not significantly differ in age, with site 2 having the oldest patients (age, 64.43 ± 9.08) on average. The proportion of female patients was consistent across the sites ($\chi^2 = 2.35$, *df* = 3, *P* = 0.50). Forty-eight patients achieved remission after ECT-IS. Remitting patients were significantly older (*t* = -3.75, *df* = 108.54, *P* < 0.05), with the mean age of remitting and nonremitting patients being 57.6 and 47.9 years, respectively. Proportions of males and females did not differ significantly between remitting and nonremitting patients ($\chi^2 = 0.67$, *df* = 1, *P* = 0.41).

Pretreatment HDRS Factor Structure

Baseline items exhibited a Kaiser-Meyer-Olkin score³⁴ of 0.62, suggesting that they are only moderately amenable to EFA.

Individual item-level measures of sampling adequacy (iMSA) were mostly moderate. However, several items' iMSAs were low, including middle insomnia (0.58), psychomotor retardation (0.58), psychomotor agitation (0.55), weight loss (0.55), and insight (0.49), suggesting they have poor psychometric properties or are unrelated to more dominant symptom constellations in this sample. The internal validity of baseline HDRS-17 items was acceptable with a Cronbach α (an estimate of reliability³⁵) of .73, which was unaffected by dropping items with low iMSA.

A 3-factor solution was favored for baseline HDRS-17 items (Fig. 1A). All items cross-loaded, but the following items were predominantly loaded on factor 1: work and interests, weight loss, psychomotor retardation, and depressed mood. Factor 2 consisted predominantly of somatic gastrointestinal (GI) symptoms, hypochondriasis, feelings of guilt, genital symptoms, general somatic symptoms, somatic anxiety, anxiety psychic, and psychomotor agitation. Factor 3 included early insomnia, middle insomnia, and late insomnia. Suicide was spread across all 3 factors with loadings less than 0.2. Insight failed to adequately load onto a specific factor. Cronbach α scores for each factor were moderate: factor 1, 0.66; factor 2, 0.69; and factor 3, 0.63. In Supplemental Figure 1 (Supplemental Digital Content, <http://links.lww.com/JECT/A85>) we illustrate the clustering of HDRS-17 items by time point using hierarchical clustering. Hierarchical clustering of items largely mirrored the factor structure. No significant difference was observed between the percent change in the 3 factors over ECT-IS.

Posttreatment HDRS Factor Structure

The Kaiser-Meyer-Olkin score for items at follow-up was 0.87. Individual MSA scores were high (above 0.8) except for late insomnia (0.73), weight loss (0.63), and insight (0.59). Cronbach

α was also high (.88). Two- and 3-factor solutions were comparably viable; however, the average correlation between latent factors was lower in the 2-factor solution ($r = 0.63$ vs 0.73 in the 3-factor solution). Here, factor 1 consisted of depressed mood, guilt, suicide, work and interests, psychomotor retardation, psychomotor agitation, anxiety psychic, somatic anxiety, somatic GI symptoms, general somatic symptoms, genital symptoms, and hypochondriasis. Factor 2 comprised depressed mood, feelings of guilt, suicide, early insomnia, middle insomnia, late insomnia, and somatic anxiety. All solutions resulted in high degrees of cross loading. Cronbach α scores for the factors were high: factor 1, .90; factor 2, .86. The posttreatment factor structure is illustrated in Figure 1B.

Treatment-related Changes in Baseline HDRS Factor Structure

We observed a significant symptom dimension-by-remission status interaction ($F = 10.50, df = 2, P < 0.05$), indicating that factors change differentially as a function of remission status. Among remitting patients, factor 1 (core mood/anhedonia) was reduced significantly more than both factor 2 (mean difference $Z = 1.13, P < 0.05$) and factor 3 (mean difference $Z = 1.51, P < 0.05$). No difference was observed between factors 2 and 3 among remitting patients. There was no evidence of significant differences in the change of symptom dimensions among nonremitting patients. All symptom dimensions were reduced significantly more among remitting patients compared with nonremitting patients (all $P < 0.05$; Fig. 2).

DISCUSSION

To determine whether ECT outcomes may benefit from patient selection based on features of a major depressive episode,

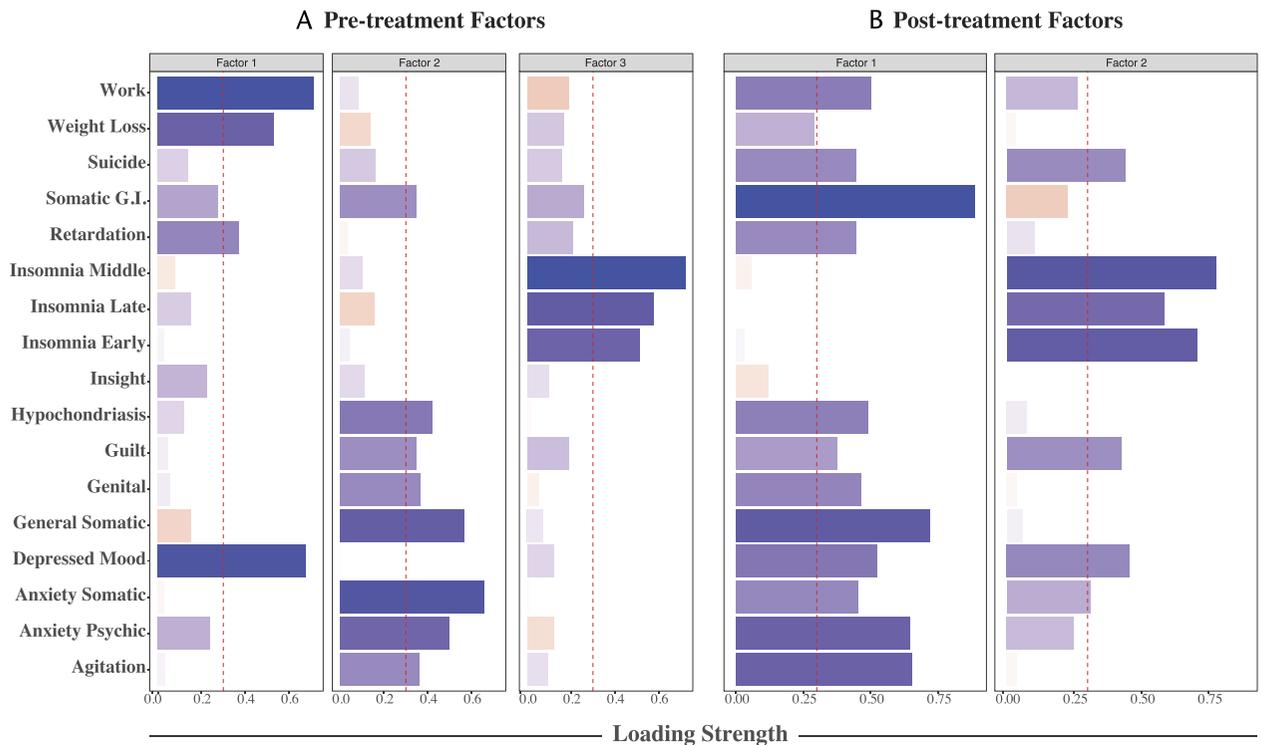


FIGURE 1. A, Pretreatment HDRS factor structure and item loadings. Vertical dashed red lines indicate loading cutoff of 0.3, below which items are not considered adequately loaded onto a factor. Blue bars indicate positive factor loadings, whereas orange bars indicate negative loadings. B, Posttreatment HDRS factor structure and item loadings.

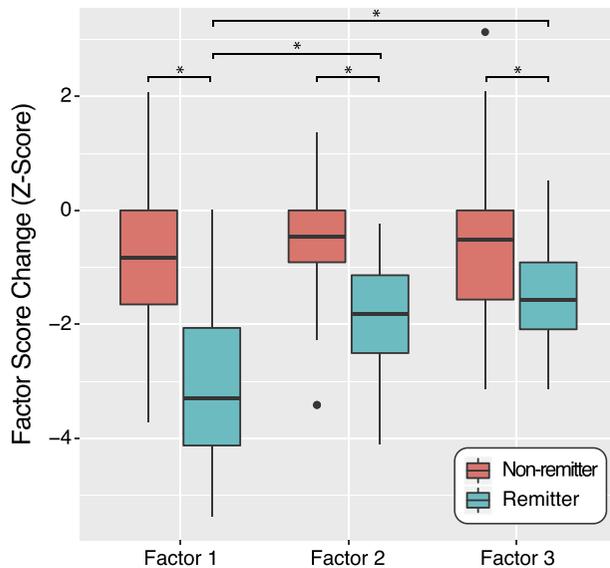


FIGURE 2. Symptom dimension changes over treatment by remission group.

we evaluated how ECT affects symptom dimensions of depression. Exploratory factor analysis examined the factor structure of symptom dimensions as captured by HDRS-17 at pretreatment and posttreatment. This revealed a 3-factor representation of HDRS-17 items at baseline and a more uniform 2-factor representation at follow-up. We further found a significant symptom dimension-by-remission status interaction wherein particular symptom dimensions changed differentially between remitting and nonremitting patients. Notably, the symptom dimension capturing core mood and anhedonia symptoms was relatively more improved than the other 2 symptom dimensions among remitting patients; however, no discernable differences in the change of symptom clusters was observed among nonremitting patients. Furthermore, the severity of symptom dimensions did not significantly differ at pretreatment between subsequent remitting and nonremitting patients.

Our overarching premise is that depressive symptoms are heterogeneous, and identifying sets of symptoms or symptom dimensions most responsive to ECT would improve clinical outcomes after treatment. As a number of previous studies have endeavored to predict response after ECT^{36–39} or identify biomarkers associated with ECT outcome,⁴⁰ a more precise measure of response defined along more homogenous symptom dimensions could improve the statistical power of related studies. Studies of antidepressant pharmacotherapeutic treatments show improved sensitivity for determining treatment efficacy by focusing only on unidimensional depression scales.^{21,25} To date, ECT studies have relied predominantly on depression symptom severity total scores, which have mainly been multidimensional in nature, to define response. Unfortunately, this approach has limited the ability to determine if ECT is more effective at treating specific depressive symptoms.

Factor Analysis of the HDRS

Because depressive symptomatology is multidimensional and the HDRS-17 captures unidimensional depressive features, we conducted EFAs to identify latent symptom dimensions that might provide homogenous bases for measuring and investigating depressive symptomatology.

Most studies^{41–43} used the principal component analysis with a varimax rotation to identify factors, requiring the eigenvalues of

each factor to be 1 or greater, and item loadings to be 0.4 or greater. However, this enforces that the recovered factors are orthogonal, which implies the absence of correlations and cross loadings across factors.⁴⁴ This restriction is unrealistic for the exploration of depressive symptom sets, which are interrelated. Consequently, we instead used an approach that allowed for cross loading of HDRS-17 items and correlation between factors.

At baseline, HDRS-17 items mapped onto a 3-factor solution. The first factor captured core aspects of MDD with contributions from depressed mood and work and interests (eg, decreased pleasure, anhedonia). The second factor was largely composed of items reflecting somatic symptoms (eg, headache, GI) and anxiety. The third factor was more clearly defined as it was composed exclusively of the insomnia items.

These factor structures are somewhat consistent with previous findings. A meta-analysis by Bagby et al¹⁰ reviewed 15 studies that factor analyzed the HDRS-17 and reported that the number of factors ranged between 2 and 8. The Bagby report showed that with 13 factorizations, the insomnia items loaded on a single factor, consistent with our third factor. Furthermore, a “general depression” factor that consisted of depressed mood, feelings of guilt, and suicide was observed in 6 studies. Moreover, 6 samples identified a common factorization of psychomotor agitation, psychic anxiety, somatic anxiety, and somatic GI symptoms, which support the existence of an anxiety and somatization factor. Indeed, multiple studies have supported that the HDRS-17 has an anxiety and somatization factor score.⁴⁵

Similar to the Bagby meta-analysis, our baseline factorization observed a unidimensional sleep disturbance factor and evidence for an overlapping anxiety/somatization factor. However, the general depression factor was not replicated here as depressed mood, work and interests, and weight loss loaded onto the same factor. Interestingly, the suicide item was not significantly loaded onto any baseline factor but exhibited subthreshold cross loadings onto each factor. As suicide was not exclusionary for any site, this is unlikely to be an artifact of inclusion criteria.

The HDRS-17 items at follow-up appeared more homogeneous as our analysis found a 2-factor solution. The second factor was composed predominantly of sleep disturbance items alongside suicide, feelings of guilt, and depressed mood, which were heavily cross loaded with the first factor. The first factor had significant contributions from all items with the exception of the insight and 3 insomnia items. Because most HDRS-17 items were more similar at posttreatment due to the robust antidepressant effects of ECT, the data may have been more spherical and expressed fewer discernible dimensions.

Differential Changes in Symptom Dimensions

Although all 3 pretreatment symptom dimensions were significantly reduced among remitting patients, the core mood/anhedonia symptom dimension was improved to a differentially higher degree compared with the somatic disturbances and insomnia symptom dimensions. This, however, was not observed among nonremitting patients. This finding supports that ECT disproportionately affects core symptoms of depression.

Taken together, our findings suggest that depressive symptoms cluster into discernable constellations, but these constellations become less distinct after ECT-IS. Although certain core symptoms of depression are disproportionately improved by ECT, each symptom dimension was significantly reduced among remitting patients. Among nonremitting patients however, no discernible difference in the change of symptoms was observed. Furthermore, remitters and nonremitters were not distinguished on the basis of pretreatment symptom severities. These findings beg the question of whether

unique neural mechanisms underlie these pretreatment symptom constellations and if they uniquely or uniformly are affected by ECT, which warrants additional research. Further work is also warranted to identify pretreatment biomarkers predictive of the degree of response along each of these symptom dimensions.

Limitations

Several limitations must be considered. As a multisite study, treatment protocols were naturalistic and uncontrolled across site. However, this is also a strength, as it allowed us to capture diverse and realistic implementations of clinically administered ECT protocols. Although ECT stimulation parameters were uncontrolled across sites, we did control for such variables in the analyses. Prior studies have shown that ECT stimulus parameters and other treatment manipulations can affect the extent of response and magnitude of cognitive adverse effects.^{46–48} These parameters might also influence the trajectory of symptom changes. We evaluated the effect of treatment parameters, however, and observed no significant associations with the change along each of the 3 latent symptom dimensions identified at baseline. Associations with ECT parameters were confounded with the study site, which is unavoidable in a naturalistic multisite study. There were also confounds between patient age and site; however, no significant associations were found between symptom changes and patient age. Inclusion and exclusion criteria varied though the data were collected at sites that required that patients had failed at least 1 previous treatment or be in immediate need of ECT. Furthermore, a minority of patients with bipolar disorder, psychotic features, and single-episode depression were included in this analysis. Although symptom constellations in these groups might differ from those with recurrent unipolar depression, they reflect the naturalistic design of this study and help account for the expected variability in patients eligible for ECT. Notably, patients from site 1 exhibited the least symptom improvement (Table 1), perhaps due to the higher proportion of males or absence of concurrent antidepressant medication.

Conclusions and Future Directions

To our knowledge, this is the first study to evaluate the trajectory of HDRS-17 symptom dimensions over ECT-IS and identify latent factors for HDRS-17 items before and after ECT. We demonstrated that there were latent depressive symptom dimensions at baseline consistent with prior research, and there were discernable changes in latent depressive symptom trajectories over ECT-IS. Our results suggested that ECT may disproportionately improve particular symptom constellations. Additional studies are needed to evaluate related antidepressant treatments to determine whether other treatment modalities differentially affect specific depressive symptom dimensions. Future studies seeking to minimize the heterogeneity of depressive symptoms and the multidimensionality inherent in the HDRS-17 scale could leverage these dimensions. Our ongoing work will investigate relationships between these depressive symptom dimensions and neuroimaging data available in the GEMRIC data to determine their underlying neurobiology to optimize antidepressant neuromodulation treatment delivery and precision medicine approaches.

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