ORIGINAL ARTICLE

A Prospective, Randomized, Double-blind Comparison of Bilateral and Right Unilateral Electroconvulsive Therapy at Different Stimulus Intensities

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Background: Controversy persists about the use of right unilateral (RUL) and bilateral (BL) electroconvulsive therapy (ECT). While RUL ECT results in less severe short-term and long-term cognitive effects, there is concern that it is less efficacious than BL ECT.

Methods: In a double-blind study, 80 depressed patients were randomized to RUL ECT, with electrical dosages 50%, 150%, or 500% above the seizure threshold, or BL ECT, with an electrical dosage 150% above the threshold. Depression severity and cognitive functioning were assessed before, during, immediately after, and 2 months after ECT. Compared with baseline, responders had at least a 60% reduction in symptom scores 1 week after ECT, and were monitored for relapse for 1 year.

Results: High-dosage RUL and BL ECT were equivalent in response rate (65%) and approximately twice as effective as low-dosage (35%) or moderate-dosage (30%) unilateral ECT. During the week after the randomized phase, BL ECT resulted in greater impairment than any dosage of unilateral ECT in several measures of anterograde and retrograde memory. Two months after ECT, retrograde amnestic deficits were greatest among patients treated with BL ECT. Thirty-three (53%) of the 62 patients who responded to ECT relapsed, without treatment group differences. The relapse rate was greater in patients who had not responded to adequate pharmacotherapy prior to ECT and who had more severe depressive symptoms after ECT.

Conclusion: Right unilateral ECT at high dosage is as effective as a robust form of BL ECT, but produces less severe and persistent cognitive effects.

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FOR DECADES there has been a controversy concerning the use of right unilateral (RUL) or bilateral (BL) electroconvulsive therapy (ECT) in major depression.[1] It has been established that RUL ECT causes less severe cognitive adverse effects than BL ECT.[2-6] However, despite 40 comparative trials, the relative efficacy of both RUL and BL ECT remains uncertain.[1,7-9] When efficacy differences have been found, they consistently favored BL ECT.[10-12] Most patients in the United States receive BL treatment. Farah and McCall[13] conducted a survey of US ECT practitioners and found that 52% initiated ECT with the BL placement. We recently conducted a survey of ECT directors at 59 facilities in the tristate New York metropolitan area (H.A.S. and J.P., unpublished data, January 1, 1997, to July 1, 1997). The mean percentage of patients receiving BL ECT was 79%.

Recently, it has been shown that the efficacy of RUL ECT is contingent on electrical dosage.[5,14-17] In a 4-group study randomizing patients to RUL and BL placement and to an electrical dosage just above (0%) or 150% above the initial seizure threshold, we found that higher-dosage RUL ECT was considerably more effective than low-dosage RUL ECT and produced less severe cognitive effects than either form of BL ECT.[5] Nonetheless, the higher-dosage RUL ECT did not match the efficacy of either type of BL ECT. This study contradicted the standard view that producing a generalized seizure of sufficient duration is necessary and sufficient for efficacy,[18-20] and raised questions about the breadth of the dose-response function for RUL ECT.[5]

See also pages 438 and 445

We report on a double-blind trial in which patients were randomized to either RUL ECT delivered at 50%, 150%, or 500% above the initial seizure threshold or to BL ECT at 150% above the threshold. We tested the hypothesis that markedly suprathreshold RUL ECT (500% above threshold) is more effective than lower-dosage

SUBJECTS AND METHODS

SUBJECTS

Patients were referred for ECT and participation in this protocol by mental health professionals in the New York metropolitan region and, in some cases, nationally. Using the Schedule for Affective Disorders and Schizophrenia,[21] administered by a senior research social worker (S.P.), and other diagnostic information, patients met the Research Diagnostic Criteria[22] for major depressive disorder. They had a pretreatment score of 18 or greater on the 24-item Hamilton Rating Scale for Depression (HRSD),[23] and provided written informed consent. Patients with a history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar illness, neurological illness or insult, alcohol or other drug abuse within the past year, ECT within the past 6 months, or severe medical illness were excluded. Three participants completed the protocol as outpatients. All others were inpatients at the New York State Psychiatric Institute, whose institutional review board approved the study.

Of 84 patients admitted to the protocol, 4 were considered dropouts because they received fewer than 5 treatments (withdrawal of consent [n = 2], need for psychotropic treatment [n = 1], and intercurrent illness [n = 1]). Except for lorazepam (up to 3 mg/d, as needed), psychotropic medications were discontinued at least 5 days before ECT (mean ± SD, 15.0 ± 7.3 days [maximum, 30 days]) until 1 week after the end of ECT. The mean ± SD dosage of lorazepam during ECT was 1.2 ± 1.0 mg/d and did not differ among the treatment groups. Thirteen patients did not receive lorazepam, and the mean ± SD dosage in the remaining 67 patients (1.4 ± 1.0 mg/d) also did not differ among the treatment groups. Seventy-four (93%) of the 80 patients were right-handed,[24] with no difference among the treatment groups.

ELECTROCONVULSIVE THERAPY

Patients were randomly assigned to the 4 treatment conditions, stratified by whether they had received an adequate antidepressant medication trial during the index episode.[25,26] The randomization used a permuted block procedure,[27] with equal distribution of the treatment conditions within each stratum. At the first treatment, the ECT psychiatrist opened a sealed envelope containing the treatment condition for the next patient in the stratum. Patients and all staff not involved in ECT administration were masked to the type and dosage of ECT.

Atropine (0.4 mg), methohexital sodium (0.75 mg/kg), and succinylcholine chloride (0.75 mg/kg) were the anesthetic medications. The standard bifrontotemporal[1] and the d'Elia[28] placements were used for BL and RUL ECT, respectively. Electroconvulsive therapy was administered 3 times per week with a customized MECTA SR1 device (MECTA Corp, Lake Oswego, Ore). Compared with the commercial device, the maximum train duration of the customized device was increased from 2 to 4 seconds and pulse frequency was extended from 40 through 90 Hz to 20 through 140 Hz. The seizure threshold was quantified at the first and last treatments using the empirical titration procedure.[29] At all other treatments, stimulus intensity was 50%, 150%, or 500% above the initial seizure threshold for the low-, moderate-, and high-dosage RUL groups, respectively, and 150% above the threshold in the high-dosage BL group. The frequency and train duration of brief pulses were the electrical parameters manipulated, keeping pulse width (1.5 milliseconds) and amplitude (0.8 A) constant. The BL group was classified as a high-dosage group since the efficacy of this treatment is established, and adverse effects are likely to increase at higher dosage without improving efficacy.[5] To be considered adequate, minimal seizure duration was 20 seconds of motor or 25 seconds of electroencephalographic manifestation.[1]

CLINICAL EVALUATIONS

A blinded clinical evaluation team (research psychiatrist [J.P.] and senior social worker [S.P.]) completed HRSD ratings 2 days before the first treatment, twice weekly during ECT, and within 1 or 2 days and 1 week after the ECT course. Interrater reliability coefficients for HRSD scores exceeded 0.98. The Clinical Global Improvement[30] scale was completed 1 week after ECT.

Patients were initial responders if they had a decrease of at least 60% in HRSD scores from pretreatment to 1 or 2 days after the final treatment and a maximum posttreatment score of 16. Final responders maintained this level of improvement 1 week after ECT, while free of psychotropic medication. At least 10 treatments were required before classification as a nonresponder, with this minimum lowered to 8 treatments for patients who had HRSD reductions of 20% or less. Patients were classified as initial remitters if they met the criteria for initial response and had an HRSD score of 10 or less 1 or 2 days after the final treatment. Final remitters met the criteria for final response and had HRSD scores of 10 or less 1 week after ECT, while free of psychotropic medication.

Nonresponders were offered an open course of high-dosage (150% above the retitrated threshold) BL ECT. Efficacy evaluations for this crossover phase followed the procedures used in the randomized phase. Patients who responded in either phase were evaluated until relapse, as defined elsewhere,[25] or for 1 year. Hamilton Rating Scale for Depression interviews were conducted every 2 weeks for the first 2 months after ECT and monthly thereafter. During the follow-up period, continuation/maintenance treatment was naturalistic. Strength (0-5 scale) and adequacy (categorical) of continuation treatments were rated using the Antidepressant Treatment History Form with respect to the type and dosage of treatment, as well as compliance.[25,26,31]

COGNITIVE EVALUATIONS

Acute neuropsychological effects were assessed at each treatment during the randomized phase by blinded, trained technicians. Before each treatment, patients memorized sets of words, geometric and nonsense shapes, and either neutral or emotionally expressive faces. After presentation of each set, immediate learning was tested.[2,5] After the seizure, recovery of orientation was assessed continuously for 90 minutes. Patients who failed to meet the orientation recovery criteria[2,32] were given scores of 100 minutes. Five minutes after the orientation criteria were met, retrograde memory was tested for the previously learned material. Twelve equivalent stimuli sets were available for each task.[2]

Continued on next page

Neurocognitive tests focusing on anterograde and retrograde memory were administered before ECT, the day after the sixth or seventh treatment, 2 to 7 days after the end of the randomized phase, and 2 months after completion of all ECT. The battery included the modified Mini-Mental State Examination (MMSE),[33] an expanded version (range, 0-57) of the original MMSE[34] with established reliability and validity.[35,36] Other tasks included complex figure copying and reproduction,[37,38] randomizing the Rey-Osterreith, Taylor, and Richie figures across testing occasions. Scores for copying and 20-minute delayed reproduction were examined. The Buschke Selective Reminding Test (SRT)[39,40] used 12 words and 10 trials. Free recall was assessed after a 2-hour delay and then the full SRT procedure was repeated. The dependent measures were total recall across the 10 trials at first administration, first trial delayed free recall, and total recall across the 10 trials at the second administration. Recognition memory for verbal and nonverbal material was assessed with paired-word and paired-face tasks.[5,41] The paired-word task involved presentation of 30 word pairs. After presentation, learning was assessed by presenting a target and 4 foils (including the paired word). The paired-face task involved presentation of 20 face pairs, followed by immediate recognition testing, using a target and 3 foils (including the paired face). After 4 hours, delayed recognition memory was assessed for both tasks. The complete Randt Memory Test was also administered,[42,43] using the immediate and delayed memory for verbal paired associates, story recall, and picture recognition subtests. The dependent measures were scores for immediate acquisition and 24-hour delayed recall.

Assessments of retrograde amnesia included a test of memory for famous events occurring between 1950 and 1990,[44] and the Columbia University Autobiographical Memory Interview (AMI).[6,32] Autobiographical Memory Interview retrograde amnesia scores were the percentage of factual items reported at retesting that were inconsistent with baseline reports, and the percentage of "don't remember" responses for factual items reported at baseline. Except for the famous event test and AMI, alternative versions of all cognitive tasks were used at each assessment. Patients also rated their subjective memory functioning with the Squire Subjective Memory Questionnaire.[45]

At the evaluations after the randomized phase, the primary dependent measures were delayed recall and reacquisition scores on the SRT (anterograde amnesia) and the 2 AMI retrograde amnesia scores. Since retrograde memory is the domain known to show persistent deficits after ECT,[4,6,32] analyses at the 2-month follow-up were restricted to scores on the retrograde famous events test and the AMI. The primary measures were selected because of their established sensitivity to ECT effects[3-6] and functional significance (ie, degree of anterograde and retrograde amnesia).

STATISTICAL ANALYSES

The results are expressed as mean ± SD. All statistical tests were 2-tailed, with a level of significance of $\alpha = .05$. The comparability of the 4 treatment groups in baseline demographic and clinical features and treatment parameters was tested with analyses of variance (ANOVAs) for continuous variables and χ^2 analyses for dichotomous variables. As an omnibus test of efficacy differences, a repeated-measures ANOVA, was conducted on HRSD scores, with the randomized ECT modality (4 levels) and medication resistance classification (2 levels) as between-subject factors, and time point (before ECT, after 6 treatments, immediately after treatment, and 1 week after treatment) as the repeated-measures factor. This was followed by analyses of covariance (ANCOVAs) on HRSD scores at the last 3 points, with baseline HRSD scores as the covariate. With all ANCOVAs, post hoc *t* tests of covariate-adjusted means were used to identify pairwise group differences. Log-linear analysis was used to compare groups in rates of response and remission (modality by medication resistance). Multiple regression analysis was used to determine whether dosage relative to threshold, or the absolute electrical dose administered, contributed to efficacy in the RUL ECT conditions. Percentage change from baseline in HRSD scores was predicted on the basis of treatment group assignment and absolute electrical dosage. Survival analyses, using both Kaplan-Meier and regression models, provided tests of treatment group differences in likelihood and speed of relapse. The regression model used the Weibull distribution, with medication resistance classification, HRSD scores 1 week after ECT, and strength of post-ECT continuation/maintenance treatment as covariates.

Similar methods were used to compare the treatment conditions in cognitive measures. For the acute measures of orientation recovery and retrograde memory, the scores for each patient were averaged across all treatments. We compared the treatment groups' scores using ANCOVAs, with age as the covariate. For measures of short-term and long-term cognitive effects, ANCOVAs were performed using the ECT modality as the between-subject factor and baseline performance as the covariate. Differences in cognitive performance among the ECT conditions at the 2-month follow-up examination were assessed using ANCOVAs to compare the groups that received a single course of RUL ECT, a single course of BL ECT, or crossover BL ECT. When significant differences were obtained, ANCOVAs were repeated comparing the groups that received only high-dosage RUL ECT, a single course of BL ECT, and crossover treatment.

RUL ECT and equal in efficacy to a robust form of BL ECT, while retaining advantages with respect to short-term and long-term cognitive adverse effects.

RESULTS

CHARACTERISTICS OF PATIENTS AND TREATMENT MEASURES

The treatment groups did not differ in demographic and clinical characteristics (**Table 1**) or in doses of anesthetic agents or seizure duration (**Table 2**) ($P>.10$ for each comparison). Replicating an established finding,[29,46,47] the initial seizure threshold was higher with BL than RUL ECT ($t_{78} = 2.84$, $P<.006$). Across the sample, the range of the initial seizure threshold was 14-fold (24-336 millicoulombs [mC]).

EFFICACY

The treatment groups differed in clinical outcome (**Figure 1**). The repeated-measures ANOVA on the serial HRSD scores yielded a main effect of time point

Table 1. Demographic and Clinical Characteristics of the Sample*

Baseline Characteristic	Unilateral ECT			High-Dosage Bilateral ECT (n = 20)
	Low-Dosage (n = 20)	Moderate-Dosage (n = 20)	High-Dosage (n = 20)	
Age, y	61.7 ± 14.7	57.9 ± 16.6	53.7 ± 16.5	55.0 ± 15.6
Female, No. (%)	12 (60)	12 (60)	14 (70)	13 (65)
Education, y	14.2 ± 3.7	14.9 ± 3.6	14.5 ± 3.6	14.7 ± 2.8
Verbal IQ	101.1 ± 13.0	101.9 ± 12.2	100.9 ± 14.9	105.4 ± 11.8
Family's socioeconomic status†	2.6 ± 1.2	2.3 ± 1.4	2.1 ± 1.0	2.2 ± 1.0
Depression, No. (%)				
Psychotic	8 (40)	7 (35)	8 (40)	6 (30)
Bipolar	6 (30)	6 (30)	6 (30)	7 (35)
Duration of current episode, wk‡	37.2 ± 33.5	45.7 ± 31.2	51.1 ± 38.4	42.1 ± 33.6
HRSD score before treatment	32.4 ± 7.9	29.6 ± 6.2	32.6 ± 7.8	29.2 ± 7.4
GAS score before treatment	33.6 ± 10.5	40.4 ± 9.6	38.5 ± 11.3	36.2 ± 11.2
History of suicide attempt, No. (%)	5 (25)	10 (50)	6 (30)	6 (30)
Suicidal ideation before treatment, No. (%)§	7 (35)	10 (50)	6 (30)	5 (25)
History of ECT, No. (%)	8 (40)	9 (45)	8 (40)	8 (40)
Medication resistance rating‖	2.7 ± 1.5	3.1 ± 1.2	2.9 ± 1.5	2.7 ± 1.3
Medication resistant, No. (%)‖	11 (55)	13 (65)	12 (60)	11 (55)
No. of medication trials during episode	4.8 ± 3.3	5.6 ± 2.8	6.0 ± 4.5	6.5 ± 7.8
No. of previous affective episodes¶	2.1 ± 2.0	3.4 ± 2.6	3.2 ± 2.8	4.1 ± 3.7
No. of previous psychiatric hospitalizations¶	2.3 ± 3.0	2.5 ± 2.0	2.0 ± 3.1	2.5 ± 3.3
Age at onset of affective disorder, y	47.2 ± 14.6	37.5 ± 19.9	33.3 ± 15.8	37.5 ± 20.6

*ECT indicates electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression; and GAS, Global Assessment Scale. Values are mean ± SD unless otherwise indicated.

†Values shown are scores on the Hollingshead 4-Factor Index, which uses a scale from 1 to 5 (1 indicates the highest socioeconomic status and 5 the lowest).

‡An upper limit of 104 weeks was used.

§Indicates a score of 3 or greater on the HRSD suicide item.

‖Values shown are ratings for the most potent antidepressant medication trial given during the index episode before ECT: a scale from 0 to 5 was used with the Antidepressant Treatment History Form. A score of 0 indicates that no antidepressant medication was administered and 5 indicates that an established antidepressant medication was given in a trial of sufficient dose and duration coupled with lithium augmentation. A score of 3 or greater was used to classify patients as medication resistant. For a trial to be considered adequate, the threshold for sufficient dosage had to correspond, for example, to a minimum of 200-mg/d imipramine equivalents for tricyclic antidepressants and 20-mg/d for fluoxetine. The threshold for sufficient duration was a minimum of 4 weeks at or above the threshold for sufficient dosage.

¶An upper limit of 10 was used.

Table 2. Electroconvulsive Therapy (ECT) Parameters*

Treatment Parameter	Unilateral ECT			High-Dosage Bilateral ECT (n = 20)
	Low-Dosage (n = 20)	Moderate-Dosage (n = 20)	High-Dosage (n = 20)	
Medications given per treatment				
Atropine, mg	0.42 ± 0.04	0.39 ± 0.09	0.43 ± 0.09	0.41 ± 0.04
Methohexital sodium, mg	57.9 ± 19.0	59.7 ± 13.1	56.1 ± 15.0	59.7 ± 15.9
Succinylcholine, mg	49.9 ± 20.8	59.5 ± 12.5	52.9 ± 20.4	58.4 ± 22.7
Initial seizure threshold, mC	88.2 ± 66.3	78.0 ± 32.0	73.2 ± 29.6	104.4 ± 35.9
Mean charge per session, mC	131.7 ± 104.2	172.8 ± 70.5	348.5 ± 136.5	244.3 ± 105.3
Mean charge in nontitration treatments, mC†	138.5 ± 110.6	195.3 ± 80.2	440.5 ± 179.5	277.2 ± 121.0
Duration of seizures, s				
Motor	44.9 ± 8.9	42.7 ± 8.0	46.3 ± 11.0	44.9 ± 7.7
Electroencephalographic	59.7 ± 12.12	55.0 ± 15.2	63.4 ± 17.7	59.1 ± 14.8

*mC indicates millicoulombs. Values are mean ± SD. Except for initial seizure threshold and mean charge in nontitration treatments, the values shown refer to the average per treatment over the entire ECT course.

†Represents the average charge per treatment, except for the first and last treatments, when the electrical dosage was titrated to the seizure threshold.

($F_{3,216} = 145.82$, $P<.001$) and interactions between treatment group and time point ($F_{9,216} = 2.20$, $P = .02$) and between medication resistance classification and time point ($F_{3,216} = 2.83$, $P = .04$). Follow-up ANCOVAs indicated that the treatment groups differed in HRSD scores at all time points after baseline (after sixth ECT: $F_{3,71} = 2.99$, $P = .04$; 1-2 days after ECT: $F_{3,71} = 3.20$, $P = .03$; 1 week after ECT: $F_{3,71} = 2.84$, $P = .04$). Post hoc comparisons indicated that the low- and moderate-dosage RUL ECT groups did not differ from each other at any point. Likewise, the high-dosage RUL and BL groups did not differ at any point. Using ANCOVA (with baseline HRSD scores as a covariate), we discovered that after the sixth treatment, the high-dosage RUL and BL groups had superior antidepressant response compared with the low- and moderate-dosage RUL groups ($F_{1,77} = 9.38$, $P = .003$). This difference was maintained immediately after the ECT course ($F_{1,77} = 10.65$, $P = .002$), and 1 week later ($F_{1,77} = 5.21$, $P = .03$).

The log-linear analysis conducted on the initial response rate produced a main effect of treatment group ($\chi^2_3 = 11.68$, $P = .009$) (**Table 3**). In the analysis of final response rate, there were main effects of both treatment group ($\chi^2_3 = 8.39$, $P = .04$) and the medication resistance classification ($\chi^2_1 = 4.99$, $P = .03$). The rates of initial and final response were identical in the high-dosage RUL and BL groups. Patients in these groups were almost twice as likely to be final responders as patients treated with low- or moderate-dosage RUL ECT ($\chi^2_1 = 8.46$, $P = .004$). Independent of treatment condition, patients classified as medication resistant (n = 46 [37%]) had a lower final response rate than patients for whom an adequate medication trial had not failed prior to ECT (n = 34 [65%]) ($\chi^2_1 = 6.03$; $P = .01$) (**Figure 2**). Immediately and 1 week after ECT, only 1 final responder had an HRSD score greater than 10. Consequently, analyses of response and remitter rates produced identical results (Table 3). For the 39 final responders, the mean ± SD HRSD scores immediately and 1 week after ECT were 4.6 ± 3.0 and 5.5 ± 3.4, respectively. Among final responders, there was no difference among the treatment groups in HRSD scores 1 week after ECT ($F_{3,35} = 0.09$, $P = .97$).

The ANOVA on Clinical Global Impressions improvement scores produced main effects of treatment group ($F_{3,72} = 2.82$, $P = .04$) and medication resistance ($F_{1,72} = 4.15$, $P = .045$). The high-dosage RUL and BL groups had greater improvement than the low- and moderate-dosage RUL groups ($F_{1,76} = 7.27$, $P = .009$).

The ANOVA on the number of treatments in the randomized phase did not produce an effect of treatment group ($F_{3,72} = 2.05$, $P = .11$). Despite the fact that the rate of early termination because of lack of efficacy was highest with low- and moderate-dosage RUL ECT, both high-dosage conditions averaged 1 fewer treatment than the less effective conditions (Table 3).

ABSOLUTE ELECTRICAL DOSE OR DOSE RELATIVE TO THRESHOLD

Among the 60 patients treated with RUL ECT, regression analyses indicated that improvement in HRSD scores was associated with dosage condition after the sixth treatment ($t_{57} = 2.58$, $P = .01$), immediately after treatment, ($t_{57} = 2.39$, $P = .02$), and 1 week later ($t_{57} = 1.78$, $P = .08$), and not with absolute electrical dose at any point. Thus, efficacy was influenced by dosage relative to seizure threshold, and not by absolute electrical dose.

CROSSOVER PHASE

Thirty-six (88%) of the 41 patients who did not respond in the randomized phase completed the crossover phase. They received a mean ± SD of 7.6 ± 2.1 high-dosage BL treatments. Their mean ± SD HRSD scores were 31.9 ± 7.1 before ECT, 24.8 ± 8.1 after the randomized phase, 8.3 ± 6.9 immediately after crossover treatment, and 11.3 ± 6.7 one week after the crossover phase; 28 (78%) and 25 (69%) were initial and final responders, respectively. Symptomatic improvement, response, and remission rates were equivalent regardless of the prior randomized assignment.

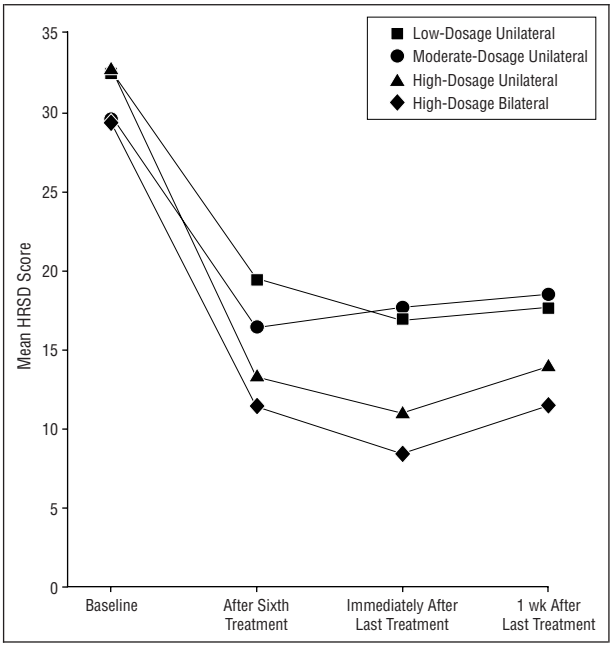

Figure 1. *Mean scores on the Hamilton Rating Scale for Depression (HRSD) at baseline, after 6 treatments, within 2 days of the last electroconvulsive therapy treatment, and 1 week after the last treatment in the randomized phase for the 4 groups (n = 20 for each group).*

RELAPSE

Sixty-two of the 64 patients who responded to randomized or crossover treatment (39 and 25 patients, respectively) were monitored for relapse. Their continuation/maintenance treatments are described in **Table 4**. In both the Kaplan-Meier and regression survival analyses, ECT modality was unrelated to relapse. This held regardless of whether patients who responded during the crossover phase were treated as a separate group or combined with patients who responded to high-dosage BL ECT in the randomized phase. Thirty-three (53%) of the 62 patients relapsed during the year; 31 (94%) of the relapses occurred during the first 6 months. The relapse rates were 62% (15/24) for patients who received crossover treatment, 54% (7/13) for the high-dosage BL ECT group, 33% (4/12) for the high-dosage RUL ECT group, and 54% (7/13) for patients treated with either low- or moderate-dosage RUL ECT. Relapse was almost twice as likely among medication-resistant patients (23 [68%] of 34) as among patients who had not received an adequate medication trial before ECT (10 [36%] of 28) (likelihood ratio, $\chi^2_1 = 4.46$; $P = .03$) (**Figure 3**). Higher HRSD scores at the end of ECT were also associated with a higher rate of relapse (likelihood ratio, $\chi^2_1 = 8.54$; $P = .004$). Strength of continuation/maintenance treatment was not related to relapse (likelihood ratio, $\chi^2_1 = 0.34$; $P = .56$). The relapse rate was 56% (25/45) for patients who received adequate continuation/maintenance treatment and 47% (8/17) for patients whose treatment was below the threshold for adequacy. However, the relapse rate was only 35% (6/17) for patients who received adequate treatment with the combination of a tricyclic antidepressant

Table 3. Initial and Final Clinical Responses*

Clinical Outcome Measure	Unilateral ECT			High-Dosage Bilateral ECT (n = 20)
	Low-Dosage (n = 20)	Moderate-Dosage (n = 20)	High-Dosage (n = 20)	
Response to treatment, No. (%)†				
Initial (1-2 d after ECT course)	7 (35)	9 (45)	16 (80)	16 (80)
Final (1 wk after ECT course)	7 (35)	6 (30)	13 (65)	13 (65)
Remitter to treatment, No. (%)‡				
Initial (1-2 d after ECT course)	7 (35)	8 (40)	15 (75)	16 (80)
Final (1 wk after ECT course)	7 (35)	6 (30)	12 (60)	13 (65)
Clinical Global Improvement (1 wk after ECT course), mean ± SD	2.5 ± 1.0	2.9 ± 1.1	1.9 ± 1.3	2.1 ± 1.1
No. of treatments, mean ± SD	9.9 ± 4.0	9.2 ± 1.8	8.3 ± 2.0	8.3 ± 2.2
Treatment terminated early, No. (%)§	7 (35)	5 (25)	3 (15)	2 (10)

*ECT indicates electroconvulsive therapy.

†Initial response was defined as at least a 60% reduction in Hamilton Rating Scale for Depression (HRSD) scores 1 to 2 days after the randomized ECT course relative to pre-ECT baseline and a post-ECT HRSD score of 16 or less. Final responders continued to meet these criteria 1 week following the randomized ECT course while free of psychotropic medication.

‡Initial remitters met the criteria for initial response and had an HRSD score of 10 or less 1 to 2 days after the randomized ECT course. Final remitters met the criteria for final response with an HRSD score of 10 or less 1 week after the randomized ECT course.

§Refers to patients for whom ECT was terminated after 8 treatments because of a markedly poor antidepressant response.

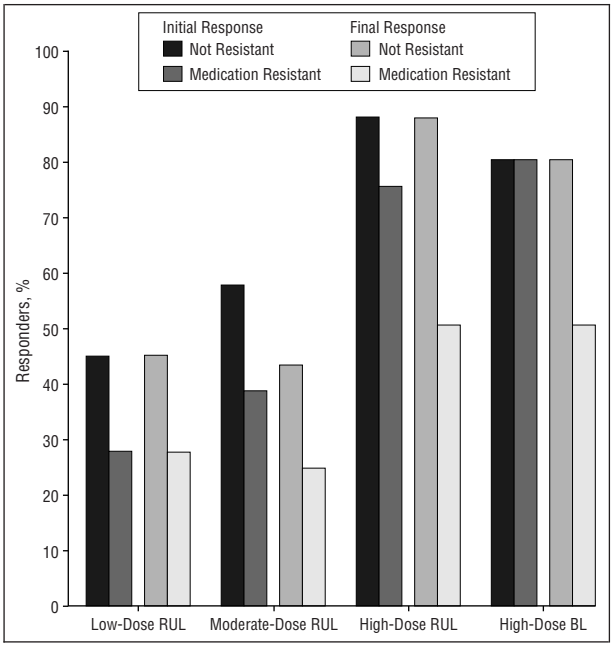

Figure 2. *Initial and final response rates for the 4 treatment groups (n = 20 for each group) as a function of whether patients did not respond to an adequate trial prior to either right unilateral (RUL) or bilateral (BL) electroconvulsive therapy (ECT) (medication resistant) or did not receive an adequate trial (not resistant).*

and lithium, compared with 68% (19/28) for adequate treatment with all other regimens (likelihood ratio, $\chi^2_1 = 5.33$; $P = .02$).

COGNITIVE ADVERSE EFFECTS

At the postictal assessments, cognition was more impaired after BL ECT compared with any other treatment (**Table 5**). The rate of prolonged disorientation was more than 6 times greater with BL ECT than with any other treatment. Bilateral ECT resulted in a significantly longer time to recovery of orientation than all other treatments, and high-dosage RUL ECT resulted in a longer recovery time than low- or moderate-dosage RUL ECT. Compared with each of the other 3 groups, BL ECT resulted in greater amnesia for the recall and recognition of words and greater amnesia than the low- and moderate-dosage RUL groups for the recognition of geometric shapes.

At the baseline assessment, before ECT, the treatment groups did not differ in any neuropsychological measure. After completion of the randomized phase, the BL ECT group had greater impairment than each of the other 3 groups on a variety of measures, including all the primary cognitive variables (**Table 6**). This pattern held for post-ECT scores on the MMSE; initial acquisition, delayed recall, and reacquisition on the SRT; immediate recognition in the anterograde paired-words task; and the Randt subtests of delayed paired-word recall and delayed picture recall. Across every test of the retention of new information over a delay (anterograde amnesia), the BL ECT group had the poorest absolute performance. For the measures of retrograde amnesia, memory of famous events and both scores on the AMI, the BL ECT group showed greater impairment than each of the other 3 groups. Bilateral and high-dosage RUL ECT could not be distinguished and produced greater impairment than low- and moderate-dosage RUL ECT in the post-ECT measures of delayed reproduction of the complex figure and delayed short story recall. Despite clear objective amnestic effects, the patient sample reported subjective improvement in memory after ECT (mean ± SD, 48.5% ± 81.2%) ($t_{71} = 5.1$, $P<.001$), as seen in a number of recent studies,[4,48,49] with no difference among the treatment groups.

Fifty-five patients participated in the 2-month follow-up. The ANCOVA comparing RUL ECT (n = 20), a single course of BL ECT (n = 10), or BL ECT as a crossover treatment (n = 25) produced differences among the groups in retrograde memory for famous events ($F_{2,51} = 4.26$; $P = .02$). Post hoc comparisons indicated that patients who had been treated only with RUL ECT had better scores

Table 4. Continuation and Maintenance Treatments Received During Follow-up*

Type of Treatment†	No. of Patients	No. of Adequate Trials‡	No. of Relapses
TCAs			
TCA alone	8	5	4
TCA and antipsychotic	2	1	0
TCA, antipsychotic, and valproic acid	1	0	1
TCA and lithium	12	12	3
TCA, lithium, and ECT	2	2	1
TCA, lithium, and SSRI	1	1	0
TCA, lithium, and valproic acid	1	1	1
TCA, lithium, and venlafaxine	1	1	1
TCA and SSRI	2	2	1
TCA, SSRI, and antipsychotic	1	1	1
TCA, SSRI, and stimulant	1	1	1
TCA and valproic acid	1	1	1
MAOIs			
MAOI alone	2	1	1
MAOI and lithium	1	0	1
MAOI, stimulant, and ECT	1	1	1
MAOI and trazodone	1	1	1
MAOI and valproic acid	1	0	1
SSRIs			
SSRI alone	4	4	1
SSRI and bupropion	1	1	1
Continuation ECT			
ECT alone	4	4	3
ECT and valproic acid	1	1	1
Other regimens			
Buspirone, stimulant, and clonidine	1	0	0
Lithium alone	3	0	2
Trazodone and antipsychotic	1	0	1
Trazodone and bupropion	1	0	0
Trazodone, bupropion, and lithium	1	1	1
Valproic acid alone	1	0	1
Venlafaxine alone	1	1	1
Venlafaxine and antipsychotic	1	1	0
Venlafaxine and valproic acid	1	1	1
Verapamil alone	1	0	0
No somatic treatment	1	0	0

*TCAs indicate tricyclic antidepressants; ECT, electroconvulsive therapy; SSRI, selective serotonin reuptake inhibitor; and MAOIs, monoamine oxidase inhibitors.

†Continuation or maintenance treatment prior to relapse or during most of the follow-up period in patients who did not relapse. Benzodiazepines, other sedatives/hypnotics, thyroid supplementation, and psychotherapy are not listed.

‡Antidepressant Treatment History Form criteria for rating the strength of treatment during episodes of major depression were applied to the continuation/maintenance treatments. Scores of 3 or higher indicated adequate treatement (see Table 1). No treatment was rated as adequate if there was evidence of noncompliance.

than patients treated with a single course of high-dosage BL ECT or patients who received crossover BL ECT. These differences were significant when restricting the RUL ECT group to those who had received high-dosage treatment (n = 10). For the AMI retrograde amnesia scores, the groups differed in the percentage of responses inconsistent with baseline ($F_{2,51} = 4.26$, $P = .02$) and the percentage of "don't remember" responses ($F_{2,51} = 6.06$, $P = .004$). Patients treated only with RUL ECT had superior scores compared with patients treated with BL ECT; these differences were maintained

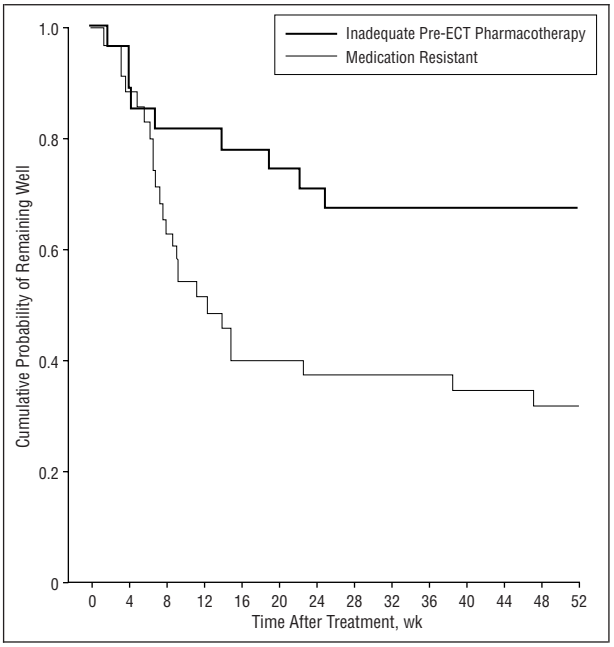

Figure 3. *Kaplan-Meier estimates of the proportion of patients who remained well after electroconvulsive therapy (ECT), for patients classified as medication resistant (n = 34), and for patients who did not have an adequate medication trial prior to ECT (n = 28).*

when restricting the RUL ECT group to those who received high-dosage treatment.

COMMENT

This study suggests that RUL ECT delivered with a high stimulus intensity relative to seizure threshold is equivalent in efficacy to a criterion standard form of BL ECT, yet retains important advantages with respect to cognitive adverse effects.

At all time points and for all efficacy measures, high-dosage RUL and BL ECT could not be distinguished in antidepressant effects. Both were considerably more effective than either low- or moderate-dosage RUL ECT. These findings confirm earlier reports that the efficacy of RUL ECT is influenced by electrical dosage,[5,14-17] and that fixed high-dosage RUL ECT can be as effective as BL ECT.[15] Specifically, this study indicates that, at sufficiently high stimulus intensity above the threshold, RUL matches BL ECT in efficacy.

In previous studies,[5,14] we found that RUL ECT administered just above the seizure threshold (0%) was remarkably ineffective (eg, 17% final response rate), while RUL ECT 150% above the threshold was more efficacious (44% final response rate). In this study, there was no difference in efficacy between the low (50% above the threshold) and moderate (150% above the threshold) RUL groups. This may indicate that a dosage increment between 50% and 150% relative to the threshold is insufficient to influence outcome.

Despite the use of high electrical intensity with high-dosage RUL ECT, this treatment produced less severe and persistent cognitive adverse effects than BL ECT. In the postictal period, recovery of orientation was prolonged with BL ECT, and BL treatment produced the greatest

Table 5. Effects of Electroconvulsive Therapy (ECT) on Recovery of Orientation and Memory Functions Assessed Immediately After Seizure Termination at Each Treatment*

Cognitive Measure	Unilateral ECT			High-Dosage Bilateral ECT (n = 18)	F	P
	Low-Dosage (n = 20)	Moderate-Dosage (n = 19)	High-Dosage (n = 20)			
Recovery of Orientation						
Prolonged disorientation†	0.7 ± 3.2[a]	0.0 ± 0.0[a]	1.9 ± 5.4[a]	13.0 ± 25.5[b]	5.41	.002
Time to recover orientation, min	18.7 ± 10.7[a]	17.1 ± 7.5[a]	30.7 ± 12.7[b]	45.5 ± 21.5[c]	17.85	<.001
Retrograde Memory‡						
Word recall	84.3 ± 15.4[a]	90.6 ± 9.3[b]	93.5 ± 6.0[b]	95.2 ± 9.2[b]	4.36	.007
Word recall and recognition	34.6 ± 21.9[a]	39.3 ± 11.7[a]	35.7 ± 14.2[a]	48.2 ± 14.4[b]	3.07	.03
Shape recognition	29.5 ± 16.6[a]	32.0 ± 15.2[a]	36.0 ± 20.6[a,b]	41.8 ± 11.9[b]	2.75	.048
Neutral face recognition	38.0 ± 20.2	37.3 ± 19.7	46.6 ± 22.1	41.4 ± 29.0	0.72	.54
Affective face recognition	25.9 ± 26.0	34.9 ± 18.6	29.5 ± 11.6	35.0 ± 16.4	0.96	.42

*Values are mean ± SD. F refers to the F value for the main effect of treatment group in the analysis of covariance; P, the level of significance of this effect. Groups with different superscripts differed significantly in post hoc comparisons of least-square adjusted means. For all variables, higher values indicate poorer cognitive performance.

†Prolonged disorientation occurred when patients did not meet the criteria for orientation recovery within 90 minutes of seizure termination. Values are the percentage of treatments in which patients manifested prolonged disorientation.

‡Values are the percentage of items not recalled or recognized during postictal assessment that were recalled or recognized prior to the treatment.

retrograde amnesia in selective measures. During the week after treatment, BL ECT resulted in more severe impairment than any of the RUL conditions in each of the primary cognitive measures. These effects were of clinical consequence. Capacity to recall words after a 2-hour delay on the SRT improved by 20% relative to baseline in patients treated with high-dosage RUL ECT, but decreased by 22% in patients treated with BL ECT. At this point, those in the BL group were 71% more likely than those in the high-dosage RUL group not to remember facts about their lives that they had reported at baseline. During the week after treatment, BL ECT also resulted in more severe cognitive adverse effects than any of the RUL treatment conditions in a variety of secondary measures assessing global cognitive status, anterograde learning and memory, and retrograde memory. At 2-month follow-up, BL ECT, either as a single course or as crossover treatment, resulted in greater retrograde amnesia than high-dosage RUL ECT. This long-term effect held for all primary measures. Thus, despite high stimulus intensity relative to seizure threshold, RUL ECT retained important cognitive advantages relative to BL ECT.

It may be questioned whether the choice of dosage for the BL ECT group biased the comparisons of cognitive effects. Previously, we reported no difference in degree of clinical improvement when BL ECT was administered just above (0%) or 150% above the threshold, although the response was slower with low-dosage BL ECT.[5,50] However, we did not detect differences between the 2 forms of BL ECT in short-term or long-term cognitive effects. Thus, it is unlikely that the differences in cognitive effects were caused by excessive doses of BL ECT. On the other hand, the use of a robust form of BL ECT should allay doubt that the equivalence with high-dosage RUL ECT in efficacy and relapse rate was caused by use of a handicapped form of BL ECT.

As in several recent studies (see Sackeim[51] for a review), the rate of relapse after response to ECT was high despite adequate continuation treatment. With the possible exception of the combination of a tricyclic antidepressant and lithium, strength or adequacy of continuation/maintenance treatment had no relationship to relapse, a finding previously reported.[25] Also in line with previous results,[5,25] the type or dosage of ECT was independent of relapse. In contrast, medication-resistant patients were less likely to respond to ECT regardless of the type of ECT used (Figure 2), and if they did respond, were more than twice as likely to relapse (Figure 3). These findings confirm earlier reports that medication resistance predicts both ECT short-term outcome and relapse.[25,26,31,52] Since resistance to antidepressant medications is the leading indication for the use of ECT,[1] research is needed on methods to improve ECT response and prevent relapse in this subgroup.

In previous studies, the differences in cognitive effects between RUL and BL ECT[2,4-6] and the impact of electrical dosage on the efficacy of RUL ECT[5,14] had large effect sizes. This study was powered to detect effects of this magnitude in the potential impact of high-dosage RUL and BL ECT on cognition and the potential impact of the dosage conditions within RUL ECT on efficacy. However, since each treatment group contained only 20 patients, the lack of difference in efficacy between high-dosage RUL and BL ECT might reflect insufficient power. This concern was mitigated by the finding that these conditions had identical initial and final response rates.

Only 55 patients (69%) were evaluated at the 2-month follow-up. This raises the possibility of selection bias caused by selective loss to follow-up of patients with more pronounced cognitive deficits. However, the patients who did and did not participate in the 2-month evaluation did not differ in cognitive measures after the randomized phase (data not shown).

This study used a customized ECT device with an extended output range. Given the marked variability in seizure threshold,[53,54] it will not be possible to treat some patients with RUL ECT at 6 times the threshold using standard devices in the United States (504-576 mC maxi-

Table 6. Short-term Effects of Electroconvulsive Therapy (ECT) on Cognitive Measures*

Short-term Cognitive Measure	Unilateral ECT: Low-Dosage (n = 20)	Unilateral ECT: Moderate-Dosage (n = 20)	Unilateral ECT: High-Dosage (n = 20)	High-Dosage Bilateral ECT (n = 19)	F	P
Modified Mini-Mental State Examination						
After 6 treatments	0.1 ± 11.3	−6.1 ± 14.7	−4.5 ± 11.5	−9.8 ± 12.3	1.71	.17
After ECT	3.4 ± 10.2[a]	−4.1 ± 10.8[a,b]	−1.2 ± 12.3[a]	−8.8 ± 11.1[b]	3.75	.01
Complex Figure						
After 7 treatments						
Copying	3.4 ± 31.8	−1.8 ± 15.8	−14.9 ± 25.0	−3.2 ± 23.5	1.13	.34
20-min delayed reproduction	3.3 ± 64.5[a]	7.4 ± 97.5[a]	−24.1 ± 67.9[a,b]	−38.6 ± 54.7[b]	2.86	.04
After ECT						
Copying	3.2 ± 33.9	4.7 ± 22.2	−2.6 ± 15.6	−2.4 ± 19.5	0.88	.46
20-min delayed reproduction	16.0 ± 53.8[a]	23.9 ± 71.9[a]	−17.5 ± 39.8[b]	−30.2 ± 46.4[b]	5.50	.002
Selective Reminding Test						
After 7 treatments						
Initial acquisition (total recall)	8.7 ± 33.5[a]	0.2 ± 31.8[a,b]	−8.2 ± 26.5[b,c]	−17.2 ± 18.5[c]	3.33	.02
2-h delayed free recall	18.5 ± 58.4[a]	−22.8 ± 24.0[b]	−26.3 ± 40.1[b]	−26.9 ± 38.8[b]	3.20	.03
Reacquisition (total recall)	4.3 ± 20.7[a]	2.6 ± 36.3[a,b]	−4.7 ± 46.1[b,c]	−14.0 ± 25.7[c]	4.12	.01
After ECT						
Initial acquisition (total recall)	9.6 ± 33.7[a]	14.6 ± 63.7[a]	6.2 ± 47.2[a]	−17.6 ± 22.5[b]	3.72	.02
2-h delayed free recall†	18.3 ± 58.1[a]	13.5 ± 27.9[a]	19.9 ± 58.8[a]	−22.1 ± 32.9[b]	3.05	.04
Reacquisition (total recall)†	4.1 ± 19.3[a]	15.0 ± 68.9[a]	7.7 ± 48.7[a]	−15.0 ± 24.8[b]	3.85	.01
Anterograde Paired Words						
After ECT						
Immediate recognition	29.0 ± 60.2[a]	22.2 ± 65.3[a]	6.4 ± 34.4[a]	−12.3 ± 59.2[b]	3.96	.01
4-h delayed recognition	14.7 ± 53.5[a]	3.5 ± 47.3[a]	−13.4 ± 25.7[a,b]	−22.8 ± 36.6[b]	3.05	.03
Anterograde Paired Faces						
After ECT						
Immediate recognition	6.3 ± 38.3	−7.3 ± 25.1	6.6 ± 56.0	−14.7 ± 24.6	1.15	.34
4-h delayed recognition	6.9 ± 42.8	−7.7 ± 27.0	2.2 ± 56.0	−20.9 ± 29.1	0.79	.50
Randt Anterograde Memory						
After ECT						
Immediate paired-word recall	14.3 ± 91.1	16.9 ± 77.3	11.3 ± 52.9	−8.0 ± 60.2	1.55	.21
24-h delayed paired-word recall	−11.2 ± 70.9[a]	24.2 ± 92.4[a]	−14.0 ± 63.2[a]	−59.4 ± 55.3[b]	6.42	.008
Immediate short story recall	17.3 ± 88.8	24.1 ± 81.4	−4.9 ± 76.8	19.7 ± 133.7	0.18	.91
24-h delayed short story recall	32.1 ± 89.5[a]	8.6 ± 80.7[a]	−29.7 ± 91.5[b]	−80.1 ± 42.6[b]	5.49	.002
Immediate picture recognition	0.7 ± 18.9	1.1 ± 6.8	1.1 ± 6.6	−3.7 ± 19.3	0.50	.68
24-h delayed picture recall	71.6 ± 174.7[a]	19.2 ± 132.8[a]	−23.9 ± 38.7[a]	−50.9 ± 79.6[b]	3.20	.03
Retrograde Famous Events						
After ECT	4.3 ± 24.6[a]	0.2 ± 10.2[a]	−2.2 ± 11.4[a]	−16.9 ± 20.3[b]	4.59	.006
Retrograde Autobiographical Memory Interview						
After ECT						
Percentage of factual responses inconsistent with baseline	−23.3 ± 8.4[a]	−24.6 ± 6.7[a]	−28.5 ± 8.0[a]	−40.4 ± 10.0[b]	13.91	.001
Percentage of "don't know" responses	−7.5 ± 7.6[a]	−5.4 ± 3.7[a]	−10.2 ± 8.8[a]	−17.4 ± 8.6[b]	11.42	.001
Squire Subjective Memory Questionnaire						
After ECT	24.6 ± 47.1	33.0 ± 41.0	52.7 ± 53.7	70.6 ± 89.7	0.65	.58

**Values are mean ± SD for the percentage change in cognitive scores from baseline to follow-up testing. F refers to the F value for the main effect of treatment group in the analysis of covariance; P, the significance level of this effect. Groups with different superscripts differed significantly in post hoc comparisons of least-square adjusted means. For all variables, negative values indicate a decrease in cognitive performance from baseline. Post-ECT assessments were conducted between 2 and 7 days after the randomized ECT course.*

mal output). In this study, 14 of 20 patients in the high-dosage RUL group were treated at the conventional maximum (576 mC). Two patients (1 BL and 1 high-dosage RUL) had substantial threshold increases during the ECT course, resulting in inadequate seizures and subsequent stimulation above conventional levels (768 and 840 mC). In a study of 267 patients treated at 3 sites with RUL ECT, we found that 10.9% had an initial threshold greater than 100 mC.[54] The findings of this study support consideration of higher electrical output for standard ECT devices.

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