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

Acute Antidepressant and Cognitive Effects

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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 supra-threshold 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 milli-coulombs [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 to 8 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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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. However, there have been few clinical trials that examine dose-response relationships of RUL ECT relative to a known seizure threshold. 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.

See also pages 425 and 445

These findings supported the recommendation of the 1990 American Psychiatric Association Task Force on ECT that the stimulus dose in ECT be “moderately suprathreshold,” 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. We and others 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. 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.). 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) 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. 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, 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. 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.

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.21 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.

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).

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.29 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.20

STATISTICS

The means of continuous variables were compared with t tests or 1-way analysis of variance. Frequency distributions were compared using the χ² 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 α = .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 side effects were measured only in the 63 patients who required no BL ECT. Significance was accepted at α = .05. All tests were 2 sided.

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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%]) (\(\chi^2 = 5.6; \ P = .02\)). 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 (SDST), with the SDST 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 SDST was the most significant predictor of antidepressant response in logistic regression when considering the following candidate predictor variables: age, sex, SDST, absolute stimulus intensity at the second treatment in millicoulombs, and the seizure threshold in millicoulombs. When SDST 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 1. Comparison of Baseline Characteristics of the 2 Treatment Groups*

<table>
<thead>
<tr>
<th></th>
<th>Titrated Moderate Dose (n = 36)</th>
<th>Fixed High Dose (n = 36)</th>
<th>(t) or (\chi^2) Test</th>
<th>df</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.1 ± 15.8</td>
<td>65.1 ± 13.0</td>
<td>-0.87</td>
<td>70</td>
<td>.39</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>26 (72)</td>
<td>28 (78)</td>
<td>0.30</td>
<td>1</td>
<td>.59</td>
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<tr>
<td>Nonwhite, No. (%)</td>
<td>5 (14)</td>
<td>4 (11)</td>
<td>0.60</td>
<td>2</td>
<td>.60</td>
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<tr>
<td>Years of education</td>
<td>11.5 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>-0.71</td>
<td>70</td>
<td>.48</td>
</tr>
<tr>
<td>Married, No. (%)</td>
<td>15 (42)</td>
<td>19 (53)</td>
<td>0.18</td>
<td>3</td>
<td>.18</td>
</tr>
<tr>
<td>Duration of MDE, wk</td>
<td>18.0 ± 18.1</td>
<td>20.9 ± 17.5</td>
<td>-0.69</td>
<td>70</td>
<td>.49</td>
</tr>
<tr>
<td>No. of prior MDE</td>
<td>3.1 ± 1.8</td>
<td>3.5 ± 1.8</td>
<td>-0.96</td>
<td>70</td>
<td>.35</td>
</tr>
<tr>
<td>Age of onset at first MDE, y</td>
<td>40.9 ± 20.3</td>
<td>42.3 ± 17.5</td>
<td>-0.32</td>
<td>70</td>
<td>.75</td>
</tr>
<tr>
<td>Baseline test scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRSD</td>
<td>28.5 ± 5.4</td>
<td>29.0 ± 4.4</td>
<td>-0.45</td>
<td>70</td>
<td>.65</td>
</tr>
<tr>
<td>MMSE</td>
<td>25.7 ± 4.1</td>
<td>26.7 ± 4.4</td>
<td>-0.96</td>
<td>70</td>
<td>.34</td>
</tr>
<tr>
<td>Edinburgh score</td>
<td>22.9 ± 2.6</td>
<td>22.1 ± 4.2</td>
<td>1.00</td>
<td>57†</td>
<td>.32</td>
</tr>
<tr>
<td>Prior adequate treatment, No. (%)‡</td>
<td>29 (81)</td>
<td>27 (75)</td>
<td>0.32</td>
<td>1</td>
<td>.57</td>
</tr>
<tr>
<td>Prior lifetime courses of ECT</td>
<td>0.86 ± 1.2</td>
<td>0.81 ± 1.1</td>
<td>0.21</td>
<td>70</td>
<td>.83</td>
</tr>
<tr>
<td>Bipolar disorder, No. (%)</td>
<td>3 (8)</td>
<td>6 (17)</td>
<td>0.29</td>
<td>1</td>
<td>.29</td>
</tr>
<tr>
<td>Patients given medications, No. (%)</td>
<td>21 (58)</td>
<td>21 (58)</td>
<td>0.00</td>
<td>1</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>7 (19)</td>
<td>4 (11)</td>
<td>0.33</td>
<td>1</td>
<td>.33</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>0.00</td>
<td>1</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Trazodone</td>
<td>15 (42)</td>
<td>12 (33)</td>
<td>0.47</td>
<td>1</td>
<td>.47</td>
</tr>
</tbody>
</table>

* 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*

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

* 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%]) (\(\chi^2 = 5.6; \ P = .02\)). 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 (SDST), with the SDST 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 SDST was the most significant predictor of antidepressant response in logistic regression when considering the following candidate predictor variables: age, sex, SDST, absolute stimulus intensity at the second treatment in millicoulombs, and the seizure threshold in millicoulombs. When SDST 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.
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%]) \( \chi^2 = 5.7; P = .02 \), 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.
Participants 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.

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REFERENCES


