Does ECT Permanently Alter Seizure Threshold?

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Recent research has raised the possibility that electroconvulsive therapy (ECT) results in a persistent elevation of seizure threshold among males. In this study, seizure threshold, quantified by the method of limits procedure, was assessed at the first and last treatments of 148 consecutive depressed patients. Patients with and without a prior history of ECT did not differ in seizure threshold at the first treatment, seizure duration at the first treatment or averaged across all treatments, or in the magnitude of the seizure threshold increase over the ECT course. No evidence was obtained that history of ECT was associated with alterations of seizure threshold or seizure duration.

Key Words: Electroconvulsive therapy, seizure threshold, kindling, electroencephalography, epilepsy

Introduction

When the phenomenon of kindled seizures in animals was first reported, concern was expressed that electroconvulsive therapy (ECT) may result in kindling, producing a persistent decrease of seizure threshold and creating a vulnerability for the later development of seizure disorder (Goddard 1967). For the most part, epidemiological studies of the frequency of spontaneous seizures and related electroencephalographic (EEG) phenomena in former ECT patients have not supported this possibility (Blackwood et al 1980; Small et al 1981; Devinsky and Duchowny 1983). Indeed, there is considerable evidence that, in the short-term, ECT has pronounced anticonvulsant effects (Sackeim et al 1983). During the ECT course, seizure threshold increases and seizure duration decreases (Sackeim et al 1987a). In animals, electroconvulsive shock (ECS) has powerful anticonvulsant effects in blocking the development or aborting the expression of amygdala-kindled seizures (Post et al 1986).

In contrast, Tomasson et al (1992) recently suggested that a prior history of ECT is associated with a persistent increase in seizure threshold. In a naturalistic, retrospective study, they reported that in men (n = 114), but not women (n = 220), history of ECT was associated with an increased frequency of subconvulsive stimulations (missed seizures) and brief or inadequate seizures, when averaging these events over a total ECT course. Patients were treated with brief pulse, constant current stimulation, with stimulus intensity varying between 144 and 336 mC. The majority of patients received bilateral ECT, presented with major depressive disorder, and received various psychotropic medication regimens during the ECT course. The finding that history of previous ECT was associated with missed and brief seizures only in men was attributed to the use of a relatively high initial stimulus intensity and the fact that seizure threshold is known to be higher among men compared to women (Sackeim et al 1987b). However, Tomasson et al's interpretation that this pattern reflected a persistent impact of previous ECT on seizure threshold was necessarily indirect, as they did not quantify the seizure thresholds of their patients. Here we report on the

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relations of history of prior ECT to seizure threshold, quantified in the first treatment of 148 consecutive depressed patients, as well as relations to motor and EEG seizure duration and to the magnitude of the increase in seizure threshold over the ECT course.

Methods

The sample comprised 148 patients who met the research diagnostic criteria (RDC) for major depressive disorder on the basis of the Schedule for the Assessment of Depressive Symptoms (SADS) interviews. Patients had participated in one of two consecutive ECT research protocols and inclusion/exclusion criteria are described elsewhere (Sackeim et al 1987b; Sackeim et al 1991). An exclusion criterion required that patients not have received ECT within the previous 6 months. The average age of the sample was 58.1 years (SD = 14.3), 62.8% were women, 26.4% met the RDC for bipolar depression, and 42.2% met the RDC for psychotic depression.

Sixty-six patients (44.6%) had a history of prior ECT. The groups with and without this prior history did not differ in gender, presence, or absence of bipolar disorder or psychosis, length of current episode, Hamilton Rating Scale for Depression (HRSD) scores prior to or following ECT, ECT treatment condition, number of treatments administered, ECT response rate, or age at onset of affective disorder. The group with a positive history was older (mean = 63.3; SD = 11.5) than the negative group (mean = 54.0; SD = 15.1), $p < 0.0001$. A positive ECT history was also associated with more prior affective episodes (mean = 4.9; SD = 3.3) and prior psychiatric hospitalizations (mean = 3.6; SD = 2.9) relative to a negative history (affective episodes: mean = 2.9, SD = 3.1; hospitalizations: mean = 1.3, SD = 2.0), $p < 0.0002$.

With the exception of p.r.n. lorazepam (maximum 3 mg/day), patients were withdrawn from psychotropic medications at least 5 days prior to the start of ECT. The group with a positive history of previous ECT did not differ in daily lorazepam dose (mg/d) in the 48 h prior to the first treatment (mean = 1.2, SD = 1.1) or in average daily dose during the ECT course (mean = 0.9, SD = 1.0) from the group with a negative history (preECT: mean = 1.0, SD = 1.0; during ECT: mean = 1.0, SD = 1.0). Using a cutoff of 30 days for longer periods, the average washout was 16.6 days (SD = 8.4). Methods of ECT administration have been described elsewhere (Sackeim et al 1987b; 1991). Briefly, atropine (0.4 mg IV), methohexital (0.75 mg/kg), and succinylcholine (.5 mg/kg) were used, with dosage after the first treatment based on anesthetic response. Patients were oxygenated from the administration of the anesthetic agent until the resumption of spontaneous respiration. Brief pulse, bidirectional, square-wave stimulation was delivered by a MECTA device, with current intensity kept constant at 800 mA.

In both protocols, seizure threshold was estimated in the first treatment of all patients, using the ascending method of limits procedure we devised (Sackeim et al 1987b). This titration procedure involves administering repeated subconvulsive stimulation at progressively higher intensity until an adequate generalized seizure is elicited. In the first protocol, 52 patients were randomized to bilateral or right unilateral electrode placements, with both groups receiving low stimulus dosage (just above threshold) throughout the ECT course. In the second protocol, 96 patients were randomized to four ECT conditions, crossing the factors of electrode placement and stimulus dosage. Two groups received bilateral or right unilateral ECT at low dosage, as in the first protocol. Two other groups received bilateral or right unilateral ECT with a stimulus intensity 2.5 times the initial seizure threshold. In both studies, seizure threshold was redetermined at the last treatment.

The "cuff" technique was used to measure the duration of motor convulsive manifestations. The criterion for an adequate seizure over the first five treatments was a motor seizure of at least 25 sec, with this criterion relaxed to 20 sec at subsequent treatments. Two frontal leads, referenced to ipsilateral ear lobes, were used to monitor EEG seizure manifestations. EEG seizure duration was determined blind to the motor seizure duration. High interrater reliability for the assessment of EEG seizure duration has been documented at this site (Warmflash et al 1987) and exceeded 0.95 in both studies. For each patient, average seizure duration across treatments was computed for the motor and EEG measures. All statistical analyses of seizure threshold and duration measures were conducted after logarithmic transformation of the raw values. The correlation across the sample in the average motor and EEG duration measures was 0.90, $p < 0.0001$. In both studies, the ECT treatment groups did not differ in either measure of seizure duration (Sackeim et al 1987a, 1991). In the analyses presented here, seizure threshold was quantified in units of charge (millicoulombs). The analyses were repeated using units of energy (Joules) and findings regarding history of previous ECT were unchanged.

Results

To enhance the likelihood of observing relations with prior history of ECT, simultaneous regression analyses were conducted predicting seizure threshold on the basis of prior ECT history (positive/negative) and known predictors of seizure threshold, namely, electrode placement, gender, and age (Sackeim et al 1987a), as well as daily lorazepam dose in 48 h prior to the first treatment. As seen in Table 1, there was no indication that prior ECT was associated

Table 1. Prediction of Seizure Threshold at the First ECT, and Average Seizure Duration during the ECT Course by History of Past ECT, Electrode Placement, Gender, Age, and Average Daily Lorazepam Dose[a]

	Initial Seizure Threshold			Motor Seizure Duration			EEG Seizure Duration		
Variable	Standardized Coefficient	*t*-test	*p*	Standardized Coefficient	*t*-test	*p*	Standardized Coefficient	*t*-test	*p*
Past ECT (1 = Yes/2 = No)	0.06	0.80	NS	−0.00	0.07	NS	0.00	0 05	NS
Electrode Placement (1 = bilateral/ 2 = unilateral)	−0.44	6.55	0.0001	0.02	0.21	NS	0.01	0.18	NS
Gender (1 = male/ 2 = female)	−0.31	4.61	0.0001	−0.04	0.55	NS	−0.01	0.16	NS
Age	0.30	4.37	0.0001	−0.38	4.84	0.0001	−0.42	5.43	0.0001
Lorazepam dose (mg/d)[b]	0.09	1.32	NS	−0.22	2.89	0.005	−0.24	3.31	0.001

[a] n = 148.

[b] Average daily lorazepam dose in the 48 hr prior to the first ECT in the analysis of initial seizure threshold and average daily dose throughout the ECT course in the analyses of seizure duration.

with the seizure threshold determined at the first ECT treatment. Furthermore, despite the positive-history group being on average 10 years older than the negative-history group, there was no difference in direct univariate comparison of their initial seizure threshold, t (146) = 0.89, NS. The same pattern of negative results held when the sample was restricted to male or to female patients. These results indicated that history of previous ECT did not have a persistent effect on initial seizure threshold.

Similar analyses were used to examine whether history of ECT treatment was associated with the duration of seizures, averaged over the ECT course. As seen in Table 1, although age and average lorazepam dose during the ECT course were potent predictors of seizure duration, history of past ECT had no effect. Null results regarding history of past ECT were also obtained in regression analyses of seizure duration at the first treatment, of subsamples restricted to men or women, and in univariate direct comparisons of positive and negative history groups. Initial seizure threshold was then introduced as an additional predictor in the simultaneous regressions on average seizure duration (Table 1). Patients with high initial threshold had shorter motor and EEG seizures ($p < 0.0001$) and initial seizure threshold uniquely accounted for more of the variance in seizure duration than any of the other predictors. In these analyses, as well, history of prior ECT was unrelated to either measure of seizure duration.

The findings of Tomasson et al (1992) of more frequent missed and brief seizures in patients with a history of prior ECT could have been due to a larger threshold increase in such patients during the ECT course. Indeed, there is some evidence linking the magnitude of the threshold increase to positive clinical outcome (Sackeim et al 1991), and ECT is frequently recommended to patients precisely because they manifested strong clinical response in prior treatment courses. By this alternative account, this type of selection bias could result in patients with a history of previous ECT being particularly likely to manifest robust seizure threshold increases during the ECT course, with unexceptional thresholds at the start of ECT.

We conducted separate analyses of the change in seizure threshold over the ECT course in 98 patients who had received low dosage ECT and 47 patients who had received high intensity treatment, as, in the most recent study, dosage condition and electrode placement interacted in influencing the threshold increase. For three patients, seizure threshold at ECT termination was unavailable. Table 2 presents the results for the low-dosage subgroup. Electrode placement and, to a lesser extent, age were significant predictors of the percentage increase in threshold, quantified by subtracting the threshold in the first treatment from that in the last treatment and dividing by initial threshold. History of prior ECT had no effect. In univariate analyses of the low-dosage subgroup, patients who had received ECT in the past (mean = 73.1%, SD = 66.6) did not differ from those with negative histories (mean = 67.4%, SD = 74.1) in their magnitude of increase. Null results for history of previous ECT were also obtained in the multivariate and univariate analyses of the high-dosage patients and when restricting analyses to each gender.

Discussion

We found no evidence that history of ECT was associated with a higher seizure threshold at the beginning of a new ECT course, with a greater increase in seizure threshold

Table 2. Prediction of the Percentage Increase in Seizure Threshold over the ECT Course by History of Previous ECT, Electrode Placement, Gender, Age, Number of Treatments and Average Daily Lorazepam Dose[a]

Variable	Standardized coefficient	*t*-test	*p*
Past ECT (1 = Yes/2 = No)	0.07	0.69	NS
Electrode placement (1 = bilateral/2 = unilateral)	−0.40	4.16	0.0001
Sex (1 = male/2 = female)	−0.15	1.66	0.10
Age	0.21	2.25	0.03
Number of ECT treatments	0.15	1.64	0.10
Lorazepam dose (mg/d)[b]	−0.12	1.28	NS

[a] $n = 98$, low dosage patients only.
[b] Average daily dose throughout the ECT course.

during the course, or with shorter seizure duration. Contradicting the interpretation offered by Tomasson et al (1992) for their findings, our results indicate that ECT does not have persistent effects on seizure threshold. Our negative findings regarding history of previous ECT were not due to unreliable or insensitive measurement of seizure threshold or seizure duration. Particularly with respect to initial seizure threshold, other patient variables (gender, age) and treatment factors (electrode placement) showed robust relations. Furthermore, in line with our early report in a smaller sample (Sackeim et al 1987a), in this enlarged sample initial seizure threshold was itself the strongest predictor of the average seizure duration during the ECT course, providing additional evidence for the validity of its assessment. Our negative findings also do not appear to be due to limited power. Given our sample size, the likelihood of detecting a significant effect exceeded 95% if history of ECT accounted for 9% or more of the variance ($r \geq 0.3$) in initial seizure threshold or the other dependent measures (Cohen 1988).

A number of differences between the studies may have contributed to the contradictory conclusions. Foremost, the methods of ECT administration used by Tomasson et al (1992) did not allow for measurement of seizure threshold. Their interpretation of a persistent elevation of this threshold was based on finding a higher rate of missed and brief seizures in male patients with a prior history of ECT. In our study, use of the titration procedure allowed for direct estimates of seizure threshold. In our work, brief seizures have been very rare (less than 3% of treatment sessions in each study), occurring at an insufficient rate to examine relations to prior history of ECT. Tomasson et al (1992) reported on a large patient cohort of mixed diagnostic and medical status, who were receiving a variety of concomitant psychotropic medications before and during ECT, including neuroleptics, antidepressants, benzodiazepines, anticonvulsants and pretreatment with caffeine. Although they attempted to control statistically for these and other possible sources of confound, it is questionable whether such statistical methods can adequately adjust for qualitative differences among medications in their effects on seizure threshold (e.g., carbamazepine versus haloperidol). A weakness of our study was absence of information on the time interval between the previous and index courses of ECT in those with a prior history. However, no patient was included in our sample who had received ECT within the previous 6 months. Tomasson et al had such information available and found no relationship between this interval and the frequency of missed or brief seizures.

In line with previous research, we did observe that a number of factors were predictive of initial seizure threshold and seizure duration. Of note, this was the first study to relate benzodiazepine exposure to quantification of seizure threshold in the human. We found that daily dose of lorazepam was not associated with initial seizure threshold, but higher daily dose was associated with shorter motor and EEG seizure duration. We have reported a similar dissociation regarding the relations of the short-acting barbiturate anesthetic agent, methohexital, to seizure threshold and seizure duration (Sackeim et al 1991). Similarly, basic research has demonstrated that pharmacological agents may have distinctly different profiles in their effects on initial seizure threshold, seizure duration, and the cumulative increase in seizure threshold with repeated ECS (Green et al 1982).

Typically, seizure threshold manifests a robust increase during the ECT course. Our data suggest that, when patients relapse months to years later and are again treated with ECT, there is no persistent effect of previous treatment on seizure threshold. We have had the opportunity of informally confirming these results by direct comparison of the initial seizure threshold of patients whom we have treated twice. Even with relatively brief intervals to relapse, seizure thresholds appear to return to the previous baseline value. This leaves open the question of how long

the seizure threshold increase is maintained in euthymic patients. Because it has been speculated that the increase marks a process related to the antidepressant effects of ECT (Sackeim et al 1983), it is possible that an elevated threshold may persist for longer periods in patients who remain euthymic. Quantification of seizure threshold in patients receiving continuation or maintenance ECT to prevent relapse/recurrence would provide an opportunity to address this question.

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References

Blackwood DH, Cull RE, Freeman CP, Evans JI, Mawdsley C (1980): A study of the incidence of epilepsy following ECT. *J Neurol Neurosurg Psychiatry* 43:1098–1102.

Cohen J (1988): *Statistical Power Analysis for the Behavioral Sciences*. Second Edition. Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Devinsky O, Duchowny MS (1983): Seizures after convulsive therapy: A retrospective case survey. *Neurology* 33:921–925.

Goddard GV (1967): Development of epileptic seizures through brain stimulation at low intensity. *Nature* 214:1020–1021.

Green A, Nutt D, Cowen P (1982): Increased seizure threshold following convulsion. In Sandler M. (ed), *Psychopharmacology of Anticonvulsants*. Oxford: Oxford University press, pp 16–26.

Post RM, Putnam F, Uhde TW, Weiss SR (1986): Electroconvulsive therapy as an anticonvulsant. Implications for its mechanism of action in affective illness. *Ann N Y Acad Sci* 462:376–388.

Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR (1983): Anticonvulsant and antidepressant properties of electroconvulsive therapy: A proposed mechanism of action. *Biol Psychiatry* 18:1301–1310.

Sackeim HA, Decina P, Portnoy S, Neeley P, Malitz S (1987a): Studies of dosage, seizure threshold, and seizure duration in ECT. *Biol Psychiatry* 22:249–268.

Sackeim HA, Decina P, Prohovnik I, Malitz S (1987b): Seizure threshold in electroconvulsive therapy. Effects of sex, age, electrode placement, and number of treatments. *Arch Gen Psychiatry* 44:355–60.

Sackeim HA, Devanand DP, Prudic J (1991): Stimulus intensity, seizure threshold, and seizure duration: Impact on the efficacy and safety of electroconvulsive therapy. *Psychiatr Clin North Am* 14:803–844.

Small JG, Milstein V, Small IF, Sharpley PH (1981): Does ECT produce kindling? *Biol Psychiatry* 16:773–778.

Tomasson K, Winokur G, Pfohl B (1992): Failed and short seizures associated with prior ECT. *Eur Arch Psychiatry Neurol Sci* 241:307–313.

Warmflash VL, Stricks L, Sackeim HA, Decina P, Neeley P, Malitz S (1987): Reliability and validity of measures of seizure duration. *Convulsive Ther* 3:18–25.