Article

ECT Stimulus Intensity: Are Present ECT Devices Too Limited?

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Objective: The maximum output charge for ECT devices is limited to 576 millicoulombs in the United States, although there are no data ensuring that this limit will allow consistently effective treatments. The authors examined whether this limit has a negative impact on therapeutic response and, therefore, whether a higher stimulus charge should be available.

Method: They retrospectively reviewed the records of 471 patients who received a clinical index course of ECT at Duke University between 1991 and 1998. These patients received conservative stimulus dosing of 2.25 times seizure threshold for unilateral ECT and 1.5 times seizure threshold for bilateral ECT.

Results: Seventy-two (15%) of the 471 patients required the maximum stimulus intensity during their index ECT course. Of these, 24 (5% of the total) had either a short EEG seizure (less than 25 seconds) or had no seizure at the maximum level. Strategies to augment therapeutic response with caffeine, ketamine, or hyperventilation were used in 14 of the 24 patients, and data on therapeutic response were available for 22 of the 24. Only seven (32%) of these 22 patients were considered ECT responders, compared with 242 (66%) of the remaining 364 patients for whom data on response to ECT were available. Older age and pre-ECT course EEG slowing were predictors of requiring the maximum stimulus level.

Conclusions: The maximum available stimulus output was therapeutically insufficient for 5% of the patients studied even when available means to augment response were instituted. This percentage would likely be even larger with the use of a less conservative dosing protocol for unilateral ECT. Increases in maximum stimulus output for ECT devices should be considered as a means to ensure adequate treatment response.

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Much has been learned about how to administer ECT to ensure therapeutic efficacy since its inception in the 1930s (1). It has long been recognized that the induction of a generalized tonic-clonic seizure is necessary to achieve a therapeutic response to ECT (1). This view is based on a series of studies that conclusively demonstrated the efficacy of ECT and the lack of efficacy of both sham ECT and the administration of electrical stimuli below the seizure threshold in intensity (1–3). More recent studies provide evidence suggesting that although exceeding the seizure threshold may be necessary to achieve efficacy, it is not sufficient to ensure therapeutic potency. These studies indicate that the degree to which ECT stimulus intensity exceeds the seizure threshold may be an important determinant of both therapeutic effectiveness and cognitive side effects (4–11). In particular, unilateral ECT appears to require at least moderately suprathreshold (roughly 2.5 times threshold) stimulus intensity to be effective (4–11).

The need to deliver stimuli with unilateral ECT that are at least moderately suprathreshold poses a challenge for clinicians because initial seizure threshold varies considerably across patients (5) and at times may approach or even exceed the maximum stimulus intensity limitation of 576 millicoulombs (mC) imposed on U.S. ECT devices by the Food and Drug Administration (FDA), which regulates these devices (12). A further clinical challenge is presented by a variable rise in seizure threshold that occurs over the course of treatment (13). This may represent an even greater risk of patients' seizure thresholds approaching or exceeding the maximum available U.S. stimulus intensity level over the course of treatment. Available evidence suggests that it is likely that the efficacy of unilateral ECT is diminished in both situations (5–7, 14). Clinical techniques aimed at augmenting seizure activity or decreasing the seizure threshold, including the use of caffeine, ketamine, or hyperventilation, are not always effective and are sometimes not practicable in patients with comorbid medical illness (15). Thus, the maximum electrical stimulus delivered by currently available U.S. ECT devices is insufficient to provide therapeutically effective seizures in some patients (4, 15).

The FDA arrived at the present maximum intensity by adopting the maximum stimulus intensity that had been built into U.S. ECT devices before FDA regulation and has subsequently refused requests for increases in the maximum stimulus intensity. The FDA limitation differs substantially from the maximum stimulus intensity allowed

in many locations outside of the United States (15). The Royal College of Psychiatrists, for example, has recommended a maximum output charge of 1,200 mC for ECT devices (16)—more than double the U.S. limit.

To address the question of whether higher-output ECT devices should be made available for use in the United States, we studied the treatment records of 471 patients who received an index course of ECT according to a seizure-threshold-based clinical protocol at Duke University (unilateral ECT 2.25 times seizure threshold and bilateral ECT 1.5 times seizure threshold) to assess what proportion of patients required the maximum possible stimulus charge. We also sought to investigate whether factors known to affect seizure threshold, such as age, sex, previous ECT treatment, and electrode placement (unilateral versus bilateral), were predictors of which patients would require the maximum stimulus intensity. Finally, we examined differences in therapeutic outcome for patients who had short (less than 25 seconds' EEG duration) or missed seizures at the maximum available stimulus intensity compared with all other patients. Thus, we compared those patients who would have received a higher stimulus intensity, were one available clinically, with all other patients.

Method

Subjects

A retrospective chart review included 471 clinically referred patients receiving index ECT at Duke University Medical Center from 1991 to 1998. Written informed consent was obtained from all subjects following the description of procedures. Diagnoses were based on DSM-III-R and included unipolar depression (N=408), bipolar depression (N=44), mania (N=5), thought disorder (schizoaffective disorder and schizophrenia) (N=8), and organic mood disorder (N=6). The patients' mean age was 58.6 years (SD=18.0); 162 men and 309 women were included. Fourteen other patients were excluded on the grounds of having incomplete data available or because they were participating in a research protocol on stimulus dosing. Data on psychotropic medications before and during the course of ECT were available for 383 patients. All of these patients had been free of antidepressant, antipsychotic, and anticonvulsant medications for at least 5 days before the beginning of the ECT course, except that 28 patients were receiving antipsychotic medication during the treatment course, 31 were discontinued from antidepressant therapy within 5 days of the first treatment, 11 continued to take antidepressant medication during the course, six patients took a benzodiazepine until 3–5 days before the first treatment, 21 had benzodiazepine therapy discontinued within 2 days of beginning the treatment course, and 26 continued to take benzodiazepines during the treatment course but received flumazenil intravenously just before each treatment (17).

ECT Administration

All patients included in the retrospective review had received ECT according to our standard clinical protocol. Seizure threshold was estimated at the first treatment by means of seizure threshold titration. The protocol for seizure threshold titration starts with the administration of an initial stimulus of 32 mC for women receiving unilateral electrode placement, 48 mC for men receiving unilateral ECT, 48 mC for women receiving bilateral ECT, and 60 mC for men receiving bilateral ECT. Any subsequent stimuli required at the first treatment are administered at successive increments of approximately 50% (with a maximum of four stimuli per session) until an EEG seizure of at least 25 seconds' duration is achieved. The stimulus required to elicit such a seizure is designated as the seizure threshold (13). Subsequent treatments were administered at 125% over (2.25 times) seizure threshold for unilateral ECT and 50% over (1.5 times) seizure threshold for bilateral ECT.

EEG data during the seizures were recorded from left and right prefrontal to mastoid Ag/AgCl electrodes. At all remaining treatments, seizures less than 25 seconds' duration were followed by restimulation at a 50% increase in intensity. A seizure duration minimum of 25 seconds was used to be consistent with previous studies, with the understanding that exceeding this minimum did not ensure therapeutic adequacy (5). Routine anesthetic agents included 1 mg/kg of methohexital, 1 mg/kg of succinylcholine, and 100% oxygen by mask. The average initial seizure threshold was 63 mC.

The maximum stimulus charge was 576 mC (MECTA SR1 device; MECTA Corp., Lake Oswego, Ore.), defined at settings of a pulse width of 2.0 msec, frequency of 90 Hz, duration of 2.0 seconds, and current of 0.8 amp.

Therapeutic Outcome

The patients were assessed with the Montgomery-Åsberg Depression Rating Scale (18) at baseline; 1–2 days after treatments 2, 5, 8, 11, and 14; and at the end of the index course. These assessments were carried out by the ward psychiatrist or a member of the ECT team. Only patients with unipolar or bipolar major depression (N=452) were included in therapeutic outcome analysis. Therapeutic outcome data were missing for 64 patients; therefore, a total of 388 patients were included in the therapeutic outcome analysis. A therapeutic responder was defined as a patient who, at the end of the ECT course, had experienced at least a 50% decrease in Montgomery-Åsberg scale score and had a final Montgomery-Åsberg scale score of 12 or less.

Data Analysis

The question of whether a maximum stimulus intensity was more likely in certain conditions was assessed with multivariate logistic regression in which use of maximum stimulus intensity served as the dependent variable and sex, stimulus electrode placement, history of previous ECT, diagnosis, therapeutic response, age, presence of an abnormality on baseline EEG, and number of treatments received were the independent variables. Follow-up univariate analyses were carried out (chi-square for dichotomous variables and analysis of variance for continuous variables) to determine significant predictors of the need for the maximum stimulus intensity. Baseline EEG was included because this was used as a screening test for the majority of our clinical population. EEG data were available for 336 (71%) of the 471 patients. As a result, the multivariate logistic regression could be carried out only with the data from these 336 patients.

The EEGs were rated dichotomously as either normal or abnormal. Abnormality was defined as clinical evidence of encephalopathy consisting of either slowing of the predominant background rhythm below 8.5 Hz or the presence of clinically abnormal amounts of either polymorphic or rhythmic activity below 8.5 Hz. This determination was made by a board-certified electroencephalographer (either A.D.K. or R.D.W.). To ensure that previous ECT was unlikely to be responsible for the abnormal EEGs identified, we tested whether the incidence of abnormalities differed between the patients with and those without a history of previous ECT and found no significant difference (32% in patients who had not received previous ECT and 39% in those who had received previous ECT).

In terms of therapeutic outcome analyses, chi-square analysis was used to test the hypothesis that having a short or missed seizure at the maximum stimulus intensity resulted in a diminished therapeutic response rate (such patients would have been given a higher-intensity stimulus, were one available). Data from two subjects were excluded from this analysis because they received "double stimulation," i.e., because they had missed a seizure at the maximum setting available on the machine, two stimuli were administered as quickly in succession as possible to enhance treatment efficacy (15). Because these subjects did not reflect the limitations in treatment efficacy imposed by the present limit on machines, they were not included in the analysis. Excluding these two patients, those who did not have the diagnosis of unipolar or bipolar depression, and those without therapeutic outcome data, the total number of subjects included in the efficacy analysis was 386.

Analysis of covariance (ANCOVA) was also carried out to determine if patients with short or missed seizures at the maximum stimulus intensity had higher Montgomery-Åsberg scale scores at the end of the treatment course, after baseline Montgomery-Åsberg scale score and age were controlled for. Electrode placement and the presence of attempts to augment efficacy with hyperventilation or the addition of ketamine or caffeine (see reference 19) also served as independent variables. We carried out an ANCOVA with this same group of 386 patients to determine whether those who had short or missed seizures at the maximum intensity required more treatments than other subjects. In this ANCOVA, the number of treatments was the dependent variable and the independent variable was whether a short seizure occurred at the maximum intensity.

Results

Seventy-two (15%) of the 471 patients received the maximum possible stimulus intensity at some point during their index course of ECT. A multivariate logistic regression to predict whether the maximum stimulus intensity was necessary was carried out in which age, sex, electrode placement, diagnosis, whether the patient had received previous ECT, and whether the patient had a normal baseline EEG were included in a stepwise fashion as predictor variables. This model was a significant predictor of the need for the maximum stimulus intensity (Table 1).

Follow-up univariate analyses revealed that a need for the maximum stimulus intensity was predicted by older age: the mean age of those requiring maximum intensity was 63.9 (SD=16.2), compared with 57.6 (SD=18.1) for those who did not require the maximum (F=7.4, df=1, 470, p<0.007). A need for the maximum stimulus intensity was also predicted by abnormality on the EEG assessed before the treatment course: 30 (24%) of the 127 patients with an abnormal baseline EEG, compared with 23 (11%) of the 209 patients with a normal baseline EEG, required maximum stimulus intensity (χ^2=11.2, df=1, p<0.001). Men were nonsignificantly more likely to require the maximum intensity than women: 39 (24%) of the 162 men compared with 46 (15%) of the 309 women required maximum intensity (χ^2=3.32, df=1, p<0.07).

Factors found in this study to lack significant predictive value for requiring maximum stimulus included bilateral versus unilateral electrode placement, diagnosis, and a history of previous courses of ECT.

TABLE 1. Results of Logistic Regression Analysis of the Need for Maximum ECT Stimulus Intensity for 336 Patients for Whom EEG Data Were Available[a]

Predictor	Regression Coefficient	χ^2 (df=1)	p	Odds Ratio	R^2
Baseline EEG	2.10	11.10	0.0008	7.80	0.23
Age	–0.28	4.10	0.04	0.98	0.03
Gender	0.28	0.34	n.s.	1.30	0.004
Diagnosis	–0.13	0.73	n.s.	0.88	0.03
Previous ECT	–0.42	0.83	n.s.	0.66	0.003

[a] The overall model was a significant predictor of which subjects required the maximum intensity (χ^2=20.7, df=6, p<0.002, R^2=0.31).

Of the 72 patients who required the maximum possible stimulus intensity, 24 (33%) had a short or missed seizure at that level, representing 5% of the total study group. The 22 patients with a short or missed seizure who were included in therapeutic response analysis (two were excluded because they received "double stimulation") had a diminished therapeutic response compared with all other subjects. Their therapeutic response rate was 32% (seven of 22 patients) compared with 66% (242 of 364 patients) for all other subjects (χ^2=8.5, df=1, p<0.003). This difference is particularly striking given that attempts were made to augment therapeutic response with the use of hyperventilation, caffeine, or ketamine in 14 of the 22 subjects who had short or missed seizures at the maximum stimulus intensity level.

These findings were paralleled by evidence that subjects who had a short or missed seizure at the maximum intensity had higher mean Montgomery-Åsberg scale scores following the treatment course (mean=15.6, SD=8.4) than all other subjects (mean=11.8, SD=9.7) (F=4.5, df=1, 375, p<0.04, ANCOVA controlling for baseline Montgomery-Åsberg scale score and age). No significant effect of electrode placement was found; however, patients whose ECT was augmented with hyperventilation, caffeine, or ketamine had nonsignificantly lower Montgomery-Åsberg scale scores. The mean score of patients not given augmentation was 20.4 (SD=66.6), compared with a mean score of 13.5 (SD=8.9) for those given augmentation (F=3.3, df=1, 21, p<0.09). Also consistent with diminished treatment efficacy in those who had short or missed seizures at the maximum available intensity is evidence that these subjects required a larger number of treatments (mean=12.4, SD=4.5) than all other subjects (mean=9.8, SD=3.6) (F=10.9, df=1, 385, p<0.001, ANOVA).

Discussion

Approximately one of six patients receiving an index course of ECT at Duke University Medical Center from 1991 to 1998 required the maximum possible ECT stimulus intensity available on U.S. ECT devices. For one-third of these individuals (24 [5%] of the total 471 patients), this intensity was insufficient to consistently induce a seizure

lasting at least 25 seconds in EEG duration. The results of this study suggest that this latter group of patients also demonstrated a significantly lower therapeutic response rate, which was approximately half that of the other subjects (32% versus 66%). They also had a significantly higher final mean Montgomery-Åsberg scale score (15.6 versus 11.8) and received significantly more ECT treatments (12.4 versus 9.8).

The clinical and economic costs of this diminished response and prolonged treatment course point to a need for the availability of higher ECT stimulus intensities in the United States. Further, a larger number of treatments may also be associated with a greater risk of memory impairment with ECT, since memory effects of ECT appear to be proportional to the number of treatments received (19, 20). In addition, the fact that the therapeutic response rate of the patients with short or missed seizures at the maximum available intensity was not affected by attempts to augment therapeutic response through the administration of caffeine, hyperventilation of the patient, and the use of ketamine rather than methohexital anesthesia (which have been suggested for this circumstance [19]) suggests that such measures are insufficient to overcome the decrease in efficacy imposed by the limitation in stimulus dose.

It should be noted that the findings of the present study and their generalizability were affected by the stimulus-dosing paradigm employed. The dosing strategy used in this study resulted in stimuli that were 2.25 times threshold for unilateral ECT and 1.5 times threshold for bilateral ECT. Such levels are within the range of what has been considered moderately suprathreshold (1.5–3.0 times threshold) (19). Some data suggest that these dosing levels may be conservative and that stimulation at levels likely to exceed the seizure threshold to an even greater extent may be necessary to produce optimally therapeutic seizures with unilateral ECT (6, 8, 9–11, 21, 22). In such cases, the frequency with which patients would require a greater stimulus intensity than currently available in the United States would be expected to be even higher than reported here.

Similarly, it is possible that different results might have been expected with the use of other sets of stimulus parameters. Some have suggested that the use of shorter pulse width and longer stimulus duration than were used in the present study may be more efficient at eliciting seizure activity and, therefore, might have allowed the induction of seizures in relatively more of the patients in the present study (22–26). However, because brief pulse width, especially below 0.5–0.75 msec, has also raised concern with respect to seizure adequacy (27, 28), more research on the utility of such parameter sets is needed to determine whether they would have any utility in improving treatment efficacy in patients with very high seizure thresholds.

The lack of a dependence of treatment efficacy on electrode placement in patients who had short or missed seizures at the maximum available intensity is not surprising. Although previous reports (5–7) suggested that the efficacy of unilateral ECT is diminished more than that of bilateral ECT when stimulus intensity approaches the seizure threshold, the present efficacy analysis focused on seizures that were subthreshold at maximum stimulus intensity, a situation that would be expected to exert a negative impact on the efficacy of both unilateral and bilateral ECT.

Predictive factors associated with a significantly increased likelihood of requiring a maximum stimulus intensity include older age and evidence for preexisting EEG encephalopathy. Men were also nonsignificantly more likely to require the maximum intensity. Patients with these clinical and demographic factors may be at greater risk of receiving treatments of diminished efficacy with the maximum stimulus charge currently available and, therefore, could be expected to benefit most from the availability of a higher stimulus level. These findings are consistent with the higher seizure threshold that has been reported in older individuals and men (5, 13). These findings may also suggest that in dementia, which accounted for the majority of abnormal EEG findings at baseline, there may be an additional decrease in neuronal excitability associated with a greater seizure threshold.

This study did not involve an assessment of cognitive effects, but available evidence indicates that an increase in the maximum stimulus output in U.S. ECT devices, when used to accommodate patients with high seizure thresholds, would not be expected to increase risks. In fact, the contrary might be expected because, as already noted, a greater number of ECT treatments was required by those having short or missed seizures at the maximum available stimulus intensity, and a greater number of ECT treatments has been associated with greater memory impairment (19, 20). Studies suggesting that the extent to which the stimulus exceeds the seizure threshold is a more important determinant of cognitive side effects than absolute stimulus intensity further support the safety of the use of stimulus intensities above present FDA limits in patients with relatively high seizure thresholds (5, 6). Finally, there is evidence that the stimulus intensity necessary to induce neuropathological changes far exceeds likely increases in maximum device output (29, 30).

In summary, this study provides further support for the suggestion that higher-output ECT devices would be clinically beneficial in the United States (12, 15). Future directions for research prompted by this study include an examination of whether greater cognitive impairment is associated with very high seizure thresholds and a determination of the extent to which the availability of supramaximal stimulus intensity increases therapeutic response and/or decreases the number of ECT treatments required.

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