Seizure threshold in electroconvulsive therapy (ECT): II. The anticonvulsant effect of ECT

C. Edward Coffey
Joseph Lucke
Richard D. Weiner
Andrew D. Krystal
Michael Aque

Available at: http://works.bepress.com/joseph_lucke/5/
Seizure Threshold in Electroconvulsive Therapy (ECT) II. The Anticonvulsant Effect of ECT

C. Edward Coffey, Joseph Lucke, Richard D. Weiner, Andrew D. Krystal, and Michael Aque

To measure the anticonvulsant effects of a course of electroconvulsive therapy (ECT), we used a flexible stimulus dosage titration procedure to estimate seizure threshold at the first and sixth ECT treatments in 62 patients with depression who were undergoing a course of brief pulse, constant current ECT given at moderately suprathreshold stimulus intensity. Seizure threshold increased by approximately 47% on average, but only 35 (56%) of the 62 patients showed a rise in seizure threshold. The rise in seizure threshold was associated with increasing age, but not with gender, stimulus electrode placement, or initial seizure threshold. Dynamic impedance decreased by approximately 5% from the first to the sixth ECT treatment, but there was no correlation between the change in dynamic impedance and the rise in seizure threshold. No relation was found between the rise in seizure threshold and either therapeutic response status or speed of response to the ECT treatment course. These findings confirm the anticonvulsant effect of ECT but suggest that such effects are not tightly coupled to the therapeutic efficacy of moderately suprathreshold ECT.

Key Words: ECT, seizure threshold, stimulus dosage titration

Introduction

Several lines of evidence suggest that electroconvulsive therapy (ECT) possesses anticonvulsant properties. In animals, electroconvulsive seizures raise the threshold for seizures induced either electrically or by certain pharmacologic agents (Green 1986; Kragh et al 1993; Post et al 1986). In humans, an ECT-induced seizure is immediately followed by a brief refractory period during which reapplication of the electrical stimulus often fails to elicit a seizure. In addition, a course of ECT induces a progressive shortening of seizure duration and a requirement for increasing electrical stimulus intensities to elicit seizures (Coffey et al 1990). ECT has also been used successfully to treat medication-resistant epilepsy (Sackeim et al 1983).

Only a few studies have directly measured the effects of a course of ECT on seizure threshold. The published findings suggest that patients vary widely in the extent to which seizure threshold may increase over a course of ECT (30–100% on average), depending in part upon stimulus electrode placement and the intensity of the electrical stimulus (Mukherjee 1989; Sackeim et al 1987b; Sackeim et al 1993). Of particular interest is a potential relation between the increase in seizure threshold and therapeutic response to ECT, suggesting that the anticonvulsant properties of ECT may be relevant to its...
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 62)</th>
<th>Right Unilateral ECT (n = 50)</th>
<th>Bilateral ECT (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>55.82 ± 16.15</td>
<td>57.74 ± 15.94</td>
<td>55.00 ± 16.25</td>
</tr>
<tr>
<td>DSM-III diagnosis, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression with melancholia</td>
<td>34 (54.83%)</td>
<td>18 (58.06%)</td>
<td>9 (47.37%)</td>
</tr>
<tr>
<td>Major depression without melancholia</td>
<td>11 (17.74%)</td>
<td>7 (22.58%)</td>
<td>2 (9.50%)</td>
</tr>
<tr>
<td>Bipolar disorder, depressed</td>
<td>11 (17.74%)</td>
<td>3 (9.68%)</td>
<td>6 (31.58%)</td>
</tr>
<tr>
<td>Bipolar disorder, mixed</td>
<td>6 (9.68%)</td>
<td>3 (9.68%)</td>
<td>2 (9.50%)</td>
</tr>
<tr>
<td>Pre-ECT MADRS score</td>
<td>30.32 ± 9.73</td>
<td>38.35 ± 7.72</td>
<td>23.50 ± 8.40</td>
</tr>
<tr>
<td>Seizure threshold at first ECT (mC)</td>
<td>55.00 ± 26.3</td>
<td>40.30 ± 14.8</td>
<td>72.00 ± 36.6</td>
</tr>
</tbody>
</table>

ECT indicates electroconvulsive therapy; MADRS indicates Montgomery–Asberg Depression Rating Scale; mC indicates millicoulombs; ± indicates mean ± standard deviation.

Significantly less than the other three groups (minimum absolute t = 3.47; df = 10; P < 0.006).

A two-way ANCOVA (electrode placement × gender) with age revealed significant main effects for electrode placement and gender. Initial seizure threshold was higher with bilateral than right unilateral ECT (F = 22.02; df = 1, 57; P < 0.0001), and in men than women (F = 29.38; df = 1, 57; P < 0.0001). There were no main effects of age, and no electrode placement × gender interaction.

The present investigation addresses these issues by focusing upon a clinical sample of carefully defined depressed patients consecutively referred for ECT who were not receiving medications known to affect seizure threshold. Seizure threshold was quantitated at the first and sixth ECT treatments with a flexible stimulus dosage titration procedure that permitted adjustment of initial stimulus intensity levels for patient factors known to affect seizure threshold (Coffey et al in press). A "moderately suprathreshold" stimulus dosage strategy (Coffey and Weiner 1990) was employed to ensure clinical efficacy and to limit cognitive side effects. As a test of the hypothesis that ECT works via an anticonvulsant mechanism, we examined potential relations between the increase in seizure threshold during ECT and therapeutic response to the course of therapy.

Method

Subjects

The sample consisted of 62 of the 111 patients included in our earlier study of initial seizure threshold in ECT (Coffey et al 1995). These 62 patients had undergone repeat stimulus dosage titration at the sixth ECT treatment to estimate seizure threshold, which was a standard component of the clinical ECT protocol. In the remaining 49 patients, stimulus dosage titration at the sixth ECT treatment was not accomplished either because they were involved in other research protocols (n = 14), they received less than six ECT treatments (n = 8, six of whom had responded and two who refused further treatments), or because their ECT administration varied from that described below (n = 27, usually due to changes in ECT technique (e.g., medications, ECT device, etc.) resulting from the exigencies of clinical practice; in no case was the decision not to titrate based upon the main outcome variables in this study, viz., stimulus dosage or therapeutic response). Finally, these 49 patients who were excluded from the study were similar to the 62 patients who were included in the study with regard to all variables listed in Table 1 (also see Coffey et al 1995), as well as with regard to therapeutic response status (78% responders vs. 73% respectively).

As previously reported, all subjects were patients at Duke University Medical Center with either DSM-III (American Psychiatric Association 1980) major depression (n = 45) or DSM-III (American Psychiatric Association 1980) bipolar disorder, depressed (n = 17). The DSM-III diagnoses were made with the use of a semistructured clinical neuropsychiatric interview and examination administered by the ECT Service clinicians, in consultation with the patients' ward treatment teams. Stated reasons for ECT referral included one or more of the following: inadequate improvement with pharmacothe-
apy (n = 57), intolerance of antidepressant medication side effects (n = 23), history of positive response to ECT (n = 21), and urgent need for rapid treatment response (n = 10). No patient had received ECT within the preceding six months.

Additional subject characteristics are presented in Table 1 for the entire sample and as a function of ECT treatment modality and gender. There were no differences between these groups with regard to age or frequency of diagnoses. A two-way ANOVA (electrode placement × gender) of group differences in baseline (pre-ECT) Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) scores revealed a significant gender × electrode placement interaction (F = 15.74; df = 1,58; P < 0.0002). Females who received bilateral ECT had significantly lower pre-ECT MADRS (Montgomery and Asberg 1979) scores than the other three groups (minimum absolute t = 3.47; df = 10; P < 0.006). As previously observed in the larger sample of 111 patients (Coffey et al. in press), initial seizure threshold in this subgroup of 62 patients was related to both electrode placement and gender (Table 1).

Many patients (n = 33) were taking medications for one or more of the following systemic conditions: hypertension or ischemic heart disease (n = 14), peptic ulcer or gastroesophageal reflux (n = 9), hypothyroidism (n = 8), arthritis (n = 6), infection (n = 4), estrogen deficiency (n = 3), diabetes mellitus (insulin, n = 1), glaucoma (n = 1), migraine headaches (n = 1), breast cancer (n = 1), and Meniere’s disease (n = 1). In general, the doses of these medications were optimized before ECT treatment and then held constant throughout the ECT treatment course. No patient was taking any systemic medications known to affect seizure threshold or duration (e.g., anti-epileptics (including benzodiazepines), beta blockers, theophylline, or methylphenidate).

**ECT Treatment Technique**

All patients were free of psychotropic medications at the time of the first ECT treatment, with the exception of as-needed doses of neuroleptics (mellaril, n = 5; haloperidol, n = 1; thiothixene hydrochloride, n = 1; loxapine hydrochloride, n = 1) for the control of severe agitation or psychosis, and chloral hydrate at bedtime for severe insomnia (n = 3). The median duration of the psychotropic drug-free interval was 12.8 days (range 3–100 days) for antidepressant preparations (n = 4), 21.4 days (range 6–60 days) for monoamine oxidase inhibitors (n = 9), 13.2 days (range 3–60 days) for lithium (n = 17), and 5.6 days (range 1–13 days) for benzodiazepines (n = 38). In addition, no subject had received any benzodiazepine with a half-life greater than 12 hours for at least 5 days before the first treatment.

The ECT treatment technique was similar for each patient. The treatments were administered three mornings a week, on Monday, Wednesday, and Friday (except for holidays). No patient missed more than one scheduled treatment. Typical modifications included anticholinergic premedication (glycopyrrolate, n = 33; or atropine sulfate, n = 3), anesthesia (methohexital sodium, 1 mg/kg intravenously), and muscle relaxation (succinylcholine chloride, 1 mg/kg intravenously) (Coffey and Weiner 1990). For some patients, the doses of the latter two medications were titrated at subsequent treatment sessions as a function of anesthetic and muscle relaxant response, respectively (titrated mean ± SD dose per ECT treatment: methohexital sodium = 68.7 mg ± 16.2; succinylcholine chloride = 79.8 mg ± 20.7). Patients received 100% oxygen via mask as the anesthetic was administered, and once apneic their respirations were held constant at 20–25 breaths per minute with positive pressure ventilation by bag until spontaneous respirations returned. All patients were monitored with electrocardiography and two-channel (bilateral frontotemporal) electroencephalography (EEG).

Choice of electrode placement was determined by the patient’s attending physician and clinical treatment team, in consultation with the ECT Service. The standard bifrontal electrode placements were employed for bilateral ECT (n = 12) and right unilateral ECT (n = 50), respectively. At the request of their clinical treatment team, 11 (22%) of the 50 patients who began on right unilateral ECT were switched during their course of treatments to bilateral ECT because of poor therapeutic response. These patients received an average (± SD) of 7.9 (±2.07) right unilateral ECT treatments before the switch to bilateral electrode placement, and no patient was switched until after at least the sixth ECT treatment (i.e., the treatment at which the change in seizure threshold was estimated—see below). The patient’s skin/scalp at the stimulus electrode contact sites was scrubbed gently with an abrasive gel (Omni Prep, D.O. Weaver & Co., Aurora, CO) and then rinsed with normal saline. A thin film of electrode jelly (Spectra 360, Parker Laboratories, Orange, NJ) was applied to the 5.0-cm stainless steel stimulus electrodes, which were then held in place on the patient’s head with an adjustable rubber headband. For bilateral ECT, the stimulus electrodes were flat; for right unilateral ECT, the high centroparietal electrode was concave and held in place with a handle. The ECT stimulus was administered by a brief-pulse ECT device (MECTA SRI, MECTA Corp, Lake Oswego, OR). The total number of ECT treatments administered in the course was determined by the patient’s ward treatment team, and was based
Table 2. ECT Stimulus Dosage Titration Protocol

<table>
<thead>
<tr>
<th>Stimulus Dosage Level</th>
<th>Mecta SRI Settings</th>
<th>Pulse Width (sec)</th>
<th>Frequency (sec⁻¹)</th>
<th>Duration (sec)</th>
<th>Current (amp)</th>
<th>Charge (mc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Right unilateral ECT, female</td>
<td>1.0</td>
<td>40</td>
<td>0.5</td>
<td>0.8</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>2 Right unilateral ECT, male; or bilateral ECT, female</td>
<td>1.0</td>
<td>40</td>
<td>0.75</td>
<td>0.8</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>3 Bilateral ECT, male</td>
<td>1.0</td>
<td>40</td>
<td>1.25</td>
<td>0.8</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>40</td>
<td>2.0</td>
<td>0.8</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>60</td>
<td>2.0</td>
<td>0.8</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>90</td>
<td>2.0</td>
<td>0.8</td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.4</td>
<td>90</td>
<td>2.0</td>
<td>0.8</td>
<td>403</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>90</td>
<td>2.0</td>
<td>0.8</td>
<td>576</td>
<td></td>
</tr>
</tbody>
</table>

*ECT indicates electroconvulsive therapy; sec indicates seconds; amp indicates amperage; mc indicates milli-coulombs.

Charge was calculated as the product of pulse width × frequency (2) × train duration × current. The increment between stimulus dosage levels is approximately 50%.

on therapeutic response and extent of cognitive side effects.

Seizure duration was determined retrospectively from two-channel EEG by a single rater (ADK) from our laboratory with established reliabilities (Krystal et al 1993) who was blind to ECT treatment number and all seizure threshold data. The presence and duration of convulsive (motor) activity was also monitored in the cuffed right ankle by the ECT team psychiatrist.

DETERMINATION OF SEIZURE THRESHOLD. ECT seizure threshold was estimated at the first and sixth ECT treatments with use of a modification of the stimulus dosing titration procedure described by Sackeim et al (1987b). These modifications were based upon empirical trials in our laboratory and included a lower starting titration dosage (32 mc vs. 48 mc), adjustment of starting titration dosage for electrode placement and gender (vs. using the same starting dosage for all patients), smaller increments between dosing steps (50% vs. 75-100%), and initial adjustment of pulse train duration (rather than pulse frequency) to set stimulus dosage (Table 2).

At the first ECT treatment, a starting stimulus dosage was selected that was assumed to be below seizure threshold, based upon stimulus electrode placement (seizure threshold is lower for unilateral than bilateral) and the patient’s gender (seizure threshold is lower in women than men) (Table 2) (Coffey et al in press). By adjusting the starting titration stimulus dosage for stimulus electrode placement and gender, we hoped to avoid exposing patients to multiple subconvulsive ECT stimuli and their potentially harmful cardiovascular effects. This adjustment was also expected to produce a roughly equivalent number of stimulations across groups, thereby limiting the potential confounding effects of subconvulsive stimuli on determinations of initial seizure threshold (Swartz 1990). If the starting stimulus dose failed to elicit a seizure of at least 25 seconds duration by standard EEG criteria (Weiner et al 1991), stimulus charge was increased by approximately 50% (one level in Table 2) and the patient restimulated. No additional anesthetic or muscle relaxant medications were given after the initial bolus. Seizure threshold was defined as the stimulus dosage that elicited an EEG seizure of at least 25 seconds duration. (This definition is an overestimate, since the “true” seizure threshold could be between the defining dosage level and the next lower level.) In all patients, such a seizure was observed by the fourth stimulation (median number of stimulations at the first ECT treatment = 1.0). None of the patients who received subconvulsive stimuli (n = 21) experienced any complications (including cardiac bradyarrhythmias) requiring medical intervention (Decina et al 1984; Welch et al 1989; Wells et al 1988; Zielenski et al 1993).

STIMULUS DOSAGE. For the second and subsequent ECT treatments, stimulus dosage was set at a fixed percentage above the initial seizure threshold established at the first ECT treatment, since the efficacy of ECT may be markedly diminished when it is given at barely suprathreshold stimulus dosages (Sackeim et al 1993). Because this dependence of treatment efficacy on stimulus dosage appears to be more critical for right unilateral ECT than for bilateral ECT (Sackeim et al 1993), stimulus settings were increased to approximately 2.25 times initial seizure threshold (i.e., two levels above threshold level in Table 2) for patients who received right unilateral ECT, and to approximately 1.5 times initial seizure threshold (i.e., one level above threshold level in Table 2) for those who received bilateral ECT. These “moderately suprathreshold” stimulus dosage levels were chosen empirically in an effort to strike a balance between ensuring efficacy and limiting the adverse cognitive side effects that may accompany ECT given at maximally suprathreshold stimulus
Effect of ECT on Seizure Threshold

To examine the extent to which seizure threshold may rise during a course of ECT, the stimulus dosage titration procedure was repeated at the sixth ECT. The sixth ECT treatment was chosen for retitration rather than the final ECT treatment because it is not always possible to identify in advance which treatment will in fact be the patient’s final treatment, and because most patients receive at least six treatments. Furthermore, obtaining information regarding changes in seizure threshold during (rather than at the end of) a course of ECT would provide the practitioner with information necessary to make an informed decision about adjustments in stimulus dosage for the remainder of the course of therapy (assuming that stimulus dosage should exceed seizure threshold by a minimum amount). This titration procedure was similar to that described for the first ECT treatment, except that the titration began with the stimulus dosage that defined the initial seizure threshold at the first ECT treatment. With this modification the patients were not exposed to an excessive number of stimulations that had been subconvulsive at the first ECT treatment. As with the first ECT treatment, stimulus charge was increased when necessary by approximately 50% (one level in Table 2) until the patient has a 25-second EEG seizure. In all patients, such a seizure was observed by the fourth stimulation (median number of stimulations = 2.0).

Stimulus charge was calculated from the stimulus parameters using the formula: charge = 800 mA × pulse width × 2 × pulse frequency × stimulus duration. Stimulus (dynamic) energy (in joules) and dynamic impedance were both calculated from the readings provided on the chart recorder.

Assessment of Therapeutic Response

Therapeutic response was assessed with the seven-point Clinical Global Impression (CGI) severity scale (Guy 1976), the MADRS (Montgomery and Asberg 1979), and the Carroll Self-Rating Depression Scale (CSRDS) (Carroll et al. 1981). These scales were administered by the patient’s ward treatment team at 2–3 days before ECT, weekly during the course of treatment, and at 2–3 days after the final treatment. Although data regarding ECT stimulus settings were recorded on the ECT treatment record sheet, the ward treatment team was unaware of the patient’s seizure threshold since there was no indication on this sheet that any stimulus settings defined a seizure threshold. Furthermore, information regarding ECT stimulus settings was not routinely perused by the patients’ ward treatment teams and thus did not enter into decisions regarding clinical response.

Patients were defined as ECT responders if they achieved a score of 3 (mildly ill) or less on the CGI severity scale completed 2 to 3 days after the final treatment. This CGI determination was supplemented by assessments of symptom severity (i.e., the MADRS and CSRDS scores) in order to provide measures of concurrent validity.

Statistical Analysis

As previously discussed (Coffey et al, 1995), seizure threshold data were log transformed. Relationships among discrete variables were assessed by log linear analyses. Relationships between a discrete variable and a set of predictor variables were analyzed by logistic regression. Relationships between a continuous outcome variable and a set of predictor variables were analyzed by regression, analysis of variance (ANOVA), or analysis of covariance (ANCOVA) as appropriate.

Results

Effect of ECT on Seizure Threshold

A two-way ANCOVA was conducted to assess the effects of electrode placement, gender, and age (all predictors of initial ECT seizure threshold) on the difference in seizure threshold (in units of charge) between the first and the sixth ECT treatments. For the entire sample, seizure threshold increased by approximately 47% on average (F = 64.28; df = 1,57; P < 0.0001) (Table 3). There were no main effects of electrode placement or gender, i.e., the percentage increases in seizure threshold were comparable with right unilateral ECT (48.2 ± 52.9%, mean ± SD) and bilateral ECT (39.2 ± 50.4%), and in women (50.1% ± 53.3%) and men (40.4 ± 50.7%). There was no gender × electrode placement interaction. The ANCOVA did reveal however, a relationship between age and the difference in seizure threshold (F = 6.59; df = 1.57; P < 0.01). Increasing age was associated with a greater increase in seizure threshold from the first to the sixth ECT treatment (r = 0.32) (Figure 1).

Only 35 (56%) of the 62 patients showed an increase in seizure threshold however (Table 3), and for this subgroup the mean ± SD change in charge was 82.3 ± 43.0%. The proportion of patients that showed an increase in seizure threshold was similar with right unilateral ECT (50%) and bilateral ECT (50%), and in women (62%) and men (48%). There was no electrode placement × gender
Table 3. Effects of ECT on Seizure Threshold and Dynamic Impedance

<table>
<thead>
<tr>
<th></th>
<th>Right Unilateral ECT (n = 50)</th>
<th>Bilateral ECT (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n = 31)</td>
<td>Male (n = 19)</td>
</tr>
<tr>
<td>Seizure threshold (mc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First ECT treatment</td>
<td>66.5 ± 26.3</td>
<td>40.3 ± 14.8</td>
</tr>
<tr>
<td>Sixth ECT treatment</td>
<td>81.5 ± 51.4</td>
<td>63.0 ± 39.6</td>
</tr>
<tr>
<td>Difference (6 - 1)</td>
<td>26.6 ± 34.0</td>
<td>22.7 ± 28.3</td>
</tr>
<tr>
<td>Percent difference</td>
<td>45.6 ± 52.9</td>
<td>49.7 ± 53.7</td>
</tr>
<tr>
<td>Increase in seizure threshold</td>
<td>35 (56%)</td>
<td>19 (61%)</td>
</tr>
<tr>
<td>Dynamic impedance (ohms)</td>
<td>208.79 ± 38.68</td>
<td>239.54 ± 33.08</td>
</tr>
<tr>
<td>First ECT treatment</td>
<td>205.87 ± 34.97</td>
<td>225.67 ± 28.11</td>
</tr>
<tr>
<td>Sixth ECT treatment</td>
<td>-12.92 ± 28.05</td>
<td>-12.87 ± 32.55</td>
</tr>
<tr>
<td>Difference (6 - 1)</td>
<td>-5.21 ± 12.21</td>
<td>-4.43 ± 12.64</td>
</tr>
<tr>
<td>Percent difference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ECT indicates electroconvulsive therapy; mc = milli-coulombs; ± indicates mean ± standard deviation.

1Seizure threshold increased significantly from the first to the sixth ECT treatment (F = 64.28; df = 1, 57; P < 0.0001). There were no main effects of electrode placement or gender, and there was no electrode placement × gender interaction. Age however, was significantly related to the difference in seizure threshold (F = 6.59; df = 1, 57; P < 0.011.

'There were no group differences in the proportion of patients who exhibited an increase in seizure threshold from the first to the sixth ECT treatment.

Dynamic impedance decreased significantly from the first to the sixth ECT treatment (F = 13.38; df = 1, 57; P < 0.0006). There were no main effects of electrode placement, gender, or age. Similar to the findings above, increasing age was associated with a greater likelihood of an increase in seizure threshold (Wald χ² = 8.78; df = 1; P < 0.003).

This analysis demonstrated that the 35 patients who showed an increase in seizure threshold at the sixth ECT treatment were older (61.9 ± 13.7 years) than the 27 patients who exhibited no change (48.2 ± 16.1 years). However, among the 35 patients who showed an increase in seizure threshold, there were no correlation between age and the magnitude of increase in seizure threshold.

There was no correlation between the difference in seizure threshold (from first to sixth ECT treatment) and initial seizure threshold, either before or after adjusting for the effects of age.

**Effect of ECT on Dynamic Impedance**

A two-way ANCOVA was also conducted to assess the effects of electrode placement, gender, and age on the difference in dynamic impedance (Table 3) between the first and the sixth ECT treatments. For the entire sample, dynamic impedance decreased by approximately 5.2% on average (F = 13.38; df = 1, 57; P < 0.0006). There were no main effects of electrode placement, gender, or age. The percentage decreases were comparable for right unilateral (5.0% ± 12.97%) and bilateral ECT (6.25% ± 8.69), and for women (5.40% ± 11.73) and men (4.89% ± 13.24). There was no gender × electrode placement interaction.

For the entire sample, significant negative correlations were observed between seizure threshold and dynamic impedance, both at the first ECT treatment (r = -0.47; P < 0.0001) and at the sixth ECT treatment (r = -0.40; P < 0.0001). At both time points, patients with higher seizure thresholds had relatively lower dynamic impedances. There was no correlation, however, between the change in seizure threshold (first to sixth ECT) and the change in dynamic impedance.

**Seizure Threshold and Therapeutic Response to ECT**

The criterion for response to ECT (CGI severity rating of "mildly ill" or less at 2–3 days after the final ECT treatment) was obtained in 45 (73%) of the 62 patients (Table 4). The responders and nonresponders were similar with regard to age, gender, number of ECT treatments, stimulus electrode placement, and average EEG seizure duration over the ECT treatment course (Table 4).

A logistic regression analysis revealed no relationship between responder status (responder vs. nonresponder) and either initial (first ECT) seizure threshold or the difference in seizure threshold from the first to the sixth ECT treatment (Table 4). This absence of any relationship also held when a simultaneous logistic regression analysis controlled for the contributions of several potential covariates including age, gender, number of ECT treatments, right unilateral vs. bilateral electrode placement, whether the patient was switched from right unilateral to bilateral electrode placement, and average EEG seizure duration (Table 4). In addition, the proportion of patients who actually exhibited an increase in seizure threshold from the
first to the sixth ECT treatment was similar among responders (55.6%) and nonresponders (58.8%) (Table 4).

The therapeutic response status observed in our sample was associated with parallel reductions (77% on average from baseline) in the MADRS scores (Table 4). No correlation was found between the difference (baseline minus final) in MADRS scores and either initial ECT seizure threshold or the difference in seizure threshold from the first to the sixth treatment. This absence of a relation also obtained when a simultaneous regression analysis controlled for the potential effects of age, gender, number of ECT treatments, right unilateral vs. bilateral electrode placement, switching from right unilateral to bilateral electrode placement, and average EEG seizure duration (Table 4).

Speed of response among the 45 responders was measured as the number of days from the first ECT treatment to the assessment interval at which the patient first achieved a CGI severity rating of “mildly ill” or less. Patients who responded to ECT were classified as fast responders (14 days or less to reach this criterion; n = 24) or slow responders (15 days or greater to reach this criterion; n = 21). A logistic regression analysis revealed no relation between fast vs. slow responder status and either initial ECT seizure threshold or difference in seizure threshold from the first to the sixth ECT treatment. Again, this negative finding also pertained when a simultaneous logistic regression controlled for the potential effects of age, gender, number of ECT treatments, right unilateral vs. bilateral electrode placement, switching from right unilateral to bilateral electrode placement, and average EEG seizure duration.

A separate analysis was also performed on the 50 patients who initially received right unilateral ECT. This sample was dichotomized into those patients who were eventually switched from right unilateral to bilateral electrode placement (n = 11) and those who were not (n = 39), to examine whether initial nonresponse to right unilateral ECT (i.e., those who were eventually switched) was related to the change in seizure threshold. A simultaneous logistic regression analysis (controlling for the effects of age) revealed no relation between “switch” status and the difference in seizure threshold from the first to the sixth ECT treatment. The percentage increase in seizure threshold over the first six ECT treatments was similar for the patients who were
Table 4. Seizure Threshold and Therapeutic Response to ECT

<table>
<thead>
<tr>
<th></th>
<th>Total Sample (n = 62)</th>
<th>Responders (n = 45)</th>
<th>Non-Responders (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure threshold (mc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First ECT treatment</td>
<td>54.97 ± 26.33</td>
<td>54.40 ± 24.93</td>
<td>56.47 ± 30.52</td>
</tr>
<tr>
<td>Sixth ECT treatment</td>
<td>81.54 ± 51.39</td>
<td>80.00 ± 51.84</td>
<td>85.64 ± 51.52</td>
</tr>
<tr>
<td>Difference (6 - 1)</td>
<td>26.58 ± 34.03</td>
<td>25.60 ± 34.01</td>
<td>29.18 ± 34.98</td>
</tr>
<tr>
<td>% Difference</td>
<td>46.47 ± 52.18</td>
<td>44.26 ± 50.33</td>
<td>52.35 ± 58.01</td>
</tr>
<tr>
<td>Number (%) of patients with increase</td>
<td>35 (56.5%)</td>
<td>25 (55.6%)</td>
<td>10 (58.8%)</td>
</tr>
</tbody>
</table>

Montgomery-Asberg Depression Rating Scale

<table>
<thead>
<tr>
<th></th>
<th>Total Sample (n = 62)</th>
<th>Responders (n = 45)</th>
<th>Non-Responders (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score</td>
<td>36.32 ± 9.72</td>
<td>36.95 ± 10.32</td>
<td>34.65 ± 7.96</td>
</tr>
<tr>
<td>Final score</td>
<td>10.43 ± 7.52</td>
<td>8.53 ± 5.64</td>
<td>15.47 ± 9.56</td>
</tr>
<tr>
<td>Difference (baseline—final)</td>
<td>25.88 ± 11.20</td>
<td>28.42 ± 10.29</td>
<td>19.18 ± 11.04</td>
</tr>
<tr>
<td>% Difference</td>
<td>70.14 ± 22.20</td>
<td>76.68 ± 15.58</td>
<td>52.81 ± 27.80</td>
</tr>
<tr>
<td>Age, yr</td>
<td>55.82 ± 16.15</td>
<td>55.15 ± 17.38</td>
<td>57.58 ± 12.59</td>
</tr>
<tr>
<td>Gender, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>39 (63%)</td>
<td>29 (64.4%)</td>
<td>10 (58.8%)</td>
</tr>
<tr>
<td>Male</td>
<td>23 (37%)</td>
<td>16 (35.6%)</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>Number of ECTs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUL only</td>
<td>8.90 ± 2.14</td>
<td>9.07 ± 2.71</td>
<td>8.45 ± 2.34</td>
</tr>
<tr>
<td>n = 39 (62.9%)</td>
<td>n = 28 (62.2%)</td>
<td>n = 11 (64.7%)</td>
<td></td>
</tr>
<tr>
<td>BL only</td>
<td>8.50 ± 2.15</td>
<td>8.50 ± 2.27</td>
<td>8.5 ± 2.12</td>
</tr>
<tr>
<td>n = 12 (19.4%)</td>
<td>n = 10 (22.2%)</td>
<td>n = 2 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Switch RUL → BL</td>
<td>13.09 ± 1.97</td>
<td>13.14 ± 1.86</td>
<td>13.0 ± 4.45</td>
</tr>
<tr>
<td>n = 11 (17.7%)</td>
<td>n = 7 (15.6%)</td>
<td>n = 4 (23.5%)</td>
<td></td>
</tr>
<tr>
<td>EEG seizure duration (sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per treatment</td>
<td>73.99 ± 23.32</td>
<td>75.22 ± 25.62</td>
<td>70.74 ± 15.92</td>
</tr>
<tr>
<td>Cumulative</td>
<td>690.56 ± 224.07</td>
<td>703.71 ± 238.35</td>
<td>655.76 ± 82.78</td>
</tr>
</tbody>
</table>

ECT indicates electroconvulsive therapy; mc = milli coulombs; ± indicates mean ± standard deviation.

"ECT indicates an increase in seizure threshold of 44% after six/seven ECT treatments in a research sample of patients with depression. Our close replication of these original observations, in a clinical sample of depressed patients and with the use of different stimulus dosing and titration schema, provides strong and direct support for the anticonvulsant properties of ECT in humans.

Our estimates of the magnitude of increase in seizure threshold during a course of ECT are limited by technical considerations inherent in any stimulus dosage titration procedure. First, estimates of seizure threshold may vary depending upon the particular parameters of the electrical stimulus used to elicit the seizure. For example, Swartz and Larsen (1989) reported that by simply changing the duration of the pulse train they could alter the likelihood of seizure elicitation in response to a fixed stimulus charge. Still, the close agreement between our findings and those of Sackeim et al (1987a; b) suggests a general applicability of results despite differences between these studies in the configuration of stimulus parameters used to estimate the change in seizure threshold during ECT.

Second, our estimates of the magnitude of increase in seizure threshold are limited by possible "floor effects" associated with a stepwise stimulus dosage titration protocol and adjustment of starting stimulus dosage for electrode placement and gender. As discussed previously, when an ECT seizure is elicited at a particular...
our dosing paradigm had other distinct methodologic advantages. These advantages included the clinically desirable minimization of restimulation and an equalization of subconvulsive stimuli across electrode placement and gender conditions (Coffey et al 1995). This design variation thus permitted a comparison of such "equalized" data titration dose for all patients (e.g., Sackeim et al 1987b; Sackeim et al 1993). The fact that our findings regarding the rise in seizure threshold were strikingly similar to the observations of these other investigations suggests that determination of rise in seizure threshold is not impacted significantly by number of restimations or exposure to subconvulsive stimuli, an observation that is, in itself, of considerable conceptual and clinical importance.

Third, while we measured the rise in seizure threshold at the sixth ECT treatment, seizure threshold may increase still further with additional treatments. In this regard, Sackeim and colleagues have observed cumulative increases in seizure threshold of approximately 65% on average after completed courses of ECT in patients with depression (Sackeim et al 1987b; 1993) or mania (Mukherjee 1989).

Finally, our results apply only to brief-pulse, constant-current forms of ECT administration, since no study has directly measured changes in seizure threshold during constant-voltage forms of ECT.

Predicting the Increase in Seizure Threshold during ECT

We examined potential relations between the increase in seizure threshold observed during ECT and variables previously found to be predictive of initial seizure threshold, viz, age, gender, and electrode placement. We found that age, but not gender or electrode placement, was related to the cumulative increase in seizure threshold observed during ECT. Our analysis also indicated however, that the majority of the variance in the increase in seizure threshold during ECT remains unaccounted for.

Increasing age was associated with a greater increase in seizure threshold during ECT, as well as a greater likelihood that seizure threshold would rise during the course of treatments. We are not aware of any published studies that have directly examined the impact of age on the anticonvulsant effects of ECT. One possible explanation for our finding is that our titration protocol was more likely to detect changes in seizure threshold during ECT in older patients, since these patients generally had initial seizure thresholds that were above the starting dosage in the stimulus titration protocol and were thus less susceptible to its "floor effects" as discussed above. As such, it is less likely that initial seizure threshold was substantially overestimated in older patients, and thereby more likely that an increase in seizure threshold could have been detected. In support of this hypothesis, no relation was found between age and rise in seizure threshold among patients whose initial seizure thresholds were not overestimated to this extent (i.e., those who received at least one subconvulsive stimulation at the first ECT treatment). A second possible explanation for the relation between age and rise in seizure threshold during ECT is that such threshold increases may be greater in patients who have higher initial seizure thresholds (as noted above, increasing age is associated with higher initial seizure thresholds). However, we found no correlation between initial seizure threshold and the difference in seizure threshold from the first to the sixth ECT treatment.

As noted above, no relation was observed in the present study between gender and the increase in seizure threshold during ECT. Although it is clear that our investigation of gender effects was confounded by adjustment of the starting titration dosage for gender, similar negative findings with regard to gender were also noted by Sackeim et al (1987b) who used the same starting titration dosage for all patients. Thus, although gender is predictive of initial
ECT seizure threshold (Coffey et al 1995; McCall et al 1993, Sackeim et al 1987b), it does not appear to affect the increase in seizure threshold during ECT, regardless of whether barely (Sackeim et al 1987b) or moderately (current study) suprathreshold stimulus dosing strategies are employed. These data suggest that the neurobiologic mechanisms (e.g., possible gender-related differences in neural excitability) which interact with gender to determine initial ECT seizure threshold do not modify the cumulative anticonvulsant effects of the treatment.

A more complex relation appears to exist between stimulus electrode placement and the cumulative anticonvulsant effects of ECT. In the present study, which employed moderately suprathreshold stimulus dosing, the rise in seizure threshold observed at the sixth ECT treatment was similar for bilateral (39% on average) and right unilateral (48% on average) electrode placement. Again, investigation of such effects was confounded in our study by adjustment of starting titration dosage for electrode placement. Nevertheless, Sackeim et al (1993) also observed similar increases in seizure threshold over an entire course of bilateral (59% on average) and right unilateral (54% on average) ECT when stimulus dosage was at 2.5-times initial seizure threshold. However, for a course of ECT given at barely suprathreshold stimulus dosages, they observed a greater increase in seizure threshold for bilateral electrode placement (87–96% on average) than for right unilateral electrode placement (27–40% on average) (Sackeim et al 1987b; Sackeim et al 1993). Taken together, these data suggest that stimulus electrode placement and stimulus dosage may interact to modify the cumulative anticonvulsant effects of ECT. It appears that a course of ECT given with at least moderately suprathreshold stimulus intensity will produce an equivalent cumulative increase in seizure threshold with bilateral or right unilateral electrode placement, whereas a course of treatment given at barely suprathreshold stimulus intensity will yield a greater cumulative increase in seizure threshold with bilateral than with right unilateral electrode placement. Whether such differences pertain to the differential therapeutic efficacy of “low dose” bilateral and right unilateral ECT remains to be determined.

We do not fully understand the process by which stimulus electrode placement and stimulus dosage might interact to influence the cumulative anticonvulsant effects of ECT. Recent EEG (Krystal et al 1993; Nobler et al 1993a) and regional cerebral blood flow studies (Nobler et al 1993b) indicate that ECT seizures induced with bilateral electrode placement or moderately suprathreshold stimulus dosage result in a greater physiologic response in the brain than do ECT seizures induced with right unilateral electrode placement or barely suprathreshold stimulus dosage. One may speculate that these more physiologically “intense” seizures produce a greater activation of the brain’s endogenous anticonvulsant mechanisms, perhaps as a result of enhancement of GABAergic (Green et al 1982, 1986; Sackeim et al 1983) or endogenous opiate (Holaday et al 1986; Tortella et al 1989) neurotransmission, which in turn could lead to a progressive rise in seizure threshold. Consistent with this speculation are preliminary data suggesting greater postictal EEG suppression (“intensity” or generalization, and whether such measures could discriminate among seizures induced by differing stimulus electrode placements or stimulus dosages.

We found that dynamic impedance decreased significantly over the ECT treatment course. To the best of our knowledge, this is the first report of such a relation. The relatively small decline in dynamic impedance observed during the course of ECT may reflect electrochemical changes at the stimulus electrode—scalp interface (Sackeim et al 1994), including for example, a progressive alteration of the skin’s resistive components, as well as the response of the resistive components to the increasing stimulus dosages used over the course of the treatments (i.e., the act of passing current produces a change in the resistance of the circuit, hence “dynamic” impedance).

**Relations between ECT Seizure Threshold and the Therapeutic Effects of ECT**

**INITIAL SEIZURE THRESHOLD.** We found no relation between initial seizure threshold and any measure of therapeutic response, including final responder status, change in severity of depressive symptoms, the speed of antidepressant response (for responders), or a need to switch some patients from right unilateral ECT to bilateral ECT. Sackeim et al (1987a) observed a correlation between initial seizure threshold—the therapeutic response relations, the small number of patients receiving bilateral ECT in our study ($n = 12$) may have produced insufficient power to resolve such an effect. On the other hand, it may be that relations between clinical response and initial seizure threshold such as observed by Sackeim et al (1987a) pertain only under conditions of low (i.e., barely suprathreshold) stimulus intensity and thus are not seen with ECT given at higher stimulus dosages. To resolve this issue, studies with larger numbers of subjects are needed.
that examine initial seizure threshold—efficacy relations under conditions of varying ECT stimulus intensity.

**THE ANTICONVULSANT EFFECT OF ECT.** We found no relation between the therapeutic response to either right unilateral or bilateral ECT and the frequency or extent of increase in seizure threshold observed at the sixth ECT treatment. These data suggest that the efficacy of ECT given at moderately suprathreshold stimulus intensity is unrelated to the cumulative anticonvulsant properties of the treatment. Mukherjee (1989) administered moderately suprathreshold ECT to 22 patients with mania and also observed significant increases in seizure threshold over the treatment course for both responders and nonresponders. Although the increase in seizure threshold was equivalent (about 39%) for responders and nonresponders to right unilateral ECT, responders to bilateral ECT had a greater mean increase in seizure threshold (about 125%) than nonresponders (about 34%). In a study of low-dose (barely suprathreshold) ECT given to 52 patients with depression, Sackeim et al (1987a) observed equivalent cumulative increases in seizure threshold (averaging 87%) among responders and nonresponders to bilateral ECT. In contrast, the absence of a significant increase in seizure threshold was associated with nonresponse to right unilateral ECT.

Taken together, these studies suggest that a robust increase in seizure threshold during ECT may be a necessary, but not a sufficient, condition for the therapeutic effects of the treatment in some patients. Forms of ECT that are clinically ineffective (e.g., low-dose right unilateral ECT) appear to be relatively weak anticonvulsants (Krystal et al 1993; Nobler et al 1993a; 1993b), yet some patients appear to respond to forms of ECT that produce relatively little cumulative increase in seizure threshold. Still other patients may fail to respond to forms of ECT that are powerful anticonvulsants (e.g., moderate or high-dose bilateral ECT). More research is needed to investigate the potential implications of these observations for the pathophysiology of mood disorders (Sackeim et al 1991).

The cumulative increase in seizure threshold during ECT may also have practical implications for the clinician. A progressive increase in seizure threshold will lessen the degree to which a fixed stimulus dosage exceeds seizure threshold and thus result in a greater probability of brief or missed seizures, as well as the possibility of diminished efficacy (assuming that in some patients therapeutic potency may depend on the stimulus dose relative to seizure threshold). As such, the ECT practitioner may need to make upward adjustments in stimulus dosage during the treatment course (APA Task Force 1990), or as was done in the present study, remeasure seizure threshold after a standard number of treatments and adjust stimulus dosage accordingly. In our clinical practice we often employ this latter procedure in initial ECT nonresponders, so that objective information can be used to ensure maximally effective stimulus dosing for any subsequent treatments. Research is currently underway by our group to assess the clinical utility of such approaches, and their implications for the mechanism of action for ECT.

---

Supported in part by a grant (Dr. Coffey) from the Allegheny Singer Research Institute, Pittsburgh, PA.


---

**References**


