CME

Speed of Response and Remission in Major Depressive Disorder With Acute Electroconvulsive Therapy (ECT): A Consortium for Research in ECT (CORE) Report

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Background: Remission of illness in patients with major depressive disorder (MDD) is achieved in less than half of patients initially treated with medication. Electroconvulsive therapy (ECT) is another treatment option. We report the speed of response and remission rates in a cohort of depressed patients who received a course of acute-phase ECT in the initial phase of an ongoing multicenter randomized trial of continuation ECT versus pharmacotherapy.

Method: Patients with MDD according to DSM-IV criteria received bilateral ECT 3 times weekly. Prior to each treatment, a 24-item Hamilton Rating Scale for Depression (HAM-D-24) score was obtained by a clinical rater. Sustained response was defined as a ≥ 50% reduction in baseline HAM-D-24 score for at least 2 and all subsequent measurement occasions. Remission was defined as HAM-D-24 scores of ≤ 10 for at least the last 2 consecutive assessments. Data were collected from May 1997 through November 2000.

Results: Of the 253 patients who entered the study, 86% (N = 217) completed the acute course of ECT. Sustained response occurred in 79% of the sample, and remission occurred in 75% of the sample (N = 253); 34% (85/253) of patients achieved remission at or before ECT #6 (week 2), and 65% (164/253) achieved remission at or before ECT #10 (weeks 3–4). Over half (54%; 136/253) had an initial first response by ECT #3 (end of week 1).

Conclusion: ECT was associated with rapid response and remission in a high percentage of patients. ECT warrants early consideration in treatment algorithms for patients with MDD.

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Major depressive disorder (MDD) is a common, disabling, and typically recurrent or chronic psychiatric condition[1–3] accompanied by masked functional impairment,[4,5] high health care utilization,[1,6–8] suicide attempts,[9] and a worse prognosis for co-occurring general medical conditions.[10]

Early symptomatic remission is the aim of treatment.[5,11–15] For optimal treatment planning, clinicians, patients, and their families need to know the probability and time to onset of a clinically meaningful benefit, defined as either a sustained response (i.e., a clinically important reduction in the severity of baseline symptoms that persists) or remission (i.e., a symptom-free state).[16]

Prior to 1988, medications for MDD were limited to tricyclic antidepressants, monoamine oxidase inhibitors, and lithium. Newer agents have expanded treatment options and reduced the side effect burden.[17] Despite the availability of these better tolerated antidepressant medi-

cations, only about 50% of patients with MDD evidence a sustained response with any single antidepressant medicine, and only about one third attain full symptom remission in 8-week medication monotherapy trials.[18,19] The more chronic forms of depression may not respond to medication until after 8 to 10 weeks of treatment,[20,21] and for many of these patients, remission may not occur until some time during continuation-phase treatment.[22–24]

Psychosis accompanies one third of the depressed patients admitted to psychiatric inpatient services. For these patients, efficacy of antidepressant monotherapy drops precipitously, with less than 35% remitting with tricyclic antidepressants alone.[25–28] Typically, these patients require potent antipsychotic medications.

Electroconvulsive therapy (ECT) is a highly effective treatment for patients with severe or medication-resistant depression, including those with psychosis.[25–31] Modern ECT includes the routine use of oxygenation, anesthesia, brief pulse electrical stimulation, and continuous physiologic monitoring. These advancements have made ECT more effective and much safer than in the past and, therefore, justify a second look at its role in the treatment of patients with MDD.[29–31] The rates of response and remission in representative populations treated with ECT, however, are not well defined. In fact, only a few reports have focused on response and remission rates.[29,32–35]

This report evaluates the speed of response and remission in patients with severe MDD treated with ECT and addresses the following questions: When does the response begin? How often do those with an initial response attain a sustained response? When does remission occur? What is the time between the onset of response and the onset of remission?

METHOD

The data for these analyses are drawn from the Consortium for Research in ECT (CORE) trial "Continuation ECT Versus Pharmacotherapy," an ongoing, National Institute of Mental Health–funded, multicenter study of patients with psychotic or nonpsychotic MDD (single or recurrent type). The study consists of 2 phases. In the first phase, all patients receive a course of bilateral ECT (3 times per week). Those who remit and remain in remission for 1 week following discontinuation of acute-phase ECT are then randomized (phase 2) to 2 arms: continuation ECT or continuation pharmacotherapy (nortriptyline + lithium). They are followed for 6 additional months to evaluate relapse. Eligible patients are recruited from those referred for ECT at the 4 clinical sites (Minn., N.Y., S.C., and Tex.).

We report on results for 253 patients from the first phase (acute ECT) of the study for whom all data cleaning have been completed. These data were collected from May 1997 through November 2000. The protocols and consent processes were approved by the Institutional Review Boards at each center.

Subjects

Depressed patients between the ages of 18 and 85 referred to the 4 major medical centers for ECT were evaluated to participate in the study. Exclusion criteria were major neurologic or general medical illnesses that limited the use of ECT, nortriptyline, or lithium (the latter 2 treatments being part of the randomized continuation phase of this study). Patients who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[36] criteria for MDD on the basis of the Structured Clinical Interview (SCID-I)[37] obtained by a trained research associate or by the study psychiatrist were included in the study. A baseline 24-item Hamilton Rating Scale for Depression (HAM-D-24)[38,39] score of ≥ 21 assessed for the previous week was required for study entry.

Treatment

Bilateral ECT was delivered using a Thymatron DGx device (Somatics, LLC, Lake Bluff, Ill.). Antidepressant medications and mood stabilizers were tapered prior to initiating ECT. Seizure threshold was estimated at the first treatment by the dose titration method.[40] This method involves delivery of a series (usually 1–3) of successively higher stimulations until an adequate seizure is elicited.[40] An adequate seizure was defined as a motor seizure of at least 20 seconds' duration. Subsequent ECT treatments were conducted 3 times per week at 1.5 times the seizure threshold. Subconvulsive stimuli during the course were followed by stimuli at a 50% greater charge after an interval of > 20 seconds. ECT treatments were continued until the patient was asymptomatic (i.e., met remission criteria) or until a plateau in benefits had been reached, defined as no change (i.e., a change of less than 3 points in either direction) in HAM-D-24 total scores over 2 consecutive measurements. Remission was achieved when 2 consecutive HAM-D-24 total scores were < 10.

Outcome

The primary outcome measure, HAM-D-24 score, was obtained at baseline and between each ECT treatment by trained clinical raters. At specified timepoints (baseline and final for phase 1), independent ratings were obtained by 2 separate raters (study psychiatrist and continuous clinical rater) and the average of the ratings was used for analyses. Ratings were subjected to longitudinal quality control by videotaping and having an independent evaluator ensure close agreement (or provide feedback to achieve close agreement).

Response was defined as a > 50% reduction in baseline HAM-D-24 score. A first response was defined as the first time a > 50% reduction in baseline HAM-D-24 total score

Table 1. Demographic and Clinical Characteristics of the Total Sample of Patients With Major Depressive Disorder Receiving an Acute Course of Electroconvulsive Therapy (ECT)

Variable	Sample (N = 253)
Age, mean (SD), y	56.2 (16.2)
Range	19–85
Female, % (N)	66.4 (168)
Psychotic, % (N)	30.4 (77)
Ethnicity, % (N)	
White	90.1 (228)
African-American	6.7 (17)
Other	3.2 (8)
Age at illness onset, mean (SD), y	40.8 (19.7)
Range	6–83
No. of prior episodes, mean (SD)	2.5 (4.6)
Range	0–50
% (N)[a]	
0	27.4 (61)
1	26.9 (60)
2	16.1 (36)
≥ 3	29.6 (66)
Length of current episode, mean (SD), y	0.95 (1.9)
Range	0–16
No. of prior psychiatric hospitalizations, mean (SD)	2.4 (1.9)
Range	0–12
% (N)[b]	
0	12.6 (31)
1	25.9 (64)
2	23.1 (57)
≥ 3	38.5 (95)
No. of ECT sessions, mean (SD)	7.8 (3.3)
Range	2–20
Seizure threshold, mean (SD), % energy	24.8 (13.1)
Range	5–80

[a]N = 223 due to missing values.
[b]N = 247 due to missing values.

Table 2. Cumulative Proportion of Total Sample of Patients With Major Depressive Disorder (N = 253) Reaching First Response, Sustained Response, and Remission by Electroconvulsive Therapy (ECT) Session Number

	First Response		Sustained Response[a]		Remission[b]	
ECT Session #	%	N	%	N	%	N
1	12.6	32	6.3	16	0	
2	32.0	81	19.0	48	0.4	1
3	53.8	136	34.8	88	4.0	10
4	67.2	170	45.9	116	10.3	26
5	78.7	199	58.5	148	21.3	54
6	83.4	211	64.4	163	33.6	85
7	87.4	221	70.0	177	42.3	107
8	89.3	226	73.5	186	53.0	134
9	92.5	234	75.9	192	60.5	153
10	93.3	236	76.3	193	64.8	164
≥ 11[c]	94.1	238	79.1	200	74.7	189

[a]Sustained response is defined as a response (not necessarily a first response) that is sustained through exit; requires that at least 2 consecutive HAM-D scores meet the response criteria.
[b]Dropouts are considered nonremitters.
[c]Of the total sample, 5.9% (N = 15) never achieved a first response, 20.9% (N = 53) never achieved a sustained response, and 25.3% (N = 64) never achieved remission.

was obtained for each subject. Sustained response was defined as a response maintained on all subsequent measurements. Remission was defined as at least the last 2 consecutive HAM-D-24 total scores of < 10. Treatment "completers" were those who completed > 10 ECT treatments or who attained remission criteria prior to ECT #10.

Statistical Analyses/Quality Assurance

Standard descriptive analyses were used. Mean, median, range, and standard deviation for continuous variables and frequency distributions for categorical variables were used to describe the baseline demographic, clinical, and treatment characteristics. For some variables (e.g., number of ECT sessions required for response/remission), 10th and 90th percentile values were reported. Rates of response and remission were determined as frequencies in percentages (%). Speed of response was evaluated as the proportion of subjects who achieved response (first and sustained) and remission after each ECT treatment. For remission analyses using the full sample (N = 253), treatment noncompleters (dropouts) were considered nonremitters. For responder analyses, responder status for noncompleters was based on the last available HAM-D-24 score at study exit.

RESULTS

The demographic and clinical features of the sample are described in Table 1. The mean (SD) number of ECT sessions for the total sample was 7.8 (3.3), the median was 7.0, and the 10th and 90th percentiles were 2 and 12. Ninety-four percent (238/253) of the patients achieved a first response, 79.1% (200/253) achieved a sustained response, and 75% (189/253) attained remission (Table 2). Only 14% (36/253) withdrew from the study prematurely. Reasons for dropping out during the acute phase included patient withdrawal of consent for unspecified reasons (N = 8), adverse events (N = 20), and protocol violations (N = 8). The most common adverse events were confusion or memory problems (N = 10), intercurrent medical condition (N = 2), and other psychiatric illnesses (N = 2).

Among treatment completers (N = 217, excluding dropouts), 98.2% (213/217) achieved a first response, and 87.1% (189/217) attained remission. Among those with a first response (N = 238), 64.7% (154/238) sustained the first response, 84.0% (200/238) achieved a sustained response by study end (not necessarily following first response), and 79.4% (189/238) attained remission (Tables 2 and 3).

How Rapidly Did Response Occur?

First response occurred after ECT #1 in 12.6% (32/253) of patients (Table 2). Altogether, 53.8% (136/253) of the sample attained a first response by ECT #3 (within 1 week), and 83.4% (211/253) attained a first response

Table 3. Proportion of Patients With Major Depressive Disorder (N = 253) Achieving Sustained Response and Remission by Electroconvulsive Therapy (ECT) Session Number

	Onset of First Response		Sustained First Response[a]		Attained Remission[b]	
ECT Session #	%	N	%	N	%	N
1	12.6	32	50.0	16	78.1	25
2	19.4	49	65.3	32	81.6	40
3	21.7	55	67.3	37	85.5	47
4	13.4	34	70.6	24	91.2	31
5	11.5	29	82.8	24	82.8	24
6	4.7	12	50.0	6	75.0	9
7	4.0	10	60.0	6	50.0	5
8	2.0	5	80.0	4	80.0	4
9	3.2	8	62.5	5	50.0	4
10	0.8	2		0		0
≥ 11[c]	0.8	2		0		0

[a]Percentage of first responders who sustained the first response (based on Ns in first column); 60.9% of the total sample (154/253) sustained the first response.
[b]Percentage of first responders who eventually achieved remission (based on Ns in first column); 74.7% of the total sample (189/253) attained remission. Remission did not necessarily follow a sustained first response (remission may have followed a subsequent sustained response achieved later in the ECT course).
[c]5.9% (N = 15) of the total sample never achieved a first response.

by ECT #6 (within 2 weeks). A sustained response was achieved in 34.8% of patients at or before ECT #3 and in 64.4% at or before ECT #6. By the third week of treatment (ECT #9), a sustained response had been initiated in 75.9% of patients (Table 2).

How Rapidly Did Remission Occur?

Of the 253 patients (treating dropouts as nonremitters), 74.7% (189/253) attained remission (Table 2). Remitters received a mean (SD) of 7.4 (2.9) and median of 7.0 ECT sessions (10th and 90th percentiles: 4 and 11). For the total sample, 10% (26/253) were declared remitters at or before ECT #4, 34% (85/253) at or before ECT #6 (treatment week 2), and 65% (164/253) at or before ECT #10 (treatment weeks 3–4). Among remitters (N = 189), only 5% (10/189) required more than 12 ECT sessions (4 weeks). The largest increments in remission rates occurred between ECT #4 and #9 (weeks 2 to 3), with the proportion of remissions rising from 10% to 60% during this treatment interval.

How Often Was First Response Maintained?

Table 3 shows the outcomes of those with a first response after each ECT treatment. Among the 32 patients who had a first response after ECT #1, 50% (16/32) sustained the response through study end (i.e., they continued consistently in the response status throughout the entire course of ECT). Of this group of 32 first responders after ECT #1, 25 (78.1%) eventually achieved remission. To further illustrate, among those with first response at or before ECT #3 (N = 136), 62.5% (85/136) sustained the first response, and 82.4% (112/136) eventually remitted. Among the group who experienced their first response within the first 2 weeks of treatment (at or before ECT #6), 65.9% (139/211) sustained the response and 83.4% (176/211) eventually remitted.

What Was the Time Between First Response and Remission?

We assessed the time between first response and remission for those who achieved remission. Overall, approximately 4 additional ECT sessions were required between first response and remission. Those remitters who first responded after ECT #1 (N = 25) required, on average, 5 additional treatments, while those remitters who first responded after ECT #2 (N = 40) required 4 additional ECT sessions between first response and remission. If first response occurred after ECT #3, 4 additional ECT sessions were required before remission. The number of additional ECT sessions after first response among those who achieved remission was approximately constant (mean [SD] = 3.9 [0.9]) regardless of when first response occurred.

Did Early Symptom Change Predict Eventual Response or Remission?

If first response was attained at or before ECT #6, 83% (176/211) exited as remitters. If a patient was still in the study and had not shown a first response by ECT #6, #7, or #8, the probability of remitting at exit was 37% (13/35), 36% (8/22), and 25% (4/16), respectively.

To further investigate whether we could identify a threshold of symptom reduction after various numbers of ECT treatments that could predict in a clinically useful way whether to continue or discontinue ECT, we conducted a series of Receiver Operating Characteristic Curve analyses using various thresholds. In brief, no clinically useful thresholds could be identified through ECT #5. For the subgroups of patients who had not had a first response after ECT #6, we evaluated the utility of a > 30% reduction in baseline HAM-D-24 total score as a threshold to predict response by exit from ECT. Of the 42 patients without a first response by ECT #6, 19 had achieved a > 30% reduction in baseline HAM-D-24 score, while 23 had not achieved this threshold after ECT #6 (before ECT #7). Of those achieving this threshold, 16/19 ultimately responded, while 10/23 not achieving the threshold also ultimately responded, though 13 did not. Thus, failure to achieve the threshold is not an indication to stop ECT, but achieving the threshold is clinically useful as it recommends continuing ECT.

DISCUSSION

We observed high rates of remission in a large sample of patients with severe MDD treated with bilateral ECT. Remission occurred in 75% of the total sample (N = 253)

and in 87% of those who completed the course of ECT. The median time to first response (3 ECT sessions) was 1 week, and a mean of 4 ECT sessions (1.3 weeks) was needed to achieve a sustained antidepressant response. For remission, a mean of 8 ECT sessions was given (approximately 2.5 weeks).

There are limited studies reporting remission rates for ECT. In a study by Bailine and colleagues,[41] 47 of 48 patients receiving either bitemporal or bifrontal ECT achieved remission (defined as a HAM-D-17 score of less than 10); however, the speed of remission was not reported. Daly and colleagues[35] reported in their study that an average of 6 ECT sessions was needed to achieve initial response.

These findings of rapid response and the high likelihood of remission stand in sharp contrast to the symptomatic outcomes reported in pharmacotherapy trials in typically less severely ill outpatients with MDD. Usually, 50% to 60% of these patients achieve response, while only 35% to 45% achieve remission.[18,19] Additionally, only about two thirds of medication responses occur within 4 weeks of initiating treatment. For the more chronically depressed patients, the response to medication may not be seen for 8 to 10 weeks. Remission may not occur for weeks to months[23,24] following response.[42–45] Not only was the probability of symptomatic response and remission high, but the time to the onset of these benefits was remarkably quick with ECT (3–4 weeks). Further, many of these patients who received ECT had undergone several prior antidepressant medication trials.

Other reports also indicate that the response of patients with MDD to ECT is rapid. Segman et al.[33] reported that 47 patients with MDD treated with bilateral ECT had a > 60% reduction in HAM-D-21 score with a mean (SD) of 5.9 (3.1) ECT sessions in 13.7 (7.2) days. A mean (SD) of 24% (30%) of the total overall change that occurred over the full treatment course occurred after ECT #1, 61% (28%) occurred after 4 ECT sessions, and 92% (29%) occurred after 8 ECT sessions. Also, 15% of the responders required from 9 to 12 ECT sessions to attain remission. These authors concluded that ECT is a rapidly effective treatment for MDD with a shorter latency than that generally reported for antidepressant drugs.

Other studies describe the rapid effect of ECT in similar populations. In assessing the benefits of 2 additional ECT sessions after patients had exhibited resolution of depressive symptoms, Barton et al.,[46] treating 50 patients twice weekly, reported that 40% recovered with 2 to 4 ECT treatments, another 40% with 5 to 8 ECT treatments, and only 20% required 9 to 12 treatments. In another study of ECT administered 3 times weekly to patients with MDD, the change in HAM-D score was 6 times greater between the first and third ECT than over the rest of the course.[32] Examining the response rate of 66 depressed patients treated with unilateral ECT, Rich et al.[47] reported the greatest reduction in HAM-D scores after the first ECT session, with rapid relief during the first 4 ECT sessions, followed by marginal improvement thereafter.

The patients with psychotic depression in our sample (about 30%) had a more robust response than did nonpsychotic depressed patients.[48] This observation argues that patients with psychotic depression may warrant an earlier intervention with ECT in treatment algorithms than do nonpsychotic patients. We also assessed the role of age in the outcome with ECT and found that elderly patients had better rates of remission than did younger patients.[49]

Limitations of the present study include unblinded ratings, the use of historical comparison groups for pharmacotherapy trials, and questionable generalizability because of strict inclusion criteria and stringently defined treatment parameters. On the other hand, patients in this sample were similar to the patients usually referred for ECT at major institutions, except that they had to be able to take lithium and nortriptyline in case they were randomized to that arm in the second phase of the study. Although not blinded, the HAM-D ratings were videotaped, and scoring of the HAM-D-24 was monitored by independent blinded evaluators with periodic feedback. Further, the rapid symptom reduction was apparent even in the absence of a medication comparison group.

ECT is generally applied as the treatment of last resort, after patients have not responded adequately to multiple trials of medications. Given the rapid and robust remission rates in the present study, we suggest that ECT be considered earlier in the course of treatment than is usual in treatment algorithms. Despite the stigma associated with its use, a stigma that encourages patients to undergo one failed medication trial after another, it seems reasonable to offer ECT to seriously depressed patients after 1 to 2 adequate but failed medication trials.[50] This recommendation, of course, must take into account the associated cognitive side effects of ECT that occur in a significant proportion of ECT-treated patients.[51] Whether earlier use of ECT would result in the need for fewer ECT treatments and, therefore, be associated with lower likelihood of adverse effects is suggested by the greater efficacy in less treatment-resistant depressions.[52] Further, acute ECT, while highly and rapidly effective, must be followed by treatments that sustain the benefit. To date, the combination of lithium and nortriptyline looks promising.[53] Whether other treatments are also effective and whether continuation-phase ECT may also be of use is under study.

Drug names: lithium (Eskalith, Lithobid, and others), nortriptyline (Aventyl, Pamelor, and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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