Review article

Evidence of the effectiveness of electroconvulsive therapy in the psychiatric practice

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INTRODUCTION

Originally designed for the treatment of schizophrenia, the electroconvulsive therapy (ECT) is the only biological treatment of the 19th Century that is still widely used these days. The origin of the technique is attributed to Ladhaus Von Meduna who, in 1885, described the therapeutic benefits of camphor-induced convulsion finding support on his theory of the biological antagonism between schizophrenia and epilepsy.[1] Later, in 1938, Ugo Cerletti & Lucio Biniwith were the pioneers in the use of electrical stimuli to induce therapeutic convulsions in patients with severe psychoses, in an attempt to overcome the technical problems of the pharmacologic therapy. The method, named "electroshock", and popularly known as ECT, soon showed optimal results in the treatment of severe affective disorders of schizophrenia.[2]

As the treatment began, the ECT went through a number of technical refinements. Among these are muscular relaxation (produced by succinylcholine), short-term anesthesia, pre-oxygenation, use of more effective electrical stimulus, unilateral electrode placement and more complete monitoring of convulsion. In spite of the technical advances and benefits of ECT, its popularity underwent a large decrease from the 1960's to the 1980's.

This event was partially due to the introduction of new pharmacologic agents that were effective in the treatment of psychiatric disorders and because of the anti-psychiatric-hospitals movement. As a result, the clinical interest in the technique reduced, as well as investment on personnel training and research.

In the last 15 years, there have been efforts towards the official acknowledgement of the role of ECT in the contemporaneous psychiatric practice and there has been a real tendency towards the increase and dissemination of such a procedure. Resistance against the method, however, is still present, and this may be for several reasons, such as lack of knowledge about the treatment, both from the public and professionals, negative and stigmatizing perceptions about the technique, lack of consensus regarding its use, absence of investment from the pharmaceutical industry, and negligence by psychiatrists towards research and patient's information.

A systematic review of randomized clinical trials (RCT) was carried out in order to review indication, efficacy and adverse effects of ECT. PuBMed/MEDLINE was searched for the following MeSH with no date specification: *Electroconvulsive therapy*; *Electroconvulsive therapies*; *Therapy, electroconvulsive*; *Therapies, electroconvulsive*; *Electric convulsive therapy*; *Electroconvulsive shocks*; *Shocks, electroconvulsive*; *Electroconvulsive shock*; *Shock, electroconvulsive*; *Convulsive therapies*; *Therapies, convulsive*; *Convulsive therapy*; *Therapy, convulsive*. Eight meta-analyses and 255 RCT were found about the topic. Of the eight meta-analyses found, seven were included because they reported on the outcomes of ECT[3-9] and one was excluded since its approach covered only the anesthetic procedure aspects, which were not taken into account in the present study.[10] In the Cochrane base, 16 systematic reviews were found with the term electroconvulsive therapy and no date limit was determined. Regarding these reviews, six of them were selected to determine the efficacy of ECT,[6,11-15] and one of them was found in the PubMed/MEDLINE database.

INDICATIONS

Regarding indications, we found two RCT.[16,17] When the MeSH were associated with specific nosologies (depression, mania and schizophrenia), 185 RCT about depression, 19 about mania and 22 about schizophrenia were found. Of these, we selected only those that evaluated efficacy, indications and/or profile of ECT adverse effects. According to these studies and specialist's recommendations,[18] ECT is indicated in cases of:

- Major depression (single or recurrent episode);[3-7,18-23]
- Affective bipolar disorder (depressive, manic or mixed episodes);[18,22-23]
- Mild-schizophrenia (specially when the affective or catatonic symptomatology is prominent);[18,24-26]
- Schizoaffective disorder;[18,24-26]
- Schizophreniform disorder.[18,24-26]

Some clinical diseases as the neuroleptic malignant syndrome,[27,28] Parkinson's disease,[29-31] epilepsy[32-34] and tardive dyskinesia,[13,35,36] have also been successfully managed with ECT. The use of the technique in those conditions, however, is still not firmly established, once there is a lack of evidence to support indication in those cases. Only two RCT[37,38] were found about the use of ECT in Parkinson's disease and two RCT[19,37] and a systematic review[13] about tardive dyskinesia. These studies, which had a consistent design, could not prove the efficacy of ECT for such pathologies. It is known that the patients with some of the conditions mentioned above associated to a psychiatric diagnosis with the indication of ECT may present an improvement with the procedure, even though there is no evidence that could support the practice for these cases. A recent systematic review about the treatment of depression in individuals with Parkinson's disease indicates the need for further studies that would support the choice of the best antidepressant treatment for those patients.[14]

Even tough it is generally used as the second choice treatment (after failure in the pharmacologic treatment), the use of ECT should not be constrained to such a condition. The choice of ECT as a primary-choice treatment in depression can not be discharged, since it is more effective in the short-term reduction of this symptom than the pharmacologic approach, as shown in two systematic reviews.[5-6]

Moreover, concerning the aspects of age, previous response pattern, clinical comorbidity, symptom severity and risk should be considered in the decision of the ECT indication as a therapeutic option. Relating to the therapeutic approach to suicidal patients with mood disorders, Maris[39] suggests the use of ECT in the treatment of patients with severe risk of suicide.

CONTRAINDICATIONS

No specific RCT about contraindications was found using the MeSH described above. Nevertheless some consistent articles support the idea that there is no absolute contraindication to ECT. In some reports, authors make references to situations in which there is an increasing risk with

the procedure,[40-43] such as intracranial lesions or conditions associated to an increase in the intracranial pressure,[40,43] history of cerebrovascular accident,[41,42] recent myocardial infarction with cardiac decompensation, severe systemic arterial hypertension (especially if it is associated with pheochromocytoma), presence of risk factors for intracranial hemorrhage and any condition associated to a 4 or 5 risk score of the American Society of Anestheologists (ASA).[18,44] It is also not contraindicated during pregnancy.

A number of case reports suggest that the ECT consists of a low risk and highly effective procedure for the treatment of depression in different gestation periods.[44-49]

ADVERSE EFFECTS

It is important to mention that only two RCT reporting on adverse effects were found.[50,51]Nonetheless they were not included in this review because they dealt only with the anesthetic aspects of ECT. The contemporaneous ECT practice is associated to very low morbimortality rates. Studies about the topic suggest a rate of 2 to 4.5 deaths at every 100,000 procedures carried out,[52-54] which is comparable to the risk associated to short-term anesthesia in small surgical procedures. As to morbidity, the most consistent studies estimate that there is a complication for every 1,400 procedures (ASA).[18,55] Among these complications, we have found: laryngospasm, prolonged apnea, prolonged convulsions, dental damage and circulatory failure. Cardiac arrhythmias are frequent during the application of ECT and in the post-ictal period, and in general they are benign and resolve with no further treatment.[18]

The most important adverse effect of ECT is the memory deficit,[56-74] which presents as a post-ictal confusion, retrograde and/or anterograde amnesia, or, in a small number of patients, as a long-term subjective memory deficit (difficult to detect and quantify with accuracy). Retrograde and anterograde amnesia usually persist for 1 to 6 months after the end of ECT sessions, and in general the acquisition and retention of new memories, as well as the long-term memory, do not suffer an irreversible damage. Several studies comparing bilateral against high-dosage unilateral

ECT techniques,[57,60,66,70-72] bilateral against unilateral low-dosage ECT,[60] and high-dosage unilateral against low-dosage unilateral ECT[60,66,67] suggest that high-dosage right unilateral ECT combines the best therapeutic response with the least cognitive deficit.

Medication such as piracetam,[71] inositol,[72] naloxone,[73] and nicardipine,[74] that have already been used to minimize and/or to avoid adverse effects, were not shown to be effective.

EFFICACY

Using the MeSH with specific nosologies (depression, mania, schizophrenia) we found eight RCT about depression,[19-21,60,75-78] one about mania[79] and four about schizophrenia.[25,26,80,81] The major objective of such studies was to assess the efficacy of ECT in the referred nosologies.

Consistent evidence found in past studies but which were not found in the PubMed/MEDLINE and Cochrane searches, as RCT or meta-analysis, have already shown that ECT is substantially more effective than the simulated ECT in the treatment of major depression.[82-84] In a small number of studies with reliable methodology, ECT was shown to be superior than moderate dosages of antidepressants.[85,86] In our research, an RCT[78] showed that ECT was better than paroxetine in the treatment of patients with non-responsive depression to two types of antidepressants. A meta-analysis by Pagnin et al.[3] showed the ECT superiority not only as compared to the simulated ECT and placebo, but also compared to antidepressants in general, tricyclic antidepressants and inhibitors of monoamine oxidase inhibitors (MAOIs). Similar results were found in the systematic review by Kho et al.,[4] who stated that there are no differences between sine wave and brief pulse machines. In addition, some evidence was found proving that psychosis predicted better response to ECT.

A wide review performed by the UK ECT Review Group in 2003[5] confirmed that ECT is effective in the short-term in the treatment of depression (six studies comparing it with placebo, in a total of 256 patients) and probably more effective than pharmacotherapy within this time interval (18 RCT, 1,144 patients). Bilateral ECT was shown to be more effective than unilateral ECT (22

RCT, 1,408 patients) and high dosage procedures are superior than low dosage ones (seven RCT, 342 patients). According to a recent RCT,[87] comorbidity with borderline personality disorder implies less short-term response to the depression symptomatology.

Regarding the use of ECT in the elderly (individuals older than 60 years-old) with depression, a meta-analysis by Van der Wurff et al.[6] evidenced that there are only a few RCT about the topic and, concerning the elderly with comorbidities such as dementia, cerebral vascular disease and Parkinson's disease, no RCT was found. Possible adverse effects related to ECT could not be adequately examined in those patients. Actually we found only three RCT in the present systematic review on the efficacy and safety of ECT in elderly patients , and only one of these had outcomes that could be evaluated.[88-90] This study compared bilateral ECT against unilateral in elderly with depression and it was not very convincing as to the superiority of unilateral ECT in the improvement of such population's symptoms.

In a meta-analysis[7] about the treatment of psychotic depression events, Parker et al. analyzed 44 studies and reported a tendency of ECT superiority in comparison to a combination of an antidepressant with an antipsychotic. The ECT was significantly more effective than the isolate use of tricyclic antidepressants. Bilateral ECT was shown to be superior than unilateral ECT in the improvement of symptoms.

Mania episodes generally respond satisfactory to the procedure,[18,23,56] although there is only a few controlled studies about the efficacy of ECT in these situations. According to findings of studies carried out in the 1980's by Small et al.[91] and Mukerjee[92] the ECT is faster in the resolution of manic episodes than the combination of lithium and neuroleptic drugs. Sikdar et al.,[23] in a trial that compared the efficacy of chlorpromazine with and without the association of ECT in 2 groups of 15 patients with mania, showed the superiority of the combined treatment in the short-term improvement of symptoms.

Regarding the differences in the speed of symptomatic response between unipolar and bipolar depression with the ECT, Daly et al.[22] analyzed a group of 162 patients with unipolar

depression and a group of 60 patients with bipolar depression, submitted to uni- or bilateral ECT. All individuals who took part in the study had not taken antidepressants before, during or soon after the application of ECT. Their symptoms were assessed twice a week during the treatment period. At the end of the course of ECT, the groups did not present differences in the rates of symptoms improvement and remission, and no differences in the rates of patients who received bilateral ECT as compared to those receiving unilateral ECT were found. However, patients with bipolar depression presented faster symptoms improvement than patients with unipolar depression.

Evaluating the efficacy of ECT in schizophrenia is more difficult than in the cases of mood disorders. This event occurs partially because of the heterogeneity of individuals classified as schizophrenic and that take part in studies with more consistent methods, lately included in a review article.[15] Past studies that included non-chronic patients and did not exclude those with affective symptoms have already stated that the ECT promotes faster resolution of schizophrenia symptoms than the simulated ECT.[93,94] Prospective studies that compare ECT with neuroleptics in non-chronic patients with schizophrenia did not show any differences among groups.[95-97] Some studies, however, suggest that the combination of ECT and neuroleptics in this population results in a faster recovery than the isolate use of neuroleptics.[98,99] Former studies with acute schizophrenic patients did not show differences between ECT and simulated ECT.[100,101] We should then say that the ECT has a smaller impact on the treatment of non-selected populations of schizophrenic patients, but it continues to be worth in the second line treatment of those patients. Recently, Kupchick et al.[8] reviewed 36 reports of schizophrenic patients that used clozapine associated to ECT due to resistance to typical antipsychotic drugs, to clozapine or to ECT alone. More than two thirds of cases showed to have benefited from the combined therapy. It was shown to be safe and well tolerated. Adverse reactions, such as ECT-induced prolonged convulsions (one case), supraventricular and sinus tachycardia (one case) and increase in blood pressure, occurred in 16.6% of patients.

According to findings of the systematic review by Tharyan & Adams,[15] the combined treatment of neuroleptic drugs and ECT can be considered as a therapeutic option for patients with schizophrenia, especially when an overall fast improvement and reduction of symptoms is required, or, for individuals with partial response to antipsychotic medication. Further research, however, is required to give scientific support to the use of ECT in schizophrenia.

As for the number of sessions required for an effective treatment, it varies according to subject. Patients with depression require, in general, from 6 to 12 sessions, and those with mania or schizophrenia may require a higher number of sessions.[16,18,55] Some past studies suggest that when the complete remission is reached, it is not necessary to submit the patient to additional sessions.[102-105] No consensus has been reached as to the maximum number of courses of ECT that a patient may be submitted to, nor there is a consensus about the indication for maintenance therapy. In spite of the practice of ECT being largely employed, its long-term efficacy and safety have not been carefully tested. Only some brief studies have already suggested that the ECT as a maintenance therapy reduces the rates of relapse and recurrence in mood disorders.[104-106] The randomized controlled study by Chanpattana et al.[25] showed that the combined continuation ECT was more effective in the prevention of relapse than the continued treatment with ECT or with neuroleptics in patients with treatment-refractory schizophrenia and responsive to an ECT cycle combined to neuroleptic medication.

Currently, a very well designed study is being carried out under the coordination of Charles Kellner et al.[107] The aim is to compare ECT and the combination of lithium and nortriptyline as maintenance therapy in patients with more severe depression that have already responded to ECT. Findings have not been published yet. In fact, in the treatment of mood disorders, the ECT shows to be highly effective but frequent relapses are reported after treatment. The maintenance ECT is so far a good therapeutic option in selected patients with problems of tolerance to pharmacotherapy or in patients who continue to relapse even with the pharmacologic treatment.

In the present review, we have also found five RCT[108-112]and a systematic review about transcranial magnetic stimulation, which have been tested and introduced as a new method of convulsive therapy. Its main principle consists of the rapid alternation of strong magnetic fields. Grunhaus et al.[110] and Janicak et al.[112] suggest that the transcranial magnetic stimulation and ECT reach similar results in nonpsychotic major depressive disorder. According to the meta-analysis by Martin et al.[113] there is no strong evidence of the benefits of using transcranial magnetic stimulation to treat depression, although the small sample sizes do not exclude possible positive effects.

DISCUSSION

This systematic review evidenced that ECT is an effective and safe therapeutic method although it is not fully acknowledged, described and uniformly accepted in Brazil yet. Currently, we have seen the rise of new interest in this treatment, which is reflected in the publication of recent psychiatric periodicals. The interest for the transcranial magnetic stimulation is also observed, even though its efficacy has not yet been fully confirmed.

It is evident that during more than 60 years of ECT use it was not always properly employed, and it was even abusively used by some professionals. However, this has never invalidated the benefits obtained with the proper use of ECT. The anti-psychiatry movement benefited from the bad use of the technique, disregarding scientific evidence of the real efficacy of the psychiatric practice, as the review presented here demonstrates.

The scope of our study is not restrained to clear up pathophysiologic aspects of psychiatric disorders, nor to elucidate the mechanisms of ECT. Actually such issues remain open and there is not a single and unquestionable answer~~,~~ which ends up increasing resistance towards the method.

The literature review, however, is clear in evidencing that when accurately indicated, the ECT is an effective and safe treatment, which can improve the patient's life through a faster relief of short-term symptoms. The benefits of the ECT as a maintenance treatment, however, depend on a serious and well organized study in an attempt to prove their real efficacy.

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ABSTRACT

The electroconvulsive therapy is a biological treatment not widely used in the psychiatric practice. A number of factors contribute to resistance concerning this method. The goal of the present article is to provide scientific support to the use of electroconvulsive therapy by showing its effectiveness, indications, contraindications and adverse effects. Such factors were searched in the major randomized clinical trials and meta-analyses available in the current medical literature on the subject (PubMed/MEDLINE, Cochrane).

Keywords: *ECT, electroconvulsive therapy, electroconvulsive shock, indications, systematic review.*

Title: *Evidence of the effectiveness of electroconvulsive therapy in the psychiatric practice*

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