

## Factors Affecting Amnesia, Seizure Duration, and Efficacy in ECT

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*Twenty-nine patients given unilateral ECT were tested for memory with each treatment. Forgetting of nonverbal material correlated positively with seizure duration and with anesthetic dose. Seizure duration did not correlate with forgetting of verbal material or with changes in Hamilton depression ratings. Seizure duration was inversely related to succinylcholine and methohexital doses. These findings suggest that muscle relaxant and anesthetic doses can be adjusted to lessen the amnestic effects of ECT. There are, however, insufficient data on the relationship between seizure length and ECT efficacy to specify a minimum duration for seizures, individually or cumulatively.*

(Am J Psychiatry 142:692-696, 1985)

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Although ECT is generally acknowledged to be a useful treatment for depressive illness, the precise relationship between seizure characteristics and clinical effects is not known. A generalized brain seizure is believed to be a necessary component of treatment, because incomplete or partial seizures are not effective (1, 2). Maletzky (3, 4), using multiple-monitored ECT, reported improvement only after at least 210 seconds of cumulative seizure duration and found no further improvement after 1,000 seconds of cumulative seizure duration. Kramer (5), using conventional ECT, reported no improvement in any patient before 50 seconds of total seizure duration and no further improvement after 400 seconds of seizure duration in 90% of patients. The concept that ECT efficacy is a function of seizure length has, however, been ques-

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Presented in part at the VII World Congress of Psychiatry, Vienna, Austria, July 11-16, 1983. Received Aug. 10, 1984; revised Nov. 19, 1984; accepted Jan. 2, 1985. From the Department of Psychiatry, University of Texas Health Science Center at San Antonio. Address reprint requests to Dr. Miller, Department of Psychiatry, University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78284.

Supported in part by the Mary Yates Fund.

The authors thank Dr. Ray Costello, Ms. Susan Crandall, Ms. Colleen Kiney, Mr. Daniel Lopez, Dr. Joyce Mauk, Dr. John Plewes, Dr. Franklin Redmond, Mr. John Schoolfield, Ms. Laura Stone, Dr. Robert Terrill, and Dr. Christopher Ticknor for their help with the technical aspects of this study.

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tioned (6). The only other correlate of seizure duration reported in the literature is a direct relationship with postictal prolactin levels (7). No relationship between seizure duration and ECT-produced amnesia for autobiographical material was found in one study (8).

ECT seizure duration has been reported to be influenced by oxygenation (4, 9), hypocapnic alkalosis (4, 10), succinylcholine dose (4, 9), concomitant medications (11), electrode placement (12), electrical stimulus parameters (13, 14), type and dose of anesthetic (4, 15), and age (16). Treatment variables that have been reported to affect memory in patients receiving ECT include blood pressure (17), electrode placement (4, 18), stimulus waveform (8, 19), and stimulus intensity (20). EEG-monitored seizure duration is highly correlated with physical seizure duration in a cuffed extremity (21).

In this study, we tested patients for retrograde and anterograde amnesia and for disorientation after each of their first six ECT treatments. We attempted to identify treatment variables that affect these functions, with particular regard to the possible influence of seizure duration, anesthetic dose, and succinylcholine dose. We also attempted to determine whether antidepressant efficacy of ECT correlated with seizure duration.

### METHOD

Twenty-nine right-handed patients participated in this study after giving written informed consent to the study and to having ECT. All were inpatients with diagnoses of major depression (N=25), bipolar disorder, depressed (N=1), or dysthymic disorder (N=3), according to *DSM-III* criteria.

The average age of the 29 patients was  $49.2 \pm 11.8$  years. There were 14 men and 15 women. All but two patients had been tried on an antidepressant medication within the previous 3 months and either had not responded to it or had been intolerant of side effects.

All patients received right unilateral ECT with the electrodes in the Muller (N=7) or d'Elia (N=22) positions (22). Twenty-five were treated with a Mectra and four with a MECTA Model D ECT instrument. Methohexital was the anesthetic and succinylcholine the muscle relaxant. Doses were selected by the

anesthesiologist assigned to the case that day, in consultation with the treating physician. The fact that a number of different anesthesiologists and treating physicians made these decisions led to a wide range of doses of each agent (40–120 mg for methohexital and 35–130 mg for succinylcholine). All patients were ventilated with 100% oxygen, by mask. Seizure duration was monitored by EEG and, in most cases, also determined by observation of the physical seizure in an arm or leg cuffed with a tourniquet before succinylcholine administration. Only the first six treatments given to each patient were monitored, and all patients were treated at least six times. In instances in which the end of seizure activity was not readily apparent on the EEG recording, two readers independently marked the point at or after the end of physical seizure activity at which they thought a definite change was found, and the mean reading was used. This uncertain ending occurred in about 10% of recordings.

The verbal memory task was associate learning of word pairs taken from published lists (23, 24). The nonverbal memory task required the patients to remember which squares were black in a grid of 16 squares in which four were black and 12 were white. For each set of learning trials 10 new word pairs and three new grids were presented. Patients were instructed to mark on a sheet showing only white squares the four squares per grid that were black on the original. New materials were presented 20 minutes before each treatment and recall for them tested 20 minutes and 4 hours after each treatment. After the 4-hour recall tests, new sets of materials were presented and recall for them tested 24 hours after ECT. Forgetting scores were calculated at 20 minutes, 4 hours, and 24 hours after ECT by subtracting the number of items remembered at 20 minutes and 4 hours from the number learned before ECT (retrograde amnesia) and the number remembered 24 hours after ECT from the number newly learned 4 hours after ECT (anterograde amnesia). Orientation was tested before each treatment and at 20 minutes, 4 hours, and 24 hours after each treatment, by asking the patient to state name, year, month, day, hospital name, and name of city.

Two of us rated each patient's depression according to the 24-item Hamilton scale (25) before the first treatment and after the third and sixth treatments. The mean of the intraclass reliability coefficients (26) for the three rating sessions was .84.

In order to test for the presence of sequential effects of ECT on forgetting scores, a repeated measures analysis of variance across the six treatments was performed separately for each set of forgetting scores on the verbal and nonverbal tasks. Probability levels in statistical tests involving repeated measures were adjusted according to the method of Geisser and Greenhouse (27). The possible influence of changing clinical status on memory scores was assessed by analysis of variance after the patients were divided into two groups, by using a 50% or greater decrease in Hamilton score as the cutoff. Having established by

these techniques that forgetting scores were not significantly influenced by treatment sequence or by changes in clinical state, we combined the forgetting scores for each patient across all six treatments for each interval and type of material for correlational analyses.

All grouped data are presented as means  $\pm$  SD. Two-tailed tests of statistical significance were used.

## RESULTS

Fourteen patients had a 50% or greater reduction in Hamilton score after three ECT treatments, and 15 had improved to this extent after six treatments (15 of 29 patients, 52%). Mean methohexital and succinylcholine doses were  $70 \pm 15$  and  $61 \pm 18$  mg, respectively. Mean numbers of correct items on the word pair and design tasks for the 29 patients are shown in table 1. Mean pretreatment orientation scores were  $5.84 \pm 0.44$  (maximum score, 6), with mean changes of  $1.4 \pm 1.5$ ,  $0.1 \pm 0.5$ , and  $0.1 \pm 0.4$  at 20 minutes, 4 hours, and 24 hours, respectively.

Methohexital dose was negatively correlated with seizure duration and positively correlated with forgetting scores. Therefore, when seizure duration was correlated with forgetting scores, the influence of methohexital dose on both variables was partialled out (28). Similarly, when methohexital dose was correlated with forgetting scores, the influence of seizure duration was partialled out.

Table 2 lists the partial correlation coefficients between EEG-monitored seizure duration and forgetting scores. The slopes of the corrected regression equations are also given. There were significant correlations between seizure duration and retrograde forgetting of nonverbal material. The correlation between seizure duration and anterograde forgetting of nonverbal material (4 hours to 24 hours after ECT) approached, but did not reach, significance at the 95% confidence level. No significant correlations of seizure duration with forgetting of verbal material or with postictal changes in orientation were found.

The other treatment variable that correlated strongly with forgetting scores was dose of methohexital. The partial correlation coefficients and slopes of the regression equations are given in table 2. The strongest correlations were with forgetting of nonverbal material. The correlations between methohexital dose and forgetting of verbal material were all positive, but not significantly so.

Several factors significantly affected seizure duration. EEG-monitored seizure duration averaged  $53.3 \pm 17.9$  seconds in men and  $44.5 \pm 22.5$  seconds in women ( $t=2.84$ ,  $df=172$ ,  $p<.01$ ). Both methohexital dose and succinylcholine dose were inversely related to seizure duration. For methohexital the correlation coefficient was  $-.162$  ( $df=172$ ,  $p<.02$ ) and the equation for the best-fit linear regression was  $y=663 - 8.77x$ , where  $y$  is seizure duration (seconds) and  $x$  is dose (mg). For succinylcholine the correlation coefficient

**TABLE 1. Depression Ratings and Numbers of Correct Items on Word Pair and Design Tests for 29 Patients Given ECT**

Variable	Mean	SD
Hamilton score		
Before ECT	37.4	9.8
After three ECTs	21.0	10.5
After six ECTs	19.0	12.1
Word pairs correctly recalled		
Before ECT	6.57	1.30
20 minutes after ECT	3.08	2.14
4 hours after ECT	3.99	1.46
New word pairs correctly recalled		
4 hours after ECT	6.28	1.38
24 hours after ECT	3.65	1.52
Designs correctly recalled		
Before ECT	6.86	2.46
20 minutes after ECT	3.20	1.65
4 hours after ECT	3.27	1.63
New designs correctly recalled		
4 hours after ECT	6.42	2.36
24 hours after ECT	3.43	1.54

**TABLE 2. Partial Correlations of Forgetting Scores and Decreases in Orientation Scores With Seizure Duration or Methohexital Dose for 29 Patients Given ECT**

Variable and Interval	r (df=27)	Slope <sup>a</sup>
Correlation with seizure duration <sup>b</sup>		
Design forgetting score		
Before to 20 minutes after ECT	.391 <sup>c</sup>	0.0396
Before to 4 hours after ECT	.520 <sup>d</sup>	0.0450
4 hours after to 24 hours after ECT	.352 <sup>e</sup>	0.0351
Word pair forgetting score		
Before to 20 minutes after ECT	-.020	—
Before to 4 hours after ECT	.012	—
4 hours after to 24 hours after ECT	.155	—
Decrease in orientation score		
Before to 20 minutes after ECT	-.183	—
Before to 4 hours after ECT	-.195	—
4 hours after to 24 hours after ECT	-.150	—
Correlation with methohexital dose <sup>f</sup>		
Design forgetting score		
Before to 20 minutes after ECT	.517 <sup>d</sup>	0.0697
Before to 4 hours after ECT	.527 <sup>d</sup>	0.0558
4 hours after to 24 hours after ECT	.530 <sup>d</sup>	0.0683
Word pair forgetting score		
Before to 20 minutes after ECT	.307	—
Before to 4 hours after ECT	.182	—
4 hours after to 24 hours after ECT	.299	—
Decrease in orientation score		
Before to 20 minutes after ECT	.198	—
Before to 4 hours after ECT	.159	—
4 hours after to 24 hours after ECT	.125	—

<sup>a</sup>For correlation with seizure duration, slope is design items forgotten per second of seizure duration. For correlation with methohexital dose, slope is design items forgotten per milligram of methohexital. No slope indicated when partial correlation coefficient is not significant.

<sup>b</sup>Methohexital dose partialled out.

<sup>c</sup>p<.05.

<sup>d</sup>p<.01.

<sup>e</sup>p<.10.

<sup>f</sup>Seizure duration partialled out.

was  $-.307$  ( $df=172$ ,  $p<.001$ ) and the equation for the best-fit linear regression was  $y=286 - 3.86x$ , where  $y$  is seizure duration (seconds) and  $x$  is dose (mg).

One hundred forty-seven physical seizures were timed. The correlation between EEG seizure duration

and physical seizure duration was highly significant ( $r=.766$ ,  $df=145$ ,  $p<.001$ ). Although EEG and physical seizure activity frequently terminated simultaneously, the duration of the physical seizure was often considerably less and never more. Mean EEG-monitored seizure duration was  $48.7 \pm 20.8$  seconds. Mean physical seizure duration was  $35.8 \pm 15.4$  seconds. Correlations of physical seizure activity with forgetting scores were similar to the correlations of EEG-monitored seizure duration with forgetting scores.

Changes in depression ratings over the first three and first six treatments did not correlate significantly with cumulative seizure duration over the first three and six treatments, respectively. This was true even when the data from responders (50% or greater decrease in Hamilton score) were analyzed separately.

## DISCUSSION

A principal goal of this study was to understand how seizure duration is related to the clinical effects of ECT. A major positive finding was that retrograde and anterograde amnesia for nonverbal material after ECT correlated directly with seizure duration. The major negative finding was the lack of a relationship between seizure duration and antidepressant efficacy of ECT.

The observation that forgetting of nonverbal material correlated significantly with seizure duration, whereas forgetting of verbal material did not, may be interpreted in two ways. First, the test of verbal memory could have been less sensitive, failing to detect the influence of seizure duration. Second, the effect of seizure duration may, in reality, be greater on the stimulated or nondominant cerebral hemisphere in patients receiving unilateral ECT. If the difference were simply a question of test sensitivity, one would expect to see the same results with any amnesic agent that affects equally both types of memory functions. With methohexital, however, the correlations between dose and forgetting of verbal material were larger than those between seizure duration and forgetting of verbal material, although not as large as between methohexital dose and forgetting of nonverbal material (table 2). Thus, these data provide some support for both interpretations. Studies of bilateral ECT would test the hypothesis that with bilateral electrode placement there would be a significant correlation between seizure duration and forgetting of verbal material.

Two studies (8, 29) have not found significant relationships between seizure duration and amnesia for autobiographical material. In one, the patients were examined 2–3 days after an ECT series (29). Memory impairment was noted to be related to the number of treatments but not to total seizure duration. This work is not directly comparable to ours, because we tested for postictal amnesia with each treatment. As already noted, in this group of unilaterally stimulated patients no sequential effects on forgetting scores were observed over the first six treatments. In the other

study (8), patients were asked 24 hours after their fifth ECT treatment to recall four aspects about the presentation of a uniform complex stimulus presented 30 minutes before the fifth treatment. The smaller range of possible scores, the relative simplicity of the questions, the smaller number of treatments studied (one in each of 22 patients versus six in each of 29 patients in our study), and the use of both bilaterally and unilaterally stimulated patients are all factors that could have made these earlier results less sensitive to the effects of seizure duration on memory and may account for the difference from our results.

The failure to find any significant relationship between seizure duration or methohexital dose and postictal disorientation was not surprising, in that the observed changes in orientation scores were so small. The hypothesis that longer seizures cause more postictal disorientation might be better tested in bilaterally treated patients, who experience more problems in this regard (1).

We did not find any evidence that the antidepressant efficacy of ECT is a function of seizure duration. This observation, apparently to be reported by others as well (6), has important implications for the clinical use of ECT and for studies of its mechanism of action. Measures to produce long seizures (e.g., hyperventilation, reductions in succinylcholine or methohexital doses) may not be therapeutically useful, except in patients who have excessively short seizures. Although it is widely believed that very short seizures are ineffective (1), no studies using modern ECT techniques have been directed toward defining a critical minimum seizure length. Our data on seizure length and amnesia suggest that shorter seizures are preferable, with the caveat that it would not be useful to shorten them by increasing methohexital dose. We believe that further attention to the question of whether seizures must be of at least some minimal duration to achieve maximal antidepressant effect is warranted.

If seizure duration is a significant determinant of the amnesic effects of ECT, then it is important to identify factors affecting seizure duration that are under the physician's control. We found that both succinylcholine and methohexital doses were inversely related to seizure duration, as also reported by Maletzky (4). The correlation with succinylcholine dose was the stronger of the two. In this naturalistic study, doses of these agents were determined by the anesthesiologists, not the investigators. It remains to be seen to what extent purposeful manipulation of the doses of these drugs can influence seizure duration in individual patients.

Since succinylcholine does not ordinarily penetrate the blood-brain barrier, it is unclear how it might affect seizure duration. One possibility is that altered peripheral input to the CNS plays a role. In particular, afferents from muscle spindle fibers are activated by succinylcholine in a dose-dependent fashion (30, 31), and increased feedback to the CNS from this source could diminish seizure length. Second, blood-brain barrier permeability to succinylcholine could increase

during seizures, as has been shown for some small organic molecules (32), and this could contribute to a shortened seizure.

Methohexital dose correlated positively with postictal amnesia, especially for nonverbal material (table 2). This was not a function of its inhibitory effect on seizure duration, because shorter seizures were associated with less forgetting of nonverbal material (table 2). Further studies of the effects of systematically varying methohexital dose in individual patients are needed if we are to determine whether this treatment variable can be manipulated so as to lessen the amnesic effects and enhance the antidepressant effects of ECT.

In conclusion, our data indicate that seizure duration and methohexital dose are important variables affecting memory for nonverbal material in patients receiving right unilateral ECT. No relationship between seizure duration and antidepressant efficacy was found, although the great preponderance of evidence suggests that brain seizures are an essential part of the treatment (1). Clarification of the role of seizure duration in producing the effects of ECT and further definition of the treatment variables that affect seizure duration or postictal amnesia will permit rational adjustment of these treatment variables. It is a likely, though unproven, hypothesis that reduction of the immediate postictal amnesia with each ECT treatment will reduce the incidence of long-term subjective complaints about and objective deficits in memory function after ECT.

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