The Efficacy of Acute Electroconvulsive Therapy in Atypical Depression

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Objective: This study examined the characteristics and outcomes of patients with major depressive disorder (MDD), with or without atypical features, who were treated with acute bilateral electroconvulsive therapy (ECT).

Method: Analyses were conducted with 489 patients who met DSM-IV criteria for MDD. Subjects were identified as typical or atypical on the basis of the Structured Clinical Interview for DSM-IV obtained at baseline prior to ECT. Depression symptom severity was measured by the 24-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{24}$) and the 30-item Inventory of Depressive Symptomatology–Self-Report ($IDS\text{-}SR_{30}$). Remission was defined as at least a 60% decrease from baseline in $HAM\text{-}D_{24}$ score and a total score of 10 or below on the last 2 consecutive $HAM\text{-}D_{24}$ ratings. The randomized controlled trial was performed from 1997 to 2004.

Results: The typical (N = 453) and atypical (N = 36) groups differed in several sociodemographic and clinical variables including gender ($p = .0071$), age ($p = .0005$), treatment resistance ($p = .0014$), and age at first illness onset ($p < .0001$) and onset of current episode ($p = .0008$). Following an acute course of bilateral ECT, a considerable portion of both the typical (67.1%) and the atypical (80.6%) groups reached remission. The atypical group was 2.6 (95% CI = 1.1 to 6.2) times more likely to remit than the typical group after adjustment for age, psychosis, gender, clinical site, and depression severity based on the $HAM\text{-}D_{24}$.

Conclusion: Acute ECT is an efficacious treatment for depressed patients with typical or atypical symptom features.

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There is limited research examining the treatment of atypical depression with electroconvulsive therapy (ECT). Early research[1,2] suggested that ECT was ineffective in treating atypical depression. Although ECT resulted in minor improvement in mood,[2] many patients with atypical depressive features did not maintain the effect. However, neither study categorically defined atypical depression. They regarded atypical as being different from typical depression on the basis of undefined or varying symptom feature differences. Also, the study of West and Dally[2] was confounded by inclusion of patients who had primary anxiety disorders and secondary depression.

TAKE-HOME POINTS

- Clinicians should consider using electroconvulsive therapy (ECT) with patients with severe atypical depression, particularly with the presence of suicidality or psychosis.
- ECT should be considered in the treatment of patients with atypical depression, especially when other treatments fail.

While this early research has served as the basis for clinical decision making for decades, advances in both the understanding of atypical depression and the techniques involved in ECT recommend a reevaluation of this notion. Recently, the definition of atypical depression has been operationalized to include the presence of mood reactivity plus 1[3] or 2[4,5] of the following additional symptom(s): hypersomnia, increased appetite or weight gain, leaden paralysis, and interpersonal rejection sensitivity. More recent studies also suggest that atypical depression may be more prevalent than previously thought. Early rates of atypical depression varied between 1.4% and 2.8%,[6,7] and a lifetime prevalence of 0.7% was found in the Epidemiologic Catchment Area study.[8] However, a prevalence rate of 6% was found for atypical depression in the National Comorbidity Survey.[9] Also, in the Sequenced Treatment Alternatives to Relieve Depression trial,[10] 18% of the first 1500 patients met criteria for depression with atypical features.

Moreover, the practice of ECT has improved[11–13] with standardized lead placement (e.g., bilateral, right unilateral) and improved stimulus dosing.[14] Thus, it would be appropriate to reevaluate the clinical efficacy of ECT for the treatment of depression with atypical symptom features.

This article describes and characterizes patients with atypical major depressive disorder referred for ECT in a multisite trial examining the efficacy of maintenance ECT and examines the outcome of acute-phase ECT for patients with and without atypical depressive symptom features.

METHOD

Study Overview and Design

This study was conducted as part of the Consortium for Research in ECT (CORE) Continuation ECT (C-ECT) versus Continuation Pharmacotherapy (C-Pharm) trial, which was a multicenter, National Institute of Mental Health–funded, randomized controlled trial performed from 1997 to 2004. The rationale, methods, and design of the C-ECT versus C-Pharm study have been detailed elsewhere.[15]

The trial consisted of 2 distinct phases: phase 1 (acute phase), in which severely depressed patients received bilateral ECT 3 times per week until they met remission criteria, and phase 2 (continuation phase), in which patients who maintained remission after 1 week were randomly assigned 1:1 to either C-ECT or C-Pharm (lithium plus nortriptyline). Patients provided informed consent for this protocol, which was reviewed and approved by the institutional review boards of all 5 participating academic clinical centers.

Patient Sample

Patients enrolled in this acute treatment with ECT (phase 1) were 18 to 85 years old and referred for ECT with a 24-item Hamilton Rating Scale for Depression[16,17] (HAM-D_{24}) total score of 21 or higher. These patients were required to have a Structured Clinical Interview for DSM-IV[18] (SCID-I) diagnosis of primary major depressive disorder, unipolar type, single or recurrent, with or without psychosis. Appropriateness for ECT was determined on a clinical basis after consultation with an attending-level ECT psychiatrist. Typical reasons for referral included failed medication trials and severity or urgency of illness.[13,19,20]

Exclusion criteria included a diagnosis of schizophrenia or bipolar disorder, dementia, delirium, or other central nervous system disease with the probability of affecting cognition or response to treatment, substance dependence within the past 12 months, medical conditions contraindicating ECT or nortriptyline-lithium use, and ECT in the 3 months before phase 1.

ECT Treatment Procedures

The ECT procedures were standardized across all centers using the Thymatron DGX ECT device (Somatics Inc., Lake Bluff, Ill.), bilateral (bitemporal) electrode placement, dose titration to determine seizure threshold at initial treatment, and stimulus dosing at subsequent treatments of 1.5 times the seizure threshold.[21] Procedures for anesthesia and determination of seizure adequacy (electromyography > 20 seconds; electroencephalography > 25 seconds) followed standardized clinical protocols (e.g., American Psychiatric Association[11]). Treatments were administered 3 times per week, and no minimum or maximum number of ECT sessions was specified for classification of remission.

Clinical Assessments

The primary instrument used to rate depressive symptoms and determine outcome of treatment was the HAM-D_{24},[16,17] which was administered at baseline and within 24 to 48 hours after each ECT treatment. The 30-item

self-report version of the Inventory of Depressive Symptomatology–Self-Report[22–24] (IDS-SR_{30}) was administered as a secondary measure of depression severity. The primary outcome measure for the acute phase of the study was remission, defined as at least a 60% decrease from baseline in HAM-D_{24} score and a total score of 10 or below on the last 2 consecutive HAM-D_{24} ratings. Patients were classified as being treatment resistant based on the total resistance score of the Antidepressant Treatment History Form,[25] which determined the degree of prior medication treatment failure.

Clinical Raters

The study psychiatrist, the continuous rater, and the neuropsychological technician acquired study data. At specified time points (baseline and end), the continuous rater and study psychiatrist each performed independent HAM-D_{24} ratings, with the mean of the ratings used for analyses.

Standardization and Quality Assurance Assessment

All clinical raters underwent an intensive prestudy training period conducted by a senior-level, highly experienced psychometrician. An independent blind rater (M.M.B.) located at the University of Texas Southwestern Medical Center, but not affiliated with the clinical center, rated a random sample of time-blinded videotapes of HAM-D_{24} patient interviews (intraclass correlation[26] between the independent blind rater and clinical ratings, r = 0.9).

Definition of Atypical Depression

The presence or absence of atypical features was defined using the SCID-I[18] criteria at phase 1 baseline (i.e., study entry). Specifically, the SCID-I defines the presence of atypical features as mood reactivity (i.e., "mood brightens in response to actual or potential positive events") with 2 (or more) of the following atypical symptoms: (1) hyperphagia or increased weight, (2) hypersomnia, (3) leaden paralysis, or (4) interpersonal rejection sensitivity.

Statistical Analyses

Demographic, clinical, and treatment characteristics were compared for the atypical versus typical groups using pooled t tests or the Wilcoxon rank sum test for continuous measures and χ^2 test or Fisher exact test for categorical measures. For primary outcome analyses, logistic regression with the dichotomous outcome remitted/not remitted was used to compare remission proportions adjusted for age, psychosis status, baseline symptom severity as measured by HAM-D_{24} total score, gender, and clinical site. For these analyses, dropouts were considered nonremitters. The adjusted odds ratio and corresponding 95% confidence interval, obtained from the multivariable logistic regression analyses, were used to describe the magnitude of the effect of the atypical compared to typical responses. For the continuous efficacy outcome (HAM-D_{24} score change from baseline), a paired t test was used to compare the baseline and end of phase HAM-D_{24} scores *within* each group, and a pooled t test was used to compare unadjusted mean change *between* the 2 groups. A general linear models (GLM) approach was used to compare the adjusted least squares mean HAM-D_{24} change scores adjusted for age, psychosis status, baseline symptom severity as measured by HAM-D_{24} total score, gender, and clinical site.

Table 1. Sociodemographic and Clinical Characteristics of Patients With and Without Atypical Depression (N = 489)

Baseline Characteristic	Atypical Depression (N = 36)	Typical Depression (N = 453)	p Value
Age, mean (SD), y	46.1 (15.0)	56.3 (16.7)	.0005[a]
Gender, female, N (%)	32 (88.9)	305 (67.3)	.0071[b]
Psychotic features, N (%)	5 (13.9)	139 (30.7)	.0333[b]
Race, N (%)			.5183[b]
White	33 (91.7)	414 (91.4)	
African American	1 (2.8)	26 (5.7)	
Other	2 (5.5)	13 (2.9)	
Treatment resistant, N (%)	29 (80.6)	223 (49.2)	.0014[b]
No. of MDEs, mean (SD)	3.2 (4.2)	2.4 (4.0)	.3544[a]
Age at onset of current MDE, mean (SD), y	45.4 (15.5)	55.3 (16.9)	.0008[a]
Length of current MDE, mean (SD), wk	44.2 (74.5)	46.2 (61.4)	.8599[a]
Age at onset of first mental illness, mean (SD), y	25.3 (14.2)	39.0 (19.8)	< .0001[a]
Depression severity, mean (SD)			
HAM-D_{24} score	32.9 (6.4)	35.4 (7.0)	.0385[a]
IDS-SR_{30} score	36.9 (20.5)	31.7 (25.1)	.2254[a]

[a]p Value from independent sample t test.
[b]p Value from χ^2 test or Fisher exact test.
Abbreviations: HAM-D_{24} = 24-item Hamilton Rating Scale for Depression, IDS-SR_{30} = 30-item Inventory of Depressive Symptomatology–Self-report, MDE = major depressive episode.

RESULTS

Clinical and Sociodemographic Characteristics

Table 1 presents sociodemographic and baseline clinical characteristics for patients with atypical (N = 36) and typical (N = 453) depression. Most participants were women (69%) and the racial composition was 91% white, 6% African American, and 3% other (including 1% endorsing Hispanic ethnicity). The racial composition was comparable to those patients who are referred to and receive ECT.[27,28] The mean age of those with atypical depression was approximately 10 years younger than those with typical depression (t = 3.53, df = 487, p = .0005) and a higher percentage were women (89% vs. 67%, χ^2 = 7.24, df = 1, p = .0071).

The mean age at onset of the current major depressive episode was approximately 10 years earlier (t = 3.39, df = 448, p = .0008), and the mean age at onset of first psychiatric illness was approximately 14 years earlier (t = 5.08;

Table 2. Acute Phase Treatment Characteristics and Outcome for Patients With and Without Atypical Depression Receiving ECT

Outcome	Atypical Depression (N = 36)	Typical Depression (N = 453)	p Value, Unadjusted	p Value, Adjusted[a]
Treatment Characteristic				
Seizure threshold, mean (SD)				
Total sample	20 (10.6)	26.3 (15.4)	.0014[b]	.3242
Remitters only	19.3 (10.0)	27.2 (14.7)	.0004[c]	.2009
No. of ECT treatments, mean (SD)				
Total sample	6.9 (3.3)	7.2 (3.4)	.5988[b]	NA
Remitters only	6.6 (3.1)	7.1 (3.0)	.4230[b]	NA
Treatment Outcome				
Dropout, N (%)	5 (13.9)	99 (21.9)	.2610[c]	NA
Outcome, N (%)[d]				
Remitter	29 (80.6)	304 (67.1)	.0957[c]	.0357
Nonremitter and dropout	7 (19.4)	149 (32.9)	NA	NA

[a]p Value from logistic regression; adjustment covariables: age, psychotic status, baseline HAM-D_{24} total score, gender, and clinical site.
[b]p Value from independent sample t test.
[c]p Value from χ^2 test.
[d]Adjusted odds ratio; OR interpreted as odds of remitting for atypical compared to typical groups adjusted for age, psychotic status, baseline HAM-D_{24} total score, gender, and clinical site; effect size (95% CI) = 2.6 (1.1 to 6.2).
Abbreviations: ECT = electroconvulsive therapy, HAM-D_{24} = 24-item Hamilton Rating Scale for Depression, NA = not applicable.

df = 40,6; p < .0001) for those with atypical compared to typical depression. A higher percentage of patients with atypical depression were also found to have treatment-resistant depression relative to the typical depression group (81% vs. 49%, χ^2 = 10.30, df = 1, p = .0014); however, they presented less often with psychotic features (χ^2 = 4.53, df = 1, p = .0333). The group with atypical depression was also found to have lower depression severity at baseline (t = 2.08, df = 487, p = .0385) as measured by the HAM-D_{24}, but not with the IDS-SR_{30}.

Treatment Outcome with Acute ECT

Table 2 shows the treatment characteristics and treatment outcome for the atypical and typical depression subgroups. Regarding treatment parameters, both groups received a similar number of ECT treatments (approximately 6 to 7); however, patients with atypical depression required lower stimulus doses to induce seizure activity when both the total (t = 3.39; df = 48,3; p = .0014) and remitted samples (t = 3.90; df = 40,9; p = .0004) were examined. After adjustment for age, these differences were no longer found to be significant.

Both the atypical and the typical groups experienced a significant improvement (decrease) from baseline in mean (SD) HAM-D_{24} total scores following acute ECT (atypical = 23.6 [8.7], typical = 24.9 [10.1], p < .0001 [paired t test] for both groups). With regard to the primary treatment outcome, 80.6% of the atypical group remitted compared to 67.1% of those with typical depression (χ^2, unadjusted p value = .0957). After adjustment for age, psychosis status, baseline HAM-D_{24} total score, gender, and site, the difference in remission proportions between the groups became significant (multivariable logistic regression, p = .0357) with remission proportions significantly higher for the atypical group. The odds of remission were almost 3 times higher for the atypical compared to the typical group (adjusted OR = 2.6; 95% CI = 1.1 to 6.2). After adjustment for covariables, the mean reduction from baseline in HAM-D_{24} total score for the atypical group was 26.5 (95% CI = 23.7 to 29.2) compared to a mean reduction of 24.7 (95% CI = 23.9 to 25.4) for the typical group (GLM least squares mean difference = 1.82, 95% CI = –1.0 to 4.7, p = .2098).

DISCUSSION

This prospective study, in contrast to earlier studies,[1,2] found acute bilateral ECT to be an effective treatment for patients with atypical depression. Patients with typical or atypical depression responded to acute ECT treatment, and a majority showed a remission of depressive symptoms with the odds of remitting being greater in the atypical group, despite the fact that the atypical group had a higher likelihood of being treatment resistant at baseline. This finding echoes recent pharmacotherapy research showing that patients with atypical depression have a response rate similar to that of patients with typical depression when being treated with antidepressants[29] and contrasts with earlier reports[30,31] that indicated a preferential response to monoamine oxidase inhibitors (MAOIs) as opposed to tricyclic antidepressants in outpatients with atypical depression.

The finding that patients with atypical depression were mainly female, as well as younger at onset of their first mood episode relative to those without atypical features, is consistent with previous literature (e.g., Posternak et al.[32]). For example, in the National Comorbidity Survey,[33] of the 304 patients identified with atypical depression, approximately 70% were female, relative to 60% of the typical depression group (N = 532) who were female.[34] Moreover, in the National Comorbidity Survey study, patients with atypical depression, compared to those with typical depression, were found to be younger and to have an earlier age at illness onset. On the basis of the younger age and earlier age at onset, in addition to meeting DSM-IV criteria for atypical features, the categorization of atypicality in this investigation is considered to be valid. For instance, Stewart et al.[35] suggested adding criteria regarding age at onset and chronicity within the DSM framework in order to increase the homogeneity of the DSM diagnosis of atypical depression.[36]

Although in our study the typical group had more patients with psychotic features, the presence of psychosis was also found in the atypical group (13.9%). This is one of the first reports of atypical depressed patients with psychotic features. Psychosis has been associated with higher remission rates in depressed patients receiving ECT.[37] It is of interest to note that the higher response and remission rates in those with psychosis occurred in both those with and without atypical features. Furthermore, the fact that atypical patients benefited from ECT equal to or more than those with typical depression cannot be explained by the presence or absence of psychosis in either group.

Regarding depression severity, the group with typical depression was found to have higher depression severity at baseline as assessed with the HAM-D_{24}; however, this finding is most likely attributable to the depression measure used. Of the 24-items, none measure atypical symptoms; thus, this may not be an accurate finding. Of note, the magnitude of the difference in HAM-D_{24} mean scores between the groups was small (mean 2.5), suggesting that, while statistically significant, the difference may not be clinically important. The lack of a significant baseline difference between the groups in mean IDS-SR_{30} total scores, which includes atypical items, also suggests no meaningful difference in baseline severity.

Our observation that both the atypical and the typical groups significantly improved following acute ECT with the atypical group remitting at a higher rate challenges the utility of the concept that depression with "atypical features" has treatment selection relevance, a position also put forth by Parker and colleagues.[38] Further support for the notion that patients with atypical depression may benefit from other acute therapies aside from MAOIs was suggested by Jarrett et al.,[39] who showed cognitive behavior therapy to be equally as effective as phenelzine sulfate. The combined findings of this investigation and those of Jarrett et al.[39] suggest that alternative acute treatments, in addition to pharmacotherapy, for atypical depression are viable. Thus, in designing possible treatment algorithms, pharmacotherapy or psychotherapy may be first-line treatments for mild to moderate atypical depression, but ECT may be warranted in those cases of higher severity, especially with the presence of suicidality[19] or psychosis. Nonetheless, the long-term significance of response and remission of depression with atypical features in the acute phase will require confirmation in the continuation phase of this study.

There are several limitations to this study. First, using the HAM-D_{24} as the primary outcome tool was limiting as it is biased away from atypical symptoms. Many items on the HAM-D_{24} measure neurovegetative depressive symptoms (e.g., insomnia, decreased appetite), and there are no items that account for reversed neurovegetative symptoms (e.g., hypersomnia, hyperphagia) or mood reactivity. However, this study also employed the IDS-SR_{30}, which provides for evaluation of a broad range of depressive symptoms including both melancholic and atypical clusters.[22] Furthermore, although the SCID-I was used to diagnose atypical features, the use of the Atypical Depression Diagnostic Scale,[5] a structured interview designed to diagnose atypical depression, would have added further confirmation of the atypical diagnosis. While structured interviews for diagnosing atypical depression exist, the criterion of mood reactivity does not always receive support.[38] For instance, in a study by Fava and others,[40] patients who received a DSM-IV diagnosis of melancholic depression were not excluded from receiving a diagnosis of atypical depression. Lastly, the small number of patients with atypical features in our sample further limits the certainty of the findings. However, based on the prior clinical practice of not recommending ECT for patients with atypical symptoms (i.e., West and Dally[2]), it was not unexpected to see a small percentage of atypical patients being referred for ECT.

In summary, ECT is an effective acute treatment for patients with atypical as well as typical depression, despite previous reports to the contrary. Therefore, ECT should be strongly considered in the treatment of patients with atypical depression, especially when other interventions fail. Further investigations of the relevance or lack of relevance of atypical features in predicting acute and longer-term response to ECT with larger samples is indicated.

Drug names: lithium (Eskalith, Lithobid, and others), nortriptyline (Pamelor and others), phenelzine sulfate (Nardil).

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