A Randomized Comparison of High-Charge Right Unilateral Electroconvulsive Therapy and Bilateral Electroconvulsive Therapy in Older Depressed Patients Who Failed to Respond to 5 to 8 Moderate-Charge Right Unilateral Treatments

James D. Tew, Jr., M.D.; Benoit H. Mulsant, M.D.; Roger F. Haskett, M.D.; Diane Dolata, M.S.W.; Lois Hixson, B.S.N.; and John J. Mann, M.D.

Background: Electroconvulsive therapy (ECT) is the treatment of choice in some older patients with severe depression. When compared with younger depressed patients, older patients have been shown to be as likely to respond to ECT but more likely to develop cognitive impairment. This study addresses whether adults aged 50 years and over who have already failed to respond to at least 5 moderate-charge right unilateral (RUL) ECT treatments (150% above seizure threshold) are more likely to benefit from a switch to high-charge RUL ECT (450% above threshold) or to bilateral (BL) ECT.

Method: Twenty-four patients who were treated with 5 to 8 moderate-charge RUL ECT treatments and who failed to improve sufficiently were randomly assigned to receive either BL ECT (N = 11) or high-charge RUL ECT (N = 13). Depressive (24-item Hamilton Rating Scale for Depression) and cognitive scores (Mini-Mental State Examination [MMSE]) were compared under double-blind conditions at 3 phases of treatment.

Results: Patients in the BL ECT group exhibited significantly greater cognitive impairment (mean MMSE score decrease of 1.13) than those receiving high-charge RUL ECT (mean MMSE increase of 1.71). There were no statistically significant differences in clinical response to BL or high-charge RUL ECT (63.6% and 61.5%, respectively) or in depressive symptom remission (18.1% and 46.2%).

Conclusion: These results suggest that older patients who fail to respond to moderate-charge RUL ECT may benefit from a switch to high-charge RUL ECT rather than BL ECT. Larger future studies will be needed to compare clinical response in patients switched from moderate-dose RUL ECT to higher-dose RUL or to BL ECT.

(J Clin Psychiatry 2002;63:1102–1105)

Received Feb. 28, 2001; accepted May 3, 2002. From the Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pa. (Drs. Tew, Mulsant, and Haskett, Ms. Dolata, and Ms. Hixson); Geriatric Research, Education, and Clinical Center (GRECC), VA Pittsburgh Health System, Pittsburgh, Pa. (Dr. Mulsant); and the New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons, New York (Dr. Mann).

Supported in part by United States Public Health Service grants MH30915, MH48512, MH52247, MH61591, and MH01613 from the National Institute of Mental Health.

Corresponding author and reprints: Benoit H. Mulsant, M.D., WPIC (E837), 3811 O'Hara St., Pittsburgh, PA 15213.

Due to comorbid physical illness, poor tolerance of psychotropic medications, or marked disability or psychosis associated with depression, electroconvulsive therapy (ECT) is often the treatment of choice in older patients with severe depression.[1] As a result, older adults represent more than half of all Americans who receive ECT for the treatment of depression.[2] Older patients have been shown to be as likely to respond to ECT but more likely to develop cognitive impairment.[3,4] Since 1987, several studies have explored the relationship among electrode placement, ECT stimulus intensity, efficacy, and effect on cognition (see Table 1).[5–10] These randomized controlled trials have shown that the intensity of electrical stimulus used to induce a seizure with right unilateral (RUL) ECT can affect the likelihood of response to ECT. In all studies, a higher electrical stimulus was associated with a higher acute response rate. Until recently, a RUL stimulus charge 150% above seizure threshold was often used to induce therapeutic seizures.[8] More recent data, however, suggest that a higher charge (i.e., up to 500% above seizure threshold) may result in more efficacious RUL ECT, though perhaps at the risk of increased cognitive impairment.[5–7]

Only one of these studies focused exclusively on older patients.[7] This study compared the effect of fixed high-charge (403 mC) RUL ECT with titrated moderate-charge (125% above seizure threshold) RUL ECT and did not inform on the relative efficacy and safety of high-charge RUL versus BL ECT. Thus, we report on the results of a

Table 1. Randomized Electroconvulsive Therapy (ECT) Trials Assessing Impact of Charge and Modality on Outcome

Study	N	Age (mean, y)	Design	Efficacy	Cognition
McCall et al, 2000[5]	72	63.6	Compared patients who received RUL ECT at 150% above ST with fixed, high-charge RUL ECT	Fixed higher-charge (fixed-dose) RUL ECT response rate was 67% compared to 39% in lower-charge (150% above ST) group	Cognitive deficits more severe with fixed higher-charge treatments
Sackeim et al, 2000[6]	80	57.1	Compared patients who received RUL ECT at 50%, 150%, and 500% above ST with BL ECT at 150% above ST	BL and high-charge RUL ECT yielded 65% response rate, double that of low- (35%) and moderate-charge (30%) RUL ECT	Cognitive impairment more severe in BL ECT group than in any of the RUL ECT groups
McCall et al, 1995[7]	19	73.0	Compared older adults receiving fixed, high-charge RUL ECT with titrated, moderate-charge (125% above ST) RUL ECT	Final depression ratings similar for both groups, but high-charge group responded faster and required fewer treatments (5.7 vs 8.0)	No between-group differences in memory self-rating scale scores
Sackeim et al, 1993[8]	96	56.4	Compared patients who received RUL and BL ECT at ST and 150% above ST	Higher-charge RUL ECT response rate was 43%, approaching efficacy of both BL ECT groups (65% and 63%). Low-charge RUL ECT clearly inferior (17%)	Electrode placement had more effect on cognitive impairment than charge dose, with more severe impairment in BL ECT groups than in either RUL group
Abrams et al, 1991[9]	38	61.0	Compared patients who received fixed-charge (378 mC) RUL ECT and BL ECT at charge estimated to be 150% above ST	Equivalent antidepressant effects were observed, RUL and BL ECT resulting in 68% and 79% reduction in depressive symptoms	Cognitive outcomes not measured
Sackeim et al, 1987[10]	52	61.3	Compared BL to RUL titrated low-charge (just above ST) ECT	BL superior to RUL ECT in clinical response rate (70% vs 28%, respectively)	Cognitive outcomes not measured

Abbreviations: BL = bilateral electrode placement, RUL = right unilateral electrode placement, ST = seizure threshold.

randomized double-blind trial that compared the outcome of high-charge RUL ECT versus BL ECT in older depressed adults who had failed to respond adequately to 5 to 8 treatments of moderate-charge RUL ECT. We hypothesized that the acute response rates would be comparable in both groups, but that the BL ECT group would be more likely to experience cognitive impairment.

METHOD

Between October 1993 and December 1996, 24 patients aged 50 years and over presenting with either a first or a recurrent DSM-III-R[11] major depressive episode with or without psychotic features were enrolled in the study. Prior to initiation of ECT (T1), all psychotropic medications (with the exception of lorazepam, up to 3 mg/day) were tapered and patients were evaluated with the 24-item version of the Hamilton Rating Scale for Depression (HAM-D).[12] No distinction was made between right and left motor dominant patients. All patients initially received RUL ECT. Seizure threshold was determined using a "method of limits" procedure during the first ECT session.[8] Initially, patients were treated with RUL ECT at moderate charge (i.e., 150% above seizure threshold) during subsequent sessions. If, after administration of 5 to 8 moderate-charge RUL ECT treatments, it appeared that the patient had not improved sufficiently, the treating psychiatrist could request a change in treatment modality. At that time (T2), patients were reevaluated with the HAM-D. Patients who failed to improve (defined as a score of 20 or more on the 24-item HAM-D or a decrease of less than 33% from baseline HAM-D score) were then randomly assigned to receive either RUL ECT at 450% above seizure threshold or BL ECT at 150% above seizure threshold. Study subjects, their treating psychiatrists, and the research staff performing clinical ratings were kept blind to the treatment modality assigned randomly. To do so, electrodes were not placed until the patient was anesthetized, and conduction gel was smeared at both RUL and BL contact points, regardless of the actual electrode placement. However, psychiatrists and clinical staff performing ECT were aware of the treatment modality. At the time of randomization, seizure threshold was again determined. Patients were subsequently treated with at least 2 additional ECT treatments and were reassessed with the 24-item HAM-D within 1 to 3 days after completing ECT (T3). Treatment endpoint was determined clinically by the treatment team either when clinical improvement was judged to be satisfactory or when it was perceived that the patient had stopped improving over at least the 2 or 3 previous treatments. In addition, when clinically feasible, the Mini-Mental State Examination (MMSE)[13] was also completed at T1 (within 1 week of initiation of ECT), T2 (randomization), and T3 (completion of ECT). Remitters were defined as patients who achieved a HAM-D score of 10 or less. Responders were defined as those patients whose HAM-D score decreased by at least 50% from the time of treatment randomization.

Table 2. Characteristics and Outcomes of Patients Treated With Right Unilateral (RUL) and Bilateral (BL) Electroconvulsive Therapy (ECT)[a]

Variable	RUL ECT Group (N = 13)	BL ECT Group (N = 11)	p Value
Age, y	66.8 (10.1)	68.4 (9.0)	.704
Age range, y	50–80	51–81	
No. of treatments			
Prior to randomization	6.5 (1.1)	5.7 (0.6)	.056
After randomization	6.1 (1.7)	6.1 (2.5)	.987
Total	12.5 (1.7)	11.8 (2.8)	.442
HAM-D score			
T1	37.9 (8.7)	38.7 (9.4)	.830
T2	30.4 (6.6)	30.8 (12.0)	.486
T3	13.9 (8.7)	15.3 (8.2)	.492
Reduction between T1 and T2, %	26.9 (11.9)	21.2 (18.0)	.561
Reduction between T2 and T3, %	51.7 (34.5)	48.1 (34.5)	.802
Reduction between T1 and T3, %	67.6 (27.3)	59.5 (24.2)	.707
Remitters, %	46.2 (6/13)	18.1 (2/11)	.211
Responders, %	61.5 (8/13)	63.6 (7/11)	.999
MMSE score[b]			
T1	22.1 (7.6)	26.8 (3.1)	.227
T2	24.0 (5.5)	26.4 (2.8)	.324
T3	25.7 (4.2)	25.3 (3.7)	.903
Change between T1 and T2	1.9 (6.1)	0.38 (1.85)	.340
Change between T2 and T3	1.7 (2.1)	–1.1 (2.0)	.019
Change between T1 and T3	1.5 (5.9)	–3.6 (2.7)	.048

[a]All results are presented as mean (SD) unless indicated otherwise.
[b]N = 7 for the RUL ECT group, N = 8 for the BL ECT group.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MMSE = Mini-Mental Status Examination, T1 = prior to initiation of ECT, T2 = at time of randomization, T3 = at completion of ECT.

Clinical characteristics and outcome data were compared using paired Student t tests (within-group comparisons) and unpaired t tests (across-group comparisons), chi-square tests, and the Fisher exact test as appropriate. The study was approved by the University of Pittsburgh Institutional Review Board, and written informed consent was obtained from all subjects or their legal representatives.

RESULTS

Patient age, treatment characteristics, and clinical outcomes are presented in Table 2. The 2 treatment groups did not differ significantly at baseline. However, patients randomly assigned to high-charge RUL ECT had received an average of 1 more moderate-charge RUL treatment prior to randomization; this difference approached significance (p = .056). The total number of ECT treatments (i.e., before and after randomization) did not differ between the 2 groups. Mean HAM-D scores did not differ between groups at any phase of the study, with both groups showing similar patterns of relative improvement at each treatment phase. By the time of completion of ECT (T3), 46.2% and 18.1% of patients randomly assigned to high-charge RUL and BL ECT, respectively, were classified as remitters (Fisher exact p = .211), while 61.5% and 63.6% were classified as responders (Fisher exact p = .999).

MMSE scores at all 3 phases of the study were collected on 8 patients from the BL ECT group and 7 from the RUL group. Mean MMSE scores were similar in the 2 groups at all 3 phases of the study. However, between randomization and completion of the trial, the RUL ECT group experienced a mean improvement in MMSE score of 1.71 points, while the BL ECT group experienced a mean decrease of 1.13 points (p = .019).

DISCUSSION

Older adults (aged 50 years and over) who had failed to respond to 5 to 8 moderate-charge RUL ECT treatments (150% above seizure threshold) were as likely to benefit from a switch to higher-charge (450% above threshold) RUL ECT as to BL ECT. Patients who were switched to BL ECT were more likely to experience some global cognitive impairment. These results are of particular relevance to older patients, who are more susceptible to the cognitive side effects of ECT.[1,4] These findings are consistent with the results of a study[6] comparing high-charge RUL ECT and BL ECT in a slightly younger group of depressed patients (see Table 1). The consistency of the findings in the 2 studies suggests that prior failure of adequate response to lower-charge RUL ECT does not predict a poor response if patients are switched to a higher-charge RUL ECT or to BL ECT. This and other recent studies[5–7] suggest a greater efficacy of RUL ECT at high charges (i.e., 300% or more above threshold) than at lower charges.

A study comparing fixed higher-charge RUL ECT with RUL ECT at 150% above threshold in adults of similar age to those of this study found that the higher-charge RUL ECT, though more efficacious in inducing depressive symptom remission, resulted in relatively greater cognitive deficits on several objective measures.[5] Another study[8] observed a similar association between higher charge and worse cognitive outcomes with RUL ECT even though this was not the case with BL ECT (in that study, there were no differences in cognitive outcomes among depressed patients receiving BL ECT at 0% or 150% above seizure threshold). Thus, it may remain prudent to initiate RUL treatment at a lower charge (e.g., 150% above threshold) in some patients for whom significant cognitive side effects from ECT are of particular concern. At the very least, it seems that there is no clear clinical advantage of BL ECT over higher-charge RUL ECT in patients who failed to respond to lower-charge RUL ECT. In fact, BL ECT was associated with greater cogni-

tive adverse effects than high-charge RUL ECT in both this study and the other study that compared their cognitive effect.[6]

In conclusion, this study confirms and extends the results of several other studies (see Table 1). Taken together, these data suggest that patients who fail moderate-charge RUL ECT could be treated with RUL ECT at a higher charge rather than be switched to BL ECT. This represents a treatment pathway that may be useful in patients who are vulnerable to or concerned by the cognitive effects associated with ECT. However, this study has several limitations. First, patients were switched to an alternative treatment modality after having failed to respond to only 5 to 8 moderate-charge RUL ECT treatments. It is possible that some slow responders would have ultimately benefited from a larger number of moderate-charge RUL ECT treatments. Second, while the rates of response or remission in the 2 groups did not differ statistically, patients treated with high-charge RUL ECT were more than twice as likely to remit as those treated with BL ECT (rates of 46.2% and 18.1%, respectively). The small size of the study group may have prevented this potentially important difference from reaching statistical significance. Last, this study was limited by the small number of subjects who completed the MMSE and by the lack of cognitive measures more specific to the potential adverse effects of ECT. Future studies aiming at establishing the optimal ECT treatment pathway should seek to address these limitations.

Drug name: lorazepam (Ativan and others).

REFERENCES

1. Sackeim HA. Electroconvulsive therapy in late-life depression. In: Salzman C, ed. Clinical Geriatric Psychopharmacology. Baltimore, Md: Williams & Wilkins; 1998:262–309
2. Olfson M, Marcus M, Sackeim HA, et al. Use of ECT for the inpatient treatment of recurrent major depression. Am J Psychiatry 1998;155:22–29
3. Mulsant BH, Rosen J, Thornton JE, et al. A prospective naturalistic study of electroconvulsive therapy in late-life depression. J Geriatr Psychiatry Neurol 1991;4:3–13
4. Tew JD, Mulsant BH, Haskett RF, et al. Acute efficacy of ECT in the treatment of major depression in the old-old. Am J Psychiatry 1999;156:1865–1870
5. McCall WV, Reboussin DM, Weiner RD, et al. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy. Arch Gen Psychiatry 2000;57:438–444
6. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 2000;57:425–434
7. McCall WV, Farah BA, Reboussin D, et al. Comparison of the efficacy of titrated, moderate-dose and fixed high-dose right unilateral ECT in elderly patients. Am J Geriatr Psychiatry 1995;3:317–324
8. Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med 1993;328:839–846
9. Abrams R, Swartz CM, Chandragupta V. Antidepressant effects of high-dose right unilateral electroconvulsive therapy. Arch Gen Psychiatry 1991;48:746–748
10. Sackeim HA, Decina P, Kanzler M, et al. Effects of electrode placement on the efficacy of titrated, low-dose ECT. Am J Psychiatry 1987;144:1449–1455
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987
12. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
13. Folstein MF, Folstein S, McHugh PR. Mini-mental state: a practical method of grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198