# ELECTROCONVULSIVE THERAPY FOR DEPRESSION: SEIZURE QUALITY MARKERS AND COGNITION

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**ABSTRACT Objectives:** Electroconvulsive Therapy (ECT) is the most effective therapy for patients with treatment-resistant depression. The stimulus parameters may be related to the outcome, and also to the cognitive changes reported in this treatment. Our objective was to list which factors could be considered as markers of quality of crisis and to verify cognition impairments. **Methods:** This is a real-world study (not interventionist). Eighteen patients with a depressive episode and treatment-resistant were selected Tests applied before and 15 days after the last session: The Montreal Cognitive Assessment (MoCA), Verbal Fluency Test (TFV), The Quality of Life Satisfaction and Satisfaction Questionnaire (Q-LES-Q-SF). The mood was measured by Hamilton-D-17 (HAM-D-17) at five different times **Results:** There was a consistent decrease in the HAM-D-17 score during the sessions. There was a response in 55.55% and remission in 44.44% and an increase in the Q-LES-Q-SF score demonstrating the therapeutic value of ECT. There were no detectable cognitive changes two weeks after the end of the sessions. Statistical tests have proven that cardiac monitoring added to the monitoring of seizure duration are useful to monitor the quality of seizures. **Conclusion:** ECT is effective for treating depression and do not cause cognition impairment 15 days after treatment. Simple methods such as heart rate monitoring and duration of central and motor crises are important as a criterion for monitoring the quality of seizures. The study should be replicated in larger samples to ensure that the generalisations of these conclusions are solid.

**KEYWORDS** electroconvulsive therapy, depression, response predictor, cognition

## Introduction

The World Health Organization affirms that more than 300 million people are affected by major depressive disorder worldwide. It is a disease that, in addition to being very prevalent, is often difficult to treat [1]. The STAR * D (Sequenced Treatment Alternatives to Relieve Depression) study revealed that more 50% of patients recruited through primary and psychiatric care clinics did not achieve remission after drug treatment with the first-line antidepressant, and one third did not present remission after four cycles of acute treatment [2]. In this scenario, non-pharmacological treatments such as electroconvulsive therapy (ECT) can be considered as therapeutic approaches. For episodes of primary depression, the remission rate can reach 80-90% [3], and despite this, some clinicians avoid the indication of this treatment.

Although ECT treatment is efficient, it may cause fear, mainly due to reports of cognitive impairment. Therefore, ECT techniques have undergone constant improvements in recent decades in order to minimize such changes in cognitive functions.

It has been demonstrated that the bilateral (or bifrontotemporal) positioning is discretely more effective than the right unilateral stimulation. However, bilateral stimulation also results in more expressive cognitive side effects than right unilateral position [4].This contrast between both techniques has been relativized once it was proposed to evaluate the difference in the


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dispensed charge dose and the time to reassess the changes in cognition [5].

Prefixed charge dose considering gender and age have lost space for the empirical titration technique, which consists of using low-dose until the minimum charge dose meets the requirement to induce seizure [6]. This may have ensured the use of the lower dose, but there are still considerations regarding the effectiveness of this technique [7].

It was verified that brief pulses could decrease the adverse cognitive effects, mainly on those occurring during the treatment and immediately after its completion, preserving than the efficacy of ECT [8]. It is necessary to assure patients that the cognitive alterations will be decreased, guaranteeing safety and reliability of ECT. This article aimed to find indicators of the session quality and evaluate possible cognitive impairments while using the most ECT updated techniques.

## Material and Methods

The selection of the participants for the research was done among the patients treated with ECT at Brasilia´s Castro e Santos Institute in Brazil's Federal District. This is a prospective study, therefore purely observational. Thus, this study intends to observe the ECT in the real scenario; in addition, the physiological markers for treatment response and also the cognition after the treatment were evaluated. An independent interviewer applied scoring scales before, during the treatment period, and after the end of the ECT sessions. The data collection ran from May to December 2018. The research protocol was submitted to the Ethics Committee of the Faculty of Medicine of the University of Brasília. It has been approved and registered according to the CAAE: 70980116.7.0000.5558. The study included only patients experiencing episodes of depression who did not respond to psychotropic drugs. Patients with schizophrenia spectrum disorders were excluded; as well as other conditions.

We considered the repeated measures type from Hamilton-D-17 (HAM-D-17) rating scale to assess mood at various times in the course of treatment. Thus, the scale was applied before the first session, immediately before the fourth, immediately before the seventh, immediately before the tenth, and again two weeks after the end of the treatment. The MoCA scale (Montreal Cognitive Assessment) was applied to evaluate cognition before, and two weeks after the treatment. We also applied a verbal fluency test (TFV) in the phonological modality: verbalization of the highest number of words initiated by the letters F-A-S. This was done before, and two weeks after the treatment.

Similarly (before the first and two weeks after the last session) we applied the Quality of Life Enjoyment and Satisfaction Questionnaire – Short for (Q-LES-Q-SF) to evaluate the final response from the patient's point of view. The equipment used for electroconvulsive therapy was SPECTRUM 4000 M approved in Brazil´s INMETRO and ANVISA (RDC N º 185/01). In the bilateral ECT was used bifrontotemporal electrode placement and in the unilateral D´Elia placement. Empirical titration was used for the initial charge dose. Double of the titration intensity was fixed when using bifrontotemporal placement and six times the titration value when using D'Elia placement. For data analysis, the IBM-SPSS-Statistics 23 was used.

## Results

Eighteen patients were selected for this study. This sample has a discrete predominance of single men and patients with a long history of illness (Table 1).

A total of 228 sessions were performed (mean 12.66 and a standard deviation of 3.8). In all cases, Succinylcholine was used. The team physicians determined technical variables such as anesthetic choice and electrode positioning without the interference of the investigator (table 2). The HAM-D-17 scale showed that approximately 44.44% (eight patients) had symptom remission, and 55.55% (10 patients) responded to treatment. We used the Friedman test to study these data: a significant difference ($p < 0.000$) was found between HAM-D-17 values. In the diagram (figure 1), it was possible to observe a progressive reduction of the scale index between the initial and final measurements.

Analyzing Q-LES-Q-SF, we found an essential difference between test 1 (initial) and test 2 (final) and, after the application of T-test, we noticed a significant increase of ($p < 0.000$) in punctuation. This increase, on average, was 25 points on the Q-LES-Q-SF indicator scale. Analyzing the Verbal Fluency Test (VFT), we observed a difference between tests 1 and 2. We verified with the T-test that the VFT score increased significantly after treatment (P-value = 0.010). This increase, on average, was of 5 points. On the other hand, the MoCA scale showed no differences between tests 1 and 2 (P-value = 0.879). The means of evolution in cognition and quality of life tests are summarized below (Figure 2).

We studied the correlation between the evolution of HAM-D-17 and the moment of crisis (central, motor and the difference between them). Spearman correlation coefficient was calculated. The correlation between Hamilton evolution and the central crisis was significant, but of low intensity ($p = 0.002$ and correlation coefficient = 0.201). When comparing the difference between the central crisis and the motor crisis with Hamilton's evolution, we noticed a significant and slightly stronger correlation than that observed only with the central crisis ($P < 0.00$ and correlation coefficient = 0.285). We did not find a significant correlation between loading dose, interhemispheric symmetry, suppression intensity and the reduction pattern in the HAM-D-17 score. The number of sessions performed, the gender and the age of the patients did not influence the evolution observed by the HAM-D-17. We noticed a significant relationship between the number of antidepressants taken before ECT and the evolution of HAM-D-17 (P-value = 0.013). This relationship is inversely proportional.

Finally, we performed a linear regression model to evaluate the predictors of evolution in HAM-D-17. For the selection of variables, the stepwise technique was performed. However, the model only presented those variables that demonstrated to be significant. The result showed a model with two variables (the difference between the central and motor crises and the heart rate) with an adjusted R square of 0.861. Therefore, this may account for 86% of the Hamilton scale variability.

## Discussion

The HAM-D-17 version is often used to assess response to depression treatment [9]. Results showed a consistent reduction in this scaled score, which points to the effectiveness of ECT treatment for symptoms of depression. The response rate was 55.55% and remission 44.44%. We should consider that the sample consisted of patients who did not respond to medications, which impacted the response evaluated in the literature[10]. Contrary to what was traditionally expected about the effect of ECT on cognition, the posttreatment VFT score increased significantly compared to the value before initiation of treatment. This increase, on average by 5 points on the indicator scale, is statis-

**Table 1** Epidemiological characteristics of the selected sample.

| Variable | Mean (M), standard deviation (SD), percentage (%) and number of patients(n) |
|---|---|
| Age, yars | 40,22 (M) - 12,37 (SD) |
| Sex, male | 55,6% - 10 (n) |
| Higher education | 77,7% - 14 (n) |
| Years of illness | 12 (M) - 7,3 (SD) |
| Marital Status, single | 55,6% - 10 (n) |
| 5 or more antidepressants failed | 94,4% - 17 (n) |
| Bilateral application | 88,8% - 16 (n) |
| Number of sessions | 12,66 (M) |

**Table 2** Technical elements such as electrode placement and use of anaesthetics.

| Technical Variable | Percentage (%) and number of patients(n) |
|---|---|
| Electrodes, bilateral | 88,8 % - 16 (n) |
| Electrodes, bilateral and right-unilateral | 11,1% - 2 (n) |
| Propofol | 72,2% - 13 (n) |
| Propofol replaced by Etomidate | 16,6% - 3 (n) |
| Etomidate only | 11,1% - 2 (n) |

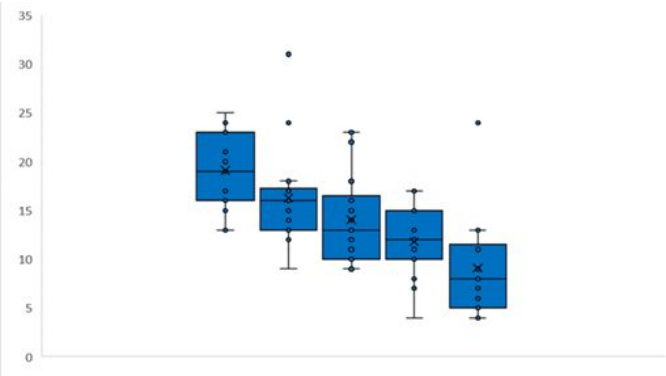


**Figure 1:** Constant regression in mean scores of the Hamilton during treatment.

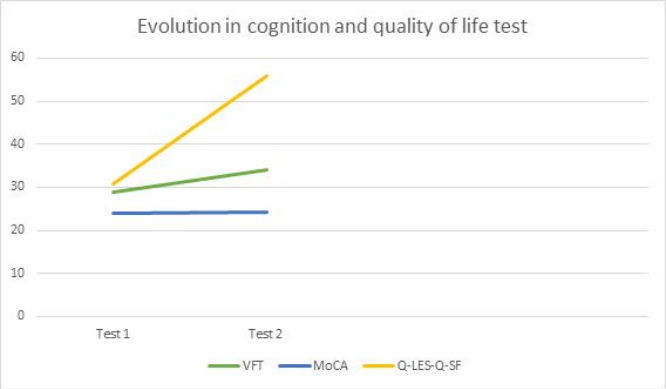


**Figure 2:** Evolution in cognition and quality of life tests.

tically significant (p-value = 0.010). We can infer that ECT did not impair semantic storage and its evocation. Similarly, MoCA results showed no worse cognitive performance after ECT. This reinforces the idea that cognitive function remains unchanged after 15 days of ECT completion. Besides, Q-LES-Q-SF showed a significant increase in the score (P <0.000). The data suggest that a nine-point increase in Q-LES-Q-SF is sufficient to indicate a change promoted by instituted therapy [25]. Thus, we found that approximately 83% of patients had a good increase in score.

Constant adjustments can explain the poor correlation between symptom decline and interhemispheric synchrony, as well as postictal volume and suppression during treatment. The electrical charge has been increased whenever any signal indicates loss of seizure quality, as well as other adjustments. Thus, the number of asymmetric crises was small, interfering with the statistical analyzes of this small group. Similarly, postictal suppression, despite showing a correlation with regression in the HAM-D-17 score, has no statistical significance.

We demonstrated that the longer the seizure time, the higher the Hamilton evolution. The merits of monitoring the duration of the EEG-based seizure concerning the duration of motor seizure in estimating the efficacy of ECT treatment were demonstrated in several trials [11]. Historically we know that the improvement of depression depends on the time of the seizure, although there are still debates and controversies mainly regarding the minimum time necessary [12]. Some studies claim that seizures of less than 15 seconds are associated with lower clinical outcomes [13], but there is not any consensus on this yet. The complex electrophysiological conditions involved in the development of generalized seizures make it problematic that the therapeutic efficacy of ECT is solely linked to the duration of the central seizure [14]. The American Psychiatric Association

recommends a seizure duration of more than 20 seconds as ideal during ECT administration [3]. This recommendation, however, was considered with consideration, as many factors influence this variable without changing the outcome of symptoms; For example, some studies with Propofol achieved an average duration of fewer than 20 seconds of seizure and the equivalent control result [15]. Therefore, some researchers criticize the ECT crisis duration guidelines by saying that the values are arbitrary and suggesting that they are too long for treatment [16]. Regardless of a consensus cutoff point for central seizure duration, our data show a correlation between symptom improvement and seizure duration. We know that the motor crisis has lost prestige as a response predictor in ECT.

This is a consequence of improved technique. At the beginning of ECT stimulation practice, there was only motor monitoring, but today EEG monitoring is more important. The motor crisis (tonic-clonic), however, is an obvious sign of the central crisis. We also know that the duration of central seizure is never less than a motor seizure. It was from this point that we proposed a new assessment of the motor crisis. We conclude that the higher the time differences between motor and central seizures, the higher the quality of the seizure, regardless of discussions about the minimum effective duration of the central seizure. Assessment of motor seizures in the case of EEG seizures may improve outcome specificity, since EEG-based seizures may occur without motor manifestation, but the opposite is not possible. We hypothesised that after-action potential spread, neural reserves respond to stimulus differently in the motor cortex and the prefrontal cortex. If effective, physiological measures combat seizure in the motor cortex and subsequently in the prefrontal area, and the time difference between motor and central seizures is reflected in this property. This idea is compatible with the prefrontal theory [17], which proposes that the efficacy of ECT is connected to a distribution of electrical current density in the prefrontal cortex, as evidenced by studies showing reduced blood flow and metabolic activity in this area [18].

Our hypothesis is also consistent with anticonvulsant theory. This theory is based mainly on findings that demonstrate an increase in the frontal region of gamma-aminobutyric acid (GABA) action after ECT [19]. Finally, our hypothesis also finds support in the hypothesis of hyperconnectivity in depression, which indicates that symptoms of depression are associated with rigid dysfunctional circuits [20]. Data show that overall mean functional connectivity decreased considerably after ECT treatment, which was related to the improvement of depressive symptoms [21].

All these theories claim that ECT can make the body react to electrical stimulation by fighting artificially triggered disorganization, restoring broken equilibrium. Consequently, there is a neurochemical reorganization that suppresses the symptoms of depression. We infer that the difference between central and motor crises may reflect the effectiveness of this prefrontal activity and, therefore, can be considered a predictor of ECT response to depression. This would give us a new parameter that is independent of simple isolated temporal measurement of seizures and offers clinicians new insight to qualify sessions as good or not. We also found out a significant relationship between the maximum heart rate and the response to ECT treatment. This measure is important because it represents an autonomic manifestation that helps prove that a given stimulus was able to promote a generalized crisis. This is because the electrical stimulus will cause a sympathetic response marked by the acceleration of heart rate shortly after the crisis becomes generalized [22]. There is still a bottleneck in determining a heart rate value that can be considered a good response marker. Minelli [23] considered 120 BPM as the cut-off value in his research, but some authors bet on a higher value. It is also necessary to consider the influence of atropine use on cardiac response. While discussing a specific value for determining the cutoff point, the correlation between cardiac acceleration and generalized seizures is a consensus. So we prefer to document the correlation without establishing a cutoff point that may be questionable.

Thus, we found in our sample a significant relationship ($P < 0.00$). Higher heart rates are related to better scores on the depression scale. The usefulness of this record in qualified crises is relevant. Changes in heart rate during ECT indicate deeper brain seizure activity than usually shown by electroencephalography and recording of motor activity [24]. Also, the simplicity of monitoring this information emphasizes its indispensability in electroconvulsive therapy routines. The two main elements that explain the Hamilton scale score variability were heart rate and the time difference between motor and central seizures. In the linear regression statistical model, the sum of these two parameters can explain 86% of the variability of Hamilton evolution.

Finally, we must consider that the reduced sample interfered with some analyzes. Few patients are undergoing ECT in Brasilia, as we did not have this treatment available until a short time ago. We also pointed out that factors such as cost of treatment and prejudice against ECT helped to limit the sample.

This reality may explain some biases in the sample as a high educational level, which differs from the average educational level in Brazil. Higher education may be related to access to information and, therefore, with less prejudice against ECT.

## Conclusion

Current ECT techniques do not impair cognition 15 days after the end of sessions. There was no difference in the MoCA scale, while there was an improvement in VFT performance and a significant improvement in patients' quality of life. These data help to prove that ECT is an effective and safe method. Besides, we have also proposed a new way of looking at motor and central seizure monitoring added to heart rate monitoring during ECT. This helps to show that simple methods are essential as criteria for monitoring the quality of crises. The study should be replicated in larger samples to ensure that the generalizations of these conclusions are sound.

## Disclosure Statement

There were no financial support or relationships between the authors and any organization or professional bodies that could pose any conflict of interests.

## Competing Interests

Written informed consent obtained from the patient for publication of this case report and any accompanying images.

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