ORIGINAL ARTICLE

Titrated Moderately Suprathreshold vs Fixed High-Dose Right Unilateral Electroconvulsive Therapy

Acute Antidepressant and Cognitive Effects

W. Vaughn McCall, MD, MS; David M. Reboussin, PhD; Richard D. Weiner, MD, PhD; Harold A. Sackeim, PhD

Background: The antidepressant and cognitive side effects of right unilateral (RUL) electroconvulsive therapy (ECT) are reported to depend on the magnitude of the electrical stimulus relative to the seizure threshold. The stimulus doses explored in previous clinical trials of RUL ECT have generally been limited to 1 to 2.5 times the convulsive threshold and the antidepressant efficacy has been low compared with bilateral (BL) ECT. The present study compares the antidepressant and cognitive side effects of 2 RUL dosing strategies: titrated moderately suprathreshold and fixed high dose.

Methods: Seventy-two adult patients with major depression were randomized to either titrated RUL ECT at 2.25 times initial seizure threshold (mean dose, 136 millicoulombes [mC]), or RUL ECT at a fixed dose of 403 mC. Primary outcome measures were antidepressant response and cognitive status 1 or 2 days after the course of ECT.

Results: The 2 treatment groups were comparable in demographic and clinical characteristics prior to ECT. Both groups received a mean of 5.7 sessions of RUL ECT. Patients receiving fixed-dose ECT were more likely to have an antidepressant response at the end of the protocol (n = 49 [67%]) compared with those receiving titrated dosing (n = 28 [39%]). Furthermore, the likelihood of both antidepressant response and cognitive deficits increased as stimulus dose increased relative to initial seizure threshold, up through 8 to 12 times the threshold.

Conclusions: The antidepressant efficacy and cognitive side effects of RUL ECT are dependent on the magnitude of the stimulus dose relative to the seizure threshold, and a dose-response relationship extends through at least 12 times the seizure threshold.

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From the Departments of Psychiatry and Behavioral Medicine (Dr McCall) and Public Health Sciences (Dr Reboussin), Wake Forest University School of Medicine, Winston-Salem, NC; the Department of Psychiatry, Duke University School of Medicine and the Department of Veterans Affairs Medical Center, Durham, NC (Dr Weiner); and the Departments of Psychiatry and Radiology, College of Physicians and Surgeons, Columbia University, and the Department of Biological Psychiatry, New York State Psychiatric Institute, New York (Dr Sackeim).

THE ANTIDEPRESSANT and cognitive side effects of right unilateral (RUL) electroconvulsive therapy (ECT) have been reported to depend on the magnitude of the electrical stimulus.[1-3] However, there have been few clinical trials that examine dose-response relationships of RUL ECT relative to a known seizure threshold.[1,2,4] These studies demonstrated poor efficacy for RUL ECT with barely suprathreshold stimuli. Efficacy was improved by increasing stimulus intensity to 2.5 times the seizure threshold, but under these conditions RUL did not match bilateral (BL) ECT 1 week after ECT.[1,2]

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These findings supported the recommendation of the 1990 American Psychiatric Association Task Force on ECT that the stimulus dose in ECT be "moderately suprathreshold,"[5] implying that ECT should be conducted with knowledge of the individual patient's seizure threshold. One survey suggested that most ECT practitioners in 1992 were either unaware of this recommendation or unconvinced of its authority, as only 39% routinely measured seizure threshold. The remaining practitioners either used a fixed stimulus dose for all patients, or chose a dose that was proportional to the patient's age.[6] We and others[7-10] have subsequently shown that neither the patient's age, nor any other combination of demographic variables, was a reliable means of estimating the seizure threshold. Given the discrepancy between the practice patterns of physicians using ECT and the recommendations of the American Psychiatric Association Task Force, we decided to compare the efficacy of 2 commonly used dosing strategies in RUL ECT: titrated moderately suprathreshold and fixed high dose. This pilot study, involving 19 patients aged 60 years or older, showed more rapid decrease in depression severity with fixed high dose, but this study was limited by lack of side effect measurements and lack of measurement of the initial seizure threshold in the fixed-dose group.[11] The present study was undertaken to replicate the pilot study, with the

PATIENTS AND METHODS

PATIENTS

The recruitment population consisted of all patients consenting to ECT at Wake Forest University School of Medicine/North Carolina Baptist Hospital, Winston-Salem, between September 1995 and February 1998. All patients met criteria for major depressive episode (MDE) according to the Structured Clinical Interview for the *DSM-III-R* as administered by one of us (W.V.M.).[12,13] All patients provided written informed consent and the protocol was approved by the local institutional review board.

Patients were 18 years or older and included either inpatients or outpatients. No patient had a prior history of schizophrenia or schizoaffective disorder, active substance abuse (either by history or by routine urine drug screen in the inpatients), mental retardation, or neurological illness. Mini-Mental State Examination (MMSE)[14] scores were 18 or higher, except for 1 patient in each treatment arm with MMSE scores of 10. No patient had received ECT within the prior 4 months. Patients had 21-item Hamilton Rating Scale for Depression (HRSD) scores of 20 or greater.[15] Patients deemed by their attending physician to require BL ECT from the onset of their ECT course by virtue of extreme severity of illness (ie, actively suicidal or refusing food) or those patients who could not cooperate with testing (ie, catatonic patients) were excluded. Handedness was measured with the Edinburgh Inventory,[16] and predominantly left-handed patients were excluded to avoid patients with right- or mixed-brain dominance for language.

CHARACTERIZATION OF CLINICAL AND DEMOGRAPHIC FEATURES

We recorded age, sex, race, marital status, duration of present MDE in weeks, age at onset of first MDE, total lifetime number of depressive episodes, and presence or absence of prior sessions of ECT. Total number of lifetime affective episodes was capped at 5, and the duration of index episodes was capped at 52 weeks.

The strength of antidepressant drug therapy during the index MDE up to 6 months prior to enrollment was determined for each patient using a dichotomized rating scale (adequate treatment vs inadequate treatment), modified from Prudic and colleagues.[17] Briefly, an adequate antidepressant trial was equivalent to 100 mg of amitriptyline for 4 weeks. Patients who received adequate antidepressant treatment at any time during the 6 months prior to enrollment were coded as having received an adequate trial even if patients were not receiving adequate treatment at time of enrollment.

MANAGEMENT OF PSYCHOTROPICS DURING ECT

Anticonvulsant medications and lithium were discontinued at least 48 hours prior to the first ECT session and throughout the course of treatment. Antidepressants were discontinued prior to the first ECT session with the exception of small doses of trazodone for sleep. Antipsychotic medications were discontinued prior to ECT unless the attending physician objected. Benzodiazepines were tapered off to the lowest possible dose prior to the first ECT session and continued to be tapered during the course. Benzodiazepine dosage at the first treatment never exceeded 4 mg/d of lorazepam or its equivalent and was withheld the morning of each ECT session. For those patients who were free of all psychotropics at their first ECT session, we recorded the number of days free of medications (maximum, 30 days).

ECT PROCEDURE

All patients received RUL ECT using the d'Elia position.[18] Anesthesia was provided with methohexital (1 mg/kg intravenously) and muscle relaxation was achieved with succinylcholine (1 mg/kg intravenously). Patients received positive-pressure ventilation at 20 breaths per minute from anesthetic administration until resumption of spontaneous respiration. A MECTA SR1 device delivered the constant current, bidirectional brief-pulse stimuli and recorded the ictal electroencephalograph (amplifier settings of 1 mV for full-scale deflection) with a single left-frontal lead-derived Fp1-M1.[19] The seizure threshold was estimated in all patients at the first ECT session with approximately 50% increments in charge between successive steps.[20] All patients were initially stimulated at 32 millicoulombs [mC]. Restimulation at 1 step higher followed after 20 seconds if no motor seizure occurred as documented by observation of the right foot (cuffed at the ankle prior to administration of the muscle relaxant). The seizure threshold was defined by the production of tonic and clonic convulsive activity lasting at least 25 seconds or by at least 30 seconds of electroencephalographic seizure activity. A maximum of 4 stimulations was allowed during the titration sequence. The seizure threshold was reached in all patients by the fourth stimulation.

Patients in the titrated moderately suprathreshold group received an ECT stimulus 2.25 times their respective initial seizure threshold at the second and subsequent treatment sessions. Patients in the fixed high-dose group received a stimulus of 403 mC at their second and subsequent treatment session, irrespective of their initial seizure threshold. An adequate seizure at the second through fifth treatment sessions was defined as a motor seizure 25 seconds or longer or an electroencephalographic seizure 30 seconds or longer. An adequate seizure at the sixth and

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addition of measurement of cognitive side effects and the initial seizure threshold in all patients.

RESULTS

DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS

The 72 patients did not significantly differ in age, sex, educational attainment, or marital status (**Table 1**). Thirty-six patients were randomized to titrated moderately suprathreshold dosing, and 36 were randomized to fixed high dosing. The 2 treatment groups did not differ significantly in the proportion of patients who had bipolar-type depression, duration of the present MDE, number of prior MDEs, age at onset of the first MDE, number of prior ECT courses, Edinburgh handedness score, baseline MMSE score, baseline HRSD score, proportion of those with adequate prior antidepressant treatment in the index MDE, proportion of those receiving benzodiaz-

subsequent treatments was defined as a motor seizure 20 seconds or longer or an electroencephalographic seizure 25 seconds or longer. An increase in stimulus dose was required to keep seizure duration above these parameters for 2 patients in the fixed-dose conditions and 3 patients in the titrated-dose condition.

RANDOMIZATION

Randomization occurred at the second ECT session. Patients were randomized either to titrated moderately suprathreshold or fixed high-dose RUL in a 50/50 proportion and were stratified on the basis of sex. The total number of treatments was determined by the patient's attending psychiatrist, who was blind to the randomization status. The attending psychiatrist reserved the right to remove from the protocol any patient whose symptoms (ie, deteriorating nutritional status) prevented ethical participation, and these patients went on to receive additional BL ECT outside the protocol.

DEPRESSION SEVERITY AND RESPONSE CRITERIA

Depression severity was measured with the 21-item HRSD by a trained rater masked to group randomization.[15,21,22] The HRSD was administered 1 to 3 days prior to the first ECT session, 24 hours after each midcourse ECT, and 1 to 2 days after the last ECT session. Administration of the HRSD followed the semistructured Structured Interview Guide for the HRSD.[23] Agreement (intraclass correlation) between the primary and secondary raters of the HRSD in 27 patients was greater than 0.95 while following this technique. Antidepressant response on an intent-to-treat basis was defined as a decrease of 60% or more in the HRSD scores and a final score of 12 or less after the last RUL ECT session.

GLOBAL COGNITIVE STATUS AND MEMORY

Global cognitive status (the MMSE) and all memory tests were measured 1 to 3 days prior and 1 to 2 days after the course of ECT by a rater masked to group randomization.[14] Global cognitive disturbance was defined as a post-ECT decrease in MMSE of 5 points or more.

The Duke Personal Memory Questionnaire is a sensitive test of retrograde autobiographical memory.[24,25] The test includes material such as place of residence, neighbors, family, New Year's Eve, present favorite television show, and best and worst experiences in the last year. At successive test sessions, questions are specifically asked in regard to responses provided at study entry. The derived amnesia index was the percentage of baseline items recalled at the follow-up session.

Anterograde amnesia for verbal memory function was assessed with the Rey Auditory-Verbal Learning Task (RAVLT). The RAVLT assesses immediate and delayed (20-minute) free recall of a list of 15 words, followed by a test of cued recognition of items in the list.[26] Different equivalent forms of this task were used at the pre-ECT and post-ECT test sessions.

Anterograde amnesia for figural memory function was tested with a complex figure reproduction task.[27] This test provides a measure of praxis (copying the figure), and measures of immediate and delayed (20-minute) free recall of newly learned figural information. Interrater reliability for scoring this test was high ($r = 0.99$; $P<.001$) (n = 35).

The patients' rating of subjective global memory was measured on a 6-point anchored scale, rated from "I have had continuous problems with memory" (6) to "I have had no memory problems at all" (1).[11] The duration of postictal disorientation was measured using the time elapsed after each ECT session from eye opening to reorientation of 4 out of 5 orientation items, including name, place, day of the week, age, and birthday, using the procedure of Sobin et al.[28]

STATISTICS

The means of continuous variables were compared with *t* tests or 1-way analysis of variance. Frequency distributions were compared using the χ^2 statistic. Odds ratios (ORs) for predicting antidepressant-responder status and global cognitive deficits were calculated from univariate logistic regression. Antidepressant response and global cognitive deficits were also evaluated with multivariate logistic regression. Antidepressant response to RUL ECT was measured in all patients, but cognitive side effects were measured only in the 63 patients who required no BL ECT. Significance was accepted at $\alpha = .05$. All tests were 2 sided.

Additional missing observations were problematic for some of the specific memory tests, largely because of patient refusal or inability to comply with the testing procedures. As a result, missing data are not missing at random, and a naive analysis of the complete data could produce biased estimates of treatment differences. Therefore, the sensitivity of our results to missing observations was assessed with both propensity score weighting and imputation methods.[29,30] The propensity score is the probability that values will be missing, which may be estimated as a function of observed covariates. For each cognitive outcome, we created 4 strata based on the quartiles of the estimated propensity score for that outcome and weighted the nonmissing value by the proportion of nonmissing data in each stratum. The weighted and unweighted analyses were compared to assess the impact of the missing data.

epines, antipsychotics, or trazodone, or proportion who were free of medication at the time of ECT (Table 1).

TREATMENT CHARACTERISTICS

Seven patients (10%) received their entire course of treatment on an outpatient basis, including 4 in the titrated group and 3 in the fixed-dose group (**Table 2**). Sixty-three (88%) of patients received all their ECT with RUL electrode placement. Nine (13%) were removed from the protocol after 3.3 ± 0.9 (mean ± SD) sessions of RUL ECT because of insufficient clinical response (mean ± SD HRSD score, 23.9 ± 5.9) before going on to receive additional BL ECT. The 2 randomized treatment groups were similar with respect to the number of inpatient days prior to initiation of ECT, initial seizure threshold, and the number of RUL ECT treatments (Table 2). The 2 groups differed in the average charge delivered at each RUL treatment, and the total number of RUL and BL ECT sessions received during treatment (Table 2).

Table 1. Comparison of Baseline Characteristics of the 2 Treatment Groups*

	Titrated Moderate Dose (n = 36)	Fixed High Dose (n = 36)	*t* or χ^2 Test	*df*	*P*
Age, y	62.1 ± 15.8	65.1 ± 13.0	−0.87	70	.39
Women, No. (%)	26 (72)	28 (78)	0.30	1	.59
Nonwhite, No. (%)	5 (14)	4 (11)	0.60	2	.60
Years of education	11.5 ± 3.6	12.1 ± 3.2	−0.71	70	.48
Married, No. (%)	15 (42)	19 (53)	0.18	3	.18
Duration of MDE, wk	18.0 ± 18.1	20.9 ± 17.5	−0.69	70	.49
No. of prior MDE	3.1 ± 1.8	3.5 ± 1.8	−0.96	70	.35
Age of onset at first MDE, y	40.9 ± 20.3	42.3 ± 17.5	−0.32	70	.75
Baseline test scores					
HRSD	28.5 ± 5.4	29.0 ± 4.4	−0.45	70	.65
MMSE	25.7 ± 4.1	26.7 ± 4.4	−0.96	70	.34
Edinburgh score	22.9 ± 2.6	22.1 ± 4.2	1.00	57†	.32
Prior adequate treatment, No. (%)‡	29 (81)	27 (75)	0.32	1	.57
Prior lifetime courses of ECT	0.86 ± 1.2	0.81 ± 1.1	0.21	70	.83
Bipolar disorder, No. (%)	3 (8)	6 (17)	0.29	1	.29
Patients given medications, No. (%)					
Benzodiazepines	21 (58)	21 (58)	0.00	1	>.99
Antipsychotics	7 (19)	4 (11)	0.33	1	.33
Trazodone	3 (8)	3 (8)	0.00	1	>.99
No psychotropics	15 (42)	12 (33)	0.47	1	.47

*MDE indicates major depressive episodes; HRSD, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Examination; and ECT, electroconvulsive therapy. Values are mean ± SD unless otherwise indicated.
†Adjusted for unequal variances.
‡Equivalent to 100 mg/d of amitriptyline for 4 weeks or longer.

Table 2. Treatment Characteristics*

	Titrated Moderate Dose (n = 36)	Fixed High Dose (n = 36)	*t* or χ^2 Test	*df*	*P*
Latency to ECT, d	5.9 ± 3.3	5.8 ± 3.5	0.00	63	.86
Seizure threshold, mC	60.4 ± 28.7	63.6 ± 27.7	−0.47	70	.64
Proportion requiring BL ECT, No. (%)	6 (17)	3 (8)	1.86	1	.29
No. of RUL ECT sessions	5.7 ± 1.6	5.6 ± 1.6	0.22	70	.83
Total ECT (RUL and BL) sessions	7.4 ± 2.8	5.9 ± 1.9	2.79	62†	.01
Average charge per RUL ECT, mC‡	135.9 ± 65.1	339.0 ± 41.6	−15.78	60†	>.001
Total charge for all RUL ECT, mC	784.1 ± 436.7	1952.6 ± 726.0	−8.28	57†	>.001

*ECT indicates electroconvulsive therapy; mC, millicoulomb; BL, bilateral; and RUL, right unilateral. Values are mean ± SD unless otherwise indicated.
†Values are adjusted for unequal variances.
‡Includes the first treatment.

ANTIDEPRESSANT RESPONSE

The overall intent-to-treat antidepressant response rate for RUL ECT was 53% (n = 38). The rate of response was significantly greater in the patients randomized to the fixed high-dose regimen (n = 49 [67%]) compared with those randomized to the titrated moderately suprathreshold regimen (n = 28 [39%]) ($\chi^2_1 = 5.6$; $P = .02$). This corresponds to an antidepressant OR of 3.14 (95% confidence interval (CI), 1.20-8.17) for the fixed high-dose regimen compared with the titrated moderately suprathreshold regimen. Furthermore, a significant dose-response relationship was evident between antidepressant response and the stimulus dose relative to the seizure threshold (SDRST), with the SDRST defined as level 1 (2.25 × threshold), level 2 (3.15-5.04 × threshold), or level 3 (8.40-12.60 × threshold) (**Table 3**). These levels were defined to produce dosing groups of nearly equal size. This model explained 11% of the variance in antidepressant response.

The SDRST was the most significant predictor of antidepressant response in logistic regression when considering the following candidate predictor variables: age, sex, SDRST, absolute stimulus intensity at the second treatment in millicoulombs, and the seizure threshold in millicoulombs. When SDRST was in any of the models, then no other candidate predictor variable was significant. Consideration of the HRSD as a continuous variable showed that the final score in protocol was marginally lower for the fixed-dose group (mean ± SD, 10.8 ± 7.1) than the titrated group (mean ± SD, 14.1 ± 9.6) ($t_{70} = 1.71$; $P = .09$), and a repeated analysis with baseline HRSD scores as a covariate (using analysis of covariance) did not materially change the results. The mean ± SD final HRSD score for responders was 6.1 ± 3.1, compared with 19.5 ± 6.9 for nonresponders.

Table 3. Antidepressant Response and Global Cognitive Disturbance by Electrical Dose Expressed as a Multiple of the Seizure Threshold*

	Antidepressant Response, OR (95% CI)†	Global Cognitive Disturbance, OR (95% CI)‡
2.25 × threshold	1.00§	1.00§
3.15-5.04 × threshold	1.77 (0.55-5.66)‖	3.50 (0.51-23.7)‖
8.40-12.60 × threshold	5.89 (1.62-21.4)¶	8.91 (1.60-49.7)¶

*OR indicates odds ratio; CI, confidence interval.
†Mantel-Haenszel test for trend: $\chi^2_1 = 7.71$; P<.01.
‡Mantel-Haenszel test for trend: $\chi^2_1 = 7.41$; P<.01.
§For antidepressant response, n = 36; for global cognitive disturbance, n = 30.
‖For antidepressant response, n = 17; for global cognitive disturbance, n = 15.
¶For antidepressant response, n = 19; for global cognitive disturbance, n = 18.

GLOBAL COGNITIVE DISTURBANCE

The overall rate of global cognitive disturbance (post-ECT decrease in MMSE ≥5) after RUL ECT was 19%. The rate of global cognitive disturbance was significantly greater in the fixed-dose group (n = 22 [30%]) compared with the titrated group (5 [7%]) ($\chi^2_1 = 5.7$; $P = .02$, corresponding to OR, 6.09; 95% CI, 1.21-30.88). Furthermore, a significant dose-response relationship was evident between global cognitive disturbance and SDRST (Table 3). This model explained 11% of the variance in global cognitive disturbance.

The SDRST was the most significant predictor of global cognitive disturbance in logistic regression when considering the following candidate predictor variables: age, sex, SDRST, absolute stimulus intensity at the second treatment in millicoulombs, and the seizure threshold in millicoulombs. The SDRST was the only significant predictor variable in any model. Consideration of the MMSE as a continuous variable again revealed significant differences between the titrated and fixed-dose groups, with greater decrement in the fixed-dose group (**Table 4**). Compared with the titrated-dose group, the fixed-dose group experienced a greater delay in reorientation when comparing the change in reorientation time from the first treatment to the second treatment (Table 4). Consideration of the delay in reorientation relative to 3 levels of relative stimulus dose again revealed significant differences (**Table 5**). Covariates did not significantly change group differences.

MEMORY

The fixed-dose group recalled a smaller percentage of autobiographical items after ECT compared with the titrated dose group (Table 4). Consideration of the change in autobiographical memory relative to 3 levels of relative stimulus dose again revealed significant differences (Table 5). Covariates did not significantly change group differences.

There were no significant group differences between the titrated- and fixed-dose groups in their change in any RAVLT, Rey Figure, or subjective memory score from pre- to post-ECT (Table 4). However, missing observations limited statistical power. Addressing the missing data through propensity scores did not produce statistical differences between the groups, but imputation methods revealed significant differences for immediate recall and delayed-cued recognition of the RAVLT and for immediate and delayed recall for the Rey Figure. Covariates did not significantly change group differences.

COMMENT

The principal finding of this study is that fixed high-dose and moderately suprathreshold dosing strategies do not have equivalent efficacy in the treatment of MDE with RUL ECT. Fixed high-dose RUL ECT produced a higher antidepressant response rate, and this was consistent with the results of our pilot study.[11] The superior efficacy of the fixed high-dose strategy was best explained by its mathematical association with a higher SDRST. Furthermore, a dose-response relationship was established between the SDRST and antidepressant response observed through a charge dose 8 to 12 times the seizure threshold. Enthusiasm for high SDRST as a means to improve efficacy needs to be tempered by the additional finding that cognitive disturbance also shows a dose-response relationship with the SDRST. Indeed, although there are differences in the scaling of antidepressant response and global cognitive disturbance, it seems that global cognitive disturbance follows a steeper dose-response trajectory than does antidepressant efficacy (Table 3).

Specific tests of memory further differentiated the 2 treatment groups. The fixed-dose group had greater loss of autobiographical memory and took longer to reorient after ECT. Our anterograde tests of verbal and figural memory did not reveal significant group differences, but the power for these comparisons was limited by those patients who were unable to cooperate with these intensive tests. The impact of missing data in this experiment on inference regarding cognitive function might have been substantial, since a reason for withdrawal from the protocol with consequent missing cognitive testing was evidence of severe cognitive impairment. The propensity score adjustment assesses this impact quantitatively, and the consistency of our results with and without this adjustment should provide confidence in their robustness. The lack of a group difference in subjective memory was not unexpected, since we and others[1,11,31] have shown that changes in subjective memory do not mirror the changes seen in objective testing, and subjective memory may actually improve after ECT.

The difference in antidepressant efficacy for the 2 groups had practical implications for the subjects. The titrated moderately suprathreshold patients received an average of 1.5 additional BL ECT sessions, thus increasing the duration of their ECT course by 3.5 days.

Our findings are strengthened by their consistency with the reports from Columbia University, New York, NY, despite important differences in our treatment settings and dosing methods.[1,2] The Columbia studies were conducted in a state-funded institution with minimal constraints on patients' length of stay, and the par-

Table 4. Group Differences in Cognition*

	Titrated Moderate Dose (n = 30)	Fixed High Dose (n = 32)	Between-Group Comparisons		
			t Test	*df*	*P*
Percentage of autobiographical recall	66.1 ± 17.5	53.5 ± 18.3	−2.65	56	.01
MMSE					
Pre-ECT	25.7 ± 4.0	26.7 ± 4.4	2.46	60	.02
Post-ECT	25.0 ± 4.1	23.4 ± 5.2			
Time to reorientation					
First ECT	13.1 ± 14.2	9.7 ± 9.7	−3.16	65	.002
Second ECT	14.0 ± 11.7	22.4 ± 16.2			
RAVLT immediate recall					
Pre-ECT	8.3 ± 3.7	8.6 ± 2.8	1.84	53	.07
Post-ECT	6.7 ± 2.6	6.1 ± 2.1			
RAVLT delayed recall					
Pre-ECT	5.3 ± 4.3	5.8 ± 3.1	0.95	53	.35
Post-ECT	2.4 ± 3.3	2.4 ± 1.7			
RAVLT delayed recognition					
Pre-ECT	30.9 ± 19.5	32.6 ± 17.7	0.74	51	.47
Post-ECT	18.4 ± 14.4	18.4 ± 11.7			
Rey Figure copy					
Pre-ECT	21.3 ± 8.6	23.2 ± 7.7	0.55	52	.58
Post-ECT	20.2 ± 8.9	20.9 ± 8.6			
Rey Figure immediate recall					
Pre-ECT	8.0 ± 5.5	10.0 ± 7.6	1.00	50	.32
Post-ECT	7.3 ± 5.8	6.4 ± 4.7			
Rey Figure delayed recall					
Pre-ECT	8.0 ± 5.9	9.7 ± 7.3	1.56	50	.13
Post-ECT	6.9 ± 5.8	5.1 ± 4.0			
Subjective memory function					
Pre-ECT	4.2 ± 1.4	4.1 ± 1.5	0.07	58	.95
Post-ECT	3.6 ± 1.5	3.7 ± 1.6			

**MMSE indicates Mini-Mental State Examination; ECT indicates electroconvulsive therapy; RAVLT, Rey Auditory-Verbal Learning Task. Values are mean ± SD unless otherwise indicated.*

ticipants could be withdrawn from psychotropic medications for a 2-week period prior to ECT. In contrast, our research was carried out under moderate managed-care pressure, the inpatients in our study began ECT within 6 days after admission, and most of them were still taking psychotropic medication at the time of the first session of ECT. Our dosing strategies also differed. The Columbia group calculated dose as a set percentage of their initial seizure threshold. The present study included a fixed-dose arm in patients who had undergone initial seizure threshold determination, allowing post hoc examination of the relationship between clinical response and the SDRST. Although this method is novel for ECT research, it is entirely analogous to the fixed-dosing studies used to determine the relationship between antidepressant response and the naturally occurring variation in serum levels of tricyclic antidepressants.[32,33]

Despite methodologic differences, the conclusions of the 2 research sites are remarkably similar, suggesting that the findings may be generalized from a highly structured research setting to a more typical clinical setting. While confirming some of the key findings of Columbia University, our results further extend the findings by demonstrating that the dose-response relationships in RUL ECT go beyond 2.5-times threshold into the 8- to 12-times threshold range.

The findings of this study are limited to right-handed patients with MDE who have no more than mild cognitive compromise. Furthermore, the conclusions apply only to the immediate posttreatment effects of RUL ECT, and did not examine patients with the most severe forms of illness referred directly for BL ECT. Further investigation should include multiple RUL stimulus dose levels as well as a BL comparison with a longer-term follow-up.

Table 5. Reorientation Time and Autobiographical Memory After Electroconvulsive Therapy (ECT) by Electrical Dose Expressed as a Multiple of the Seizure Threshold*

	Reorientation Time (in Minutes) at Second and Third ECT†	Autobiographical Memory‡§
2.25 × threshold	14.0 ± 11.7	66.1 ± 17.5
3.15-5.04 × threshold	17.6 ± 14.8	56.3 ± 22.3
8.40-12.60 × threshold	26.7 ± 16.5	50.4 ± 12.4

**Values are mean ± SD.*
†$F_{1,66}$ = 9.55; P<.005, by analysis of variance.
‡Percentage of items remembered.
§$F_{1,56}$ = 7.86; P<.001, by analysis of variance. The mean number of items described prior to ECT was 63.3 ± 25.4.

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Corresponding author: W. Vaughn McCall, MD, MS, Department of Psychiatry, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157 (e-mail: vmccall@wfubmc.edu).

REFERENCES

1. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med*. 1993;328:839-846.
2. Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S. Effects of electrode placement on the efficacy of titrated, low-dose ECT. *Am J Psychiatry*. 1987;144:1449-1455.
3. Abrams R, Swart CM, Veda C. Antidepressant effects of high-dose right unilateral electroconvulsive therapy. *Arch Gen Psychiatry*. 1991;48:746-748.
4. Letemendia FJ, Delva NJ, Rodenburg M, Lawson JS, Inglis J, Waldron JJ, Lywood DW. Therapeutic advantage of bifrontal electrode placement in ECT. *Psychol Med*. 1993;23:349-360.
5. American Psychiatric Association Task Force on ECT. *The Practice of ECT: Recommendations for Treatment, Training, and Privileging*. Washington, DC: American Psychiatric Press; 1990.
6. Farah A, McCall WV. ECT stimulus dosing: a survey of contemporary practices. *Convuls Ther*. 1993;9:90-94.
7. Colenda CC, McCall WV. A statistical model predicting the seizure threshold for right unilateral electroconvulsive therapy in 106 patients. *Convuls Ther*. 1996; 12:3-12.
8. Sackeim HA, Decina P, Prohovnik I, Malitz S. Seizure threshold in electroconvulsive therapy: effects of sex, age, electrode placement, and number of treatments. *Arch Gen Psychiatry*. 1987;44:355-360.
9. Coffey CE, Lucke J, Weiner RD, Krystal AD, Aque M. Seizure threshold in electroconvulsive therapy, I: initial seizure threshold. *Biol Psychiatry*. 1995;37:713-720.
10. Enns N, Karvelas L. Electrical dose titration for electroconvulsive therapy: a comparison with dose prediction methods. *Convuls Ther*. 1995;11:86-93.
11. McCall WV, Farah BA, Reboussin D, Colenda CC. Comparison of the efficacy of titrated, moderate dose and fixed, high dose RUL ECT in the elderly. *Am J Geriatr Psychiatry*. 1995;3:317-324.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
13. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for *DSM-III-R* (SCID), I: history, rationale, and description. *Arch Gen Psychiatry*. 1992;49:624-629.
14. Folstein MF, Folstein S, McHugh PR. Mini-Mental state exam: a practical method of grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189-198.
15. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23:56-62.
16. Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia*. 1971; 9:97-113.
17. Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA. Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry*. 1996;153:985-992.
18. D'Elia G. Unilateral electroconvulsive therapy. In: Fink M, Kety S, McGuagh J, eds. *Psychobiology of Convulsions Therapy*. Washington, DC: Winston & Sons; 1974:21-34.
19. International Federation of Societies for Electroencephalography and Clinical Neurophysiology. Ten twenty electrode system. *EEG Clin Neurophysiol*. 1958;10: 371-375.
20. McCall WV, Shelp FE, Weiner RD, Austin S, Norris J. Convulsive threshold differences in right unilateral and bilateral ECT. *Biol Psychiatry*. 1993;34:606-611.
21. Sayer NA, Sackeim HA, Moeller JR, Prudic J, Devanand DP, Coleman EA, Kiersky JE. The relations between observer-rating and self-report of depressive symptomatology. *Psychol Assess*. 1993;5:350-360.
22. Rapp SR, Smith SS, Britt M. Identifying comorbid depression in elderly medical patients: use of the extracted Hamilton Depression Rating Scale. *Psychol Assess*. 1990;2:243-247.
23. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1988;45:742-747.
24. Weiner RD, Rogers HJ, Davidson JR, Squire LR. Effects of stimulus parameters on cognitive side effects. *Ann N Y Acad Sci*. 1986;462:315-325.
25. McElhiney MC, Moody BJ, Steif BL, Prudic J, Devanand DP, Nobler MS, Sackeim HA. Autobiographical memory and mood: effects of electroconvulsive therapy. *Neuropsychology*. 1995;9:501-517.
26. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests*. New York, NY: Oxford University Press; 1991.
27. Squire LR, Slater PC. Bilateral and unilateral ECT: effects on verbal and nonverbal memory. *Am J Psychiatry*. 1978;135:1316-1320.
28. Sobin C, Sackeim HA, Prudic J, Devanand DP, Moody BJ, McElhiney MC. Prediction of anterograde amnesia following electroconvulsive therapy. *Am J Psychiatry*. 1995;152:995-1001.
29. D'Agostino RB Jr. Propensity score method for bias reduction in the comparison of a treatment to an non-randomized control group. *Stat Med*. 1998;17: 2265-2281.
30. Little RJ, Rubin DB. *Statistical Analysis With Missing Data*. New York, NY: John Wiley & Sons; 1987:55-57.
31. Coleman EA, Sackeim HA, Prudic J, Devanand DP, McElhiney MC, Moody BJ. Subjective memory complaints prior to and following electroconvulsive therapy. *Biol Psychiatry*. 1996;39:346-356.
32. Montgomery S, Braithwaite R, Dawling S, McAuley R. High plasma nortriptyline levels in the treatment of depression. *Clin Pharmacol Ther*. 1978;23:309-314.
33. Rickels K, Weisse C, Case G, Hucker H. Tricyclic plasma levels in depressed outpatients treated with amitriptyline. *Psychopharmacology (Berl)*. 1983;80:14-18.