

Factors Associated With Seizure Adequacy Along the Course of Electroconvulsive Therapy

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Objectives: Eliciting a generalized seizure is essential to electroconvulsive therapy (ECT), but there is still a need to understand how patient and session variables interact to generate a seizure of adequate quality. Here, we investigate factors associated with motor seizure length as a measure of quality in a large database of patients who underwent ECT.

Methods: This is a retrospective cohort including data from all adult inpatients who underwent ECT at a university hospital in Brazil from 2009 to 2015. We used linear mixed models to investigate the effects of patient, session, and medication on seizure length.

Results: Session information was available for 387 patients, a total of 3544 sessions and 4167 individual stimulations. Multiple stimulations were necessary in 12.4% of sessions. Median seizure length was 30 seconds. Seizure length was directly correlated with stimulus dosage and inversely correlated with the session number, patient age, prescription of anticonvulsants in the day before and β -blockers during the session, and the thiopental dose. Use of benzodiazepines was not associated with a shorter seizure duration, irrespective of dose.

Conclusions: We demonstrate here how motor seizure length evolves during a course of ECT. With a large number of sessions, we are able to integrate a host of factors in a prediction model. Seizure quality was influenced by a number of the studied factors, many of which are potentially modifiable and could be assessed before initiating and handled during treatment.

Key Words: electroconvulsive therapy, seizure quality, motor seizure length, general anesthetics, anticonvulsants, β -blockers, benzodiazepines, retrospective cohort

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In contemporary electroconvulsive therapy (ECT) thinking, eliciting a generalized seizure is regarded as essential to its efficacy, whereas the total stimulus charge applied to the patient is accountable for adverse effects.¹ However, the ability of the electrical charge to produce a generalized seizure is variable and based on several factors. As such, there is an interest to have reliable measures of seizure quality—or adequacy—that could ideally predict the outcome of a course of ECT.²

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There have been several seizure quality indices proposed in the past few years, often based on ictal parameters on electroencephalography (EEG), most recently by Kranaster and colleagues.^{3,4} Motor seizure length is another parameter traditionally measured during the ECT session and thought to be a proxy of quality. There have been relevant criticisms to this measure on account of lack of rigorous clinical studies.⁵ Nevertheless, monitoring seizure duration is recommended in clinical guidelines,⁶ at least to establish very short or missed seizures. There is also often a significant agreement between EEG seizure pattern and duration.⁷

Several factors can potentially explain variations in quality. These range from patient variables, such as age, sex, diagnosis, and current treatment, to session variables, such as anesthetic used and dosage, electrode positioning, and stimulus parameters. Ictal indices like the postictal degree,⁸ the heart-peak frequency amplitude,⁹ the interval between the time of induction and the procedure,¹⁰ preoxygenation and postoxygenation, and hyperventilation during anesthesia seem to have an influence on seizure quality.¹¹

Although individual randomized studies have evaluated the impact of specific variables—choice of anesthetic and ventilation—there have been few longitudinal investigations that attempt to integrate different sources of data, including patient, medication, and session variables. Many of the factors associated with quality are modifiable, that is, can be effectively manipulated by the clinician to improve the quality of the session. With the objective of constructing a model that predicted the trajectory of seizure length during ECT, we conducted a retrospective cohort study with patients undergoing an acute course of ECT in a university center in Brazil. In addition, we investigate the same predictors in a categorical model of restimulation.

METHODS

Session data from every inpatient who underwent ECT at Hospital de Clínicas de Porto Alegre from January 2009 to December 2015 were included. We included only data from adult patients for whom ECT was prescribed for an acute indication (ie, all maintenance procedures were excluded).

The psychiatric ward has 36 acute beds. Electroconvulsive therapy sessions are conducted at the institution's outpatient surgical center, administered thrice weekly (on Mondays, Wednesdays, and Fridays). A general anesthetic followed by a muscle relaxant is routinely administered, as per international guidelines.¹² Thiopental (3 mg/kg) and succinylcholine (0.75–1 mg/kg) were used in almost every session, as per institution protocol. Patients undergo hyperventilation before stimulus delivery. Electrode placement is determined by the patient's physician, but the service standard is high-potency right unilateral placement, with the titration method used to determine stimulus dose in the first session. From the second session onward, the stimulus charge is set at 6 times seizure threshold.

Motor seizure length and EEG seizure length are used to determine seizure adequacy, with repeated administration for abortive or missed seizures.⁶ If the seizure is judged inadequate

(either missed or shorter than 15–20 seconds, with little to no changes in peak heart rate) by the treating psychiatrist, patients can be restimulated up to 2 times. Three ECT devices were in use during this period, the MECTA 5000 M (between 2009 and 2013), the MECTA 5000 Q (between July 2013 to January 2014), and the MECTA 4000 Q (from January 2014 onward; MECTA Corporation, Tualatin, Oregon).

For each recorded session, we extracted data on ECT device parameters. Following recommendations by Peterchev et al,¹³ we report here individual stimulus parameters—pulse width, frequency, train duration, current, and energy—instead of a summary metric. We recorded the dosage of thiopental and succinylcholine and whether the patient received a β -blocker, usually metoprolol, and medications used intrasession. We recorded motor and EEG seizure length for each stimulation—first, second, and third. When there was a need for restimulation, we also recorded this information. The treating psychiatrist observes and measures the seizure length in seconds according to established protocol, motor duration is measured from the onset of clonic convulsions, and the cuff method is used to block the distribution of the muscle relaxant to the forearm. Although we understand there is a possibility that missed seizures are a separate phenomenon, in practice and because of the retrospective nature of the investigation, we elected to include all session data in the analysis. There is no natural border between adequate and inadequate seizures, and this analysis takes that into account.

We elected to use motor seizure length as the primary outcome because EEG seizure length was recorded and available only for 2350 sessions. Motor and EEG seizure length were significantly correlated ($r = 0.32$, $P < 0.001$), especially when length was shorter than 120 seconds ($r = 0.51$, $P < 0.001$).

The medical records of the patients were inspected for sex, age, and ethnicity, as well as for medications used the day before the procedure and primary *International Classification of Diseases, Tenth Revision* diagnosis at discharge.

Statistical Analysis

For the longitudinal analyses, within-patient repeated observations are used for all outcomes. For our main outcome, motor seizure length, we use random intercept and random slope linear mixed models, with session number treated as the time variable. Predictors tested as fixed effects were patient age and sex, diagnosis, routinely prescribed medications, medications used intrasession, and the session stimulus parameters (pulse width, frequency, and duration). Because the first session tends to have unique characteristics because of titration, we entered the first session (vs all other sessions) as interaction terms with session number and with stimulus within session in the model. All models use as random effects the intercept and time and unstructured covariance matrices.¹⁴ We use generalized estimating equations models to assess factors associated with the patient being restimulated, with the same predictors entered as in the aforementioned mixed model. Residuals from the final models were inspected for normality.

RESULTS

Four hundred twenty-seven individual patients fulfilled the inclusion criteria. Session information was available for 387 (91%), a total of 3544 individual sessions and 4167 individual stimulations (Table 1). Multiple stimulations were necessary in 12.4% of sessions. The median number of sessions for each participant was 8 (interquartile range, 6–12).

Median motor seizure length was 30 seconds (interquartile range, 20–37 seconds). There was no motor response to stimulus in 7.9% of trials; for 83.4% of trials, it was greater than 15 seconds,

TABLE 1. Characteristics of Included Patients (n = 387) and Session Data (n = 3544)

Characteristic	
Age, mean \pm SD, y	47.1 (16.5)
Women	52.7%
Primary diagnosis	
Depression	47.0%
Psychosis	30.3%
Mania	14.0%
Other	8.7%
Prescribed medication	
Any antipsychotic	82.5%
Any antidepressant	33.5%
Any benzodiazepine	19.1%
Any anticonvulsant	7.7%
Lithium	3.4%
Medication used intrasession	
Thiopental dose, mean \pm SD, mg	234.58 (70.34)
Succinylcholine dose, mean \pm SD, mg	77.36 (23.90)
β -Blocker	23.8%
Unilateral placement	97.8%
ECT device parameters	
Pulse width, mean \pm SD, ms	1.2 (0.4)
Frequency, mean \pm SD, Hz	67.99 (24.90)
Duration, mean \pm SD, s	2.96 (2.30)

and for 74.9%, it was greater than 20 seconds. Median seizure length was lower in the first session (because of the titration protocol). From the second session onward, it significantly decreased on average 0.56 seconds per session (95% confidence interval [CI], 0.43–0.68; $P < 0.001$). For all patients, median seizure length for the first stimulation in the second session was 35 seconds compared with 29.5 seconds in the 12th session (Fig. 1).

There were several predictors of seizure length in the multivariable mixed model. Session number, patient age, use of anticonvulsants (in the day before), β -blockers (during the session), and the thiopental dosage were all inversely correlated with length. Conversely, the variables responsible for stimulus dosage (pulse width, frequency, and duration) were directly correlated with length. Use of benzodiazepines was not associated with shorter seizure duration when adjusted for all variables in the model (Table 2).

After the first session, stimulus was repeated in 7.1% of sessions. Median seizure length for stimulations judged insufficient was 0 seconds in the first—titration—session and 14 seconds in the subsequent sessions. In the adjusted model, higher patient age, use of anticonvulsants and β -blockers, and lower stimulus parameters were associated with the need for a second stimulus (Table 3).

DISCUSSION

We found several predictors of motor seizure length as a proxy of quality in this retrospective cohort. Although there are a number of prospective studies, including randomized trials, investigating isolated variables, this report benefits from a large and consistent database of ECT procedures looking at seizure quality with the relevant predictors. As such, we are able to delineate more precisely how seizure length typically fluctuates over the sessions.

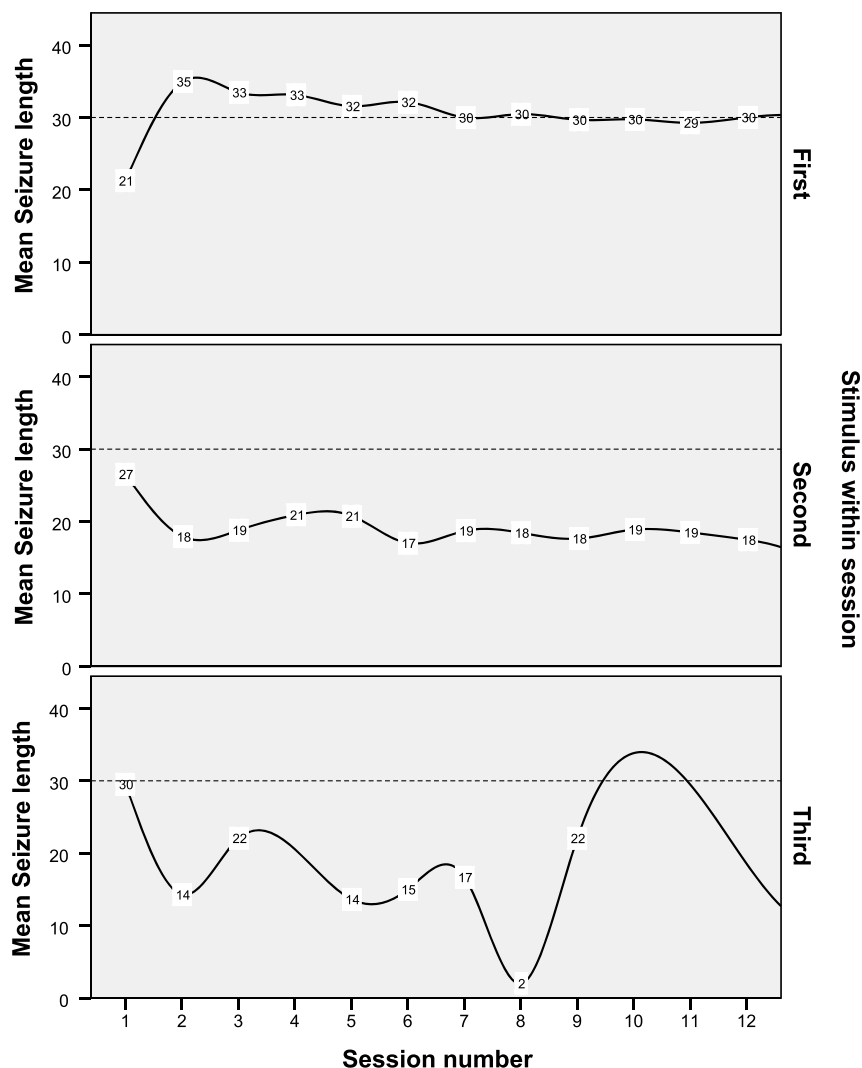


FIGURE 1. Smoother plot with mean motor seizure lengths between the first and 12th session in the first, second, and third electrical stimulations. Boxes show mean length for each session. Sample size went from 377 to 106 for the first stimulation, from 189 to 4 for the second, and from 69 to 0 for the third.

As previously described,^{15–17} seizure length tends to decrease over the course of ECT. After the titration protocol in the first session, maximum duration occurs in the second and tends to decrease significantly from there, at least for the first electrical stimulation. The second and third stimuli tend to be more variable in duration, without a clear evolving pattern. As expected, the titration protocol caused the first sessions to have particular characteristics, and correcting for this fact greatly improved the model. Although we do not correlate such changes in length with patient improvement in this report, such findings of a natural shortening in duration should have implications for the notion that an increasing threshold is a proxy of efficacy.^{15,18,19} Of patient characteristics, increasing age was associated with a shorter seizure length, but sex was not. Both variables have been associated with seizure threshold before.^{20,21}

Another consistent finding was the association of anticonvulsant therapy and seizure length.^{22–24} In this analysis, use of any anticonvulsant drug was associated with seizures 5 seconds shorter and a 75% greater risk of needing repeat stimulation. Use of benzodiazepines, on the other hand, had no significant

effect on seizure quality. Although it has been recommended that their concomitant use with ECT be avoided,²⁴ where their impact on quality has been measured, it is often found that they have no impact.^{25,26} This reinforces the point that the impact of daily medications is likely to be considerably superseded by general anesthetics that increase seizure threshold, such as barbiturates, used during the procedure.^{25,26} In that respect, dosage of sodium thiopental was clearly associated with seizure length, with every 25-mg dose increase shortening seizure duration by one second. Although this is predictable based on anticonvulsant properties of barbiturates, knowing the magnitude of this association can be useful in dose adjustment.^{27,28} There have been interesting discussions in the recent literature on possible benefits of using alternate anesthetic agents or combinations to maximize quality and minimize adverse effects,²⁹ but we are unable to evaluate other possibilities, as nearly all patients received thiopental; choice of general anesthetic may have implications for seizure quality.

A more remarkable finding is the robust association of metoprolol with shorter seizures. β -Blockers are sometimes used to block the adrenergic activation caused by seizure induction, but

TABLE 2. Final Linear Mixed Model Predicting Motor Seizure Length

Parameters	β	95% CI	P
Session number	−0.64	−0.83 to −0.45	<0.001
1st session	−18.63	−12.04 to −25.23	<0.001
1st stimulation*	19.48	15.59 to 23.38	<0.001
2nd stimulation*	8.11	4.01 to 12.2	<0.001
1st session × 1st stimulation†	−25.47	−32.04 to −18.89	<0.001
1st session × 2nd stimulation†	−9.20	−16.05 to −2.36	<0.001
Patient parameters	—	—	—
Women	0.16	−2.21 to 2.53	0.894
Age	−0.22	−0.3 to −0.14	<0.001
Diagnosis	—	—	—
Psychosis‡	0.00	−2.99 to 2.99	0.998
Mania‡	0.99	−4.37 to 2.39	0.566
Other‡	3.21	−6.99 to 0.57	0.095
Medications in use			
Any antidepressant	−0.14	−1.97 to 1.69	0.881
Lithium	0.52	−3.32 to 4.35	0.791
Any anticonvulsant	−4.96	−7.68 to −2.24	<0.001
Any antipsychotic	0.50	−1.42 to 2.41	0.61
Any benzodiazepine	−1.70	−3.58 to 0.18	0.076
ECT device parameters			
Pulse	3.72	1.72 to 5.72	<0.001
Frequency	0.15	0.1 to 0.19	<0.001
Duration	0.66	0.24 to 1.08	0.002
Session medications			
Thiopental dose	−0.04	−0.06 to −0.03	<0.001
Succinylcholine dose	0.02	−0.02 to 0.06	0.279
Use of β -blocker	−2.69	−4.61 to 0.78	0.006

Negative coefficients indicate shorter seizure length. The model includes intercept and session number as random effects.

*Compared with third stimulus.

†Session × stimulation interaction.

‡Compared with primary diagnosis of depression.

there have been reports they may have unintended effects on seizure quality.³⁰ Esmolol, for instance, can shorten seizure duration and decrease ictal regularity.^{31,32} Here, they were associated with a 66% greater chance of inadequate seizures and 2.7 seconds shorter seizures on average. A relevant caveat is that only metoprolol was used in this cohort, and recently, the use of esmolol has been advocated when prevention of tachycardia and hypertension is required. Because their benefit can be questionable for most patients, these results further question their routine use in ECT practice.

In most treatment protocols, ECT stimulus dosage is set to overcome the patient's seizure threshold; in right unilateral ECT, it does more significantly so.⁶ Nevertheless, some follow-up studies have failed to demonstrate a direct correlation between dosage and seizure quality. Inverse correlations between dosing and length have been reported, sometimes leading to suggestions that reducing dosage may improve seizure quality.^{21,33} Here we believe lies one of the strengths of our mixed-model approach to analysis, where data are analyzed longitudinally and patients may have different starting seizure threshold for a variety of reasons: age, medication, and so on. Because patients who are dosed

in the high ranges of ECT devices are those with a higher threshold, they need to be analyzed based on their trajectory. Otherwise, group effects are likely to just capture this initial association. Our results reveal that pulse width, frequency, and train duration have independent and significant effects on seizure quality, with higher parameters associated with longer durations.

Retrospective studies are inherently limited by having their data collected for purposes other than research, and important parameters that have an impact on quality may have been missed. We also report here the effect of several factors on seizure quality, not on the efficacy of the treatment. However, seizure quality is likely a key mediator of the efficacy of ECT, and studying how its proxies—such as motor seizure length—vary over time may help in influencing these parameters. It is also dynamic, and the clinician has the opportunity to take measures to improve it in the course of ECT, when efficacy may not yet be clear. Because this was standard protocol at our center, several currently interesting hypotheses could not be investigated, such as the use of alternative anesthetics, electrode positioning, and ventilation strategies. We were also unable to evaluate EEG seizures and test the most interesting literature on novel quality markers.

Nevertheless, the use of motor seizure length as one of the benchmarks for seizure adequacy is still routinely measured and used in decisions regarding seizure adequacy. So understanding what influences this parameter is relevant for the understanding of ECT. In addition, this is a longitudinal assessment of a large database, where we attempted to disentangle various predictors of quality, and conducting randomized trials on all these variables

TABLE 3. Final Generalized Estimated Equations Model With Risks of Missed or Aborted Seizures

Parameters	OR	95% CI	P
Female sex	1.47	0.98–2.2	0.062
Age*	1.03	1.02–1.04	<0.001
Primary diagnosis	—	—	—
Psychosis†	1.48	0.91–2.40	0.118
Mania†	1.46	0.89–2.39	0.138
Other†	0.76	0.41–1.39	0.37
Medications in use	—	—	—
Antidepressants	1.14	0.77–1.69	0.505
Lithium	1.43	0.71–2.88	0.318
Anticonvulsants	1.75	1.18–2.60	0.005
Antipsychotics	1.09	0.72–1.64	0.681
Benzodiazepines	0.91	0.62–1.34	0.631
Session	—	—	—
Session	1.02	0.99–1.05	0.238
1st session	16.63	8.99–30.78	<0.001
ECT device	—	—	—
Pulse	3.47	2.12–5.68	<0.001
Frequency	0.99	0.98–1.00	0.022
Duration	1.13	1.01–1.26	0.037
Bilateral electrode placement	3.37	0.92–12.28	0.066
Session medications	—	—	—
Thiopental dosage	1.00	1.00–1.01	0.271
Succinylcholine dosage	1.00	0.99–1.01	0.808
β -Blocker use	1.66	1.15–2.39	0.006

OR indicates odds ratio.

*Every 1-year increase.

†Compared with depression.

seems unlikely and unfeasible. As we demonstrated the impact of several clinical variables on motor seizure length, until further definitive studies are conducted at least, clinicians could strive to manipulate such variables. Holding back anticonvulsants and β -blockers are two obvious examples. Optimizing therapy for those patients expected to have higher thresholds and lower seizure quality could also be achieved via several actions, such as stimulus dosing and choice of anesthetics.

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