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Electroconvulsive therapy in the treatment of bipolar depression

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Since its introduction, electroconvulsive therapy is a treatment used in mood disorders, especially in the depressive phases of bipolar disorder. The advance of this technique has made it a useful and current option both in the treatment of acute phases as in the prevention of recurrences. The objective of this revision is to collect available data about the use of electroconvulsive therapy in bipolar depression. Its indications, effectiveness, prediction and patterns of response are included in this work, together with its complications, adverse events and drug interactions. Differences in response between bipolar and unipolar depression are also discussed.

Key words:
Electroconvulsive therapy. Bipolar depression. Affective disorders.

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La terapia electroconvulsiva en el tratamiento de la depresión bipolar

Desde su introducción la terapia electroconvulsiva es un tratamiento usado en los trastornos afectivos, especialmente en las fases depresivas del trastorno bipolar. El avance en su técnica lo ha convertido en una opción útil y actual tanto en el tratamiento de las fases agudas como en la prevención de las recurrencias. El objetivo de esta revisión es recoger la información disponible hasta la actualidad acerca del uso de la terapia electroconvulsiva en la depresión bipolar. Sus indicaciones, su eficacia, su predicción y su patrón de respuesta se incluyen en este trabajo, así como sus complicaciones, sus efectos adversos y sus interacciones farmacológicas. Asimismo también se recopilan las diferencias de respuesta entre la depresión bipolar y la unipolar.

Palabras clave:
Terapia electroconvulsiva. Depresión bipolar. Trastornos afectivos.

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INTRODUCTION

Electroconvulsive therapy (ECT), one of the first biological therapies of psychiatry, was initially developed by Ladiaslas Joseph von Meduna in 1934.

The theory proposed by von Meduna was based on the fact that schizophrenic patients with epilepsy had a certain protection against the development of psychotic symptoms. The initial method used to provoke convulsive attacks was by drug (use of insulin, camphor, etc.). Use of electricity to evoke critical activity in humans was begun with the experiments of Ugo Cerletti and Lucio Bini in 1938. Subsequently, in the decades of the 1940's and 1950's, its use was extended and its success was resounding, above all if we compare it with the alternative therapies. After the development of psychopharmacology (antidepressants, neuroleptics and lithium), the generalization of its use and corroboration of its therapeutical properties, together with social reluctance, the use of ECT began to decline.

However, in recent decades, its use has been recovered as knowledge of psychiatric diseases has advanced and certain social postures towards ECT (antipsychiatry) has decreased.

Currently, it is a frequent treatment in different psychiatric diseases, both due to its efficacy and its safety. Mortality for ECT between 2 and 4 per 100,000 sessions and 1 per 10,000 patients is accepted, that is, very similar to anesthetic induction in minor surgery[1]. Philibert[2] found minor morbidity-mortality in depressive patients who received ECT than in those treated with psychodrugs.

ECT INDICATIONS IN BIPOLAR DEPRESSION

The indication of initiating electroconvulsive therapy is based on its fast action (greater than that of the antidepressants) and its efficacy (much greater than that of psychodrugs in depression with psychotic symptoms, for example)[3]. In general, the more serious the depressive episode, the better the response to ECT.

Pictures with a clear indication are:

Depression with psychotic symptoms

First choice indication[4-6], above all due to their good response to ECT and the frequent refractarity to psychodrugs[7].

Elevated suicide risk

ECT does not increase the long term risk of suicide nor the suicide index[8]. It has faster action compared to antidepressants, an important quality in patients with significant associated suicide potential.

In addition, there is no risk of voluntary overdose.

Resistant depression

ECT is indicated in any serious endogenous depressive picture that does not respond to other therapy forms[9,10].

In general, half of the resistant pictures respond to ECT[11,12]. If it also deals with melancholic depressions with psychotic symptoms, the response index reaches 80%-85%[13].

Critical somatic situations associated to bipolar depression

As denutrition and/or dehydration conditions, which require rapid improvement.

Situations of contraindication to antidepressive drugs

In many cardiovascular, endocrinological, renal, digestive and even neurological diseases, ECT is safer and has lower mortality rates[14]. This point has special importance in geriatric patients, who generally have a higher rate of drug side effects, more significant comorbidity and more serious symptoms, with the need for faster recovery. Many studies have revealed that the presence of depression has a negative impact on morbidity and mortality in many medical conditions.

Intense inhibition or agitation

Given the facility of complications, use of multiple drugs or mechanical restraint it entails.

Depressive pseudodementia

ECT is generally more effective than antidepressants in these pictures[15].

Pregnant woman

No effects of ECT on the fetus have been found[16].

EFFICACY OF ECT IN BIPOLAR DEPRESSION

Both the unipolar and bipolar melancholic depressive episodes are the main indication of ECT. In turn, ECT continues to be the most effective treatment for major depression and especially for the pharmacoresistant one. The response values vary in different studies, but they are considered to be approximately 60%-85%[17]. ECT efficacy in depressive syndromes in unquestionable if the indication is correct. Not only is it superior to the placebo but also to antidepressants or to the association of antidepressants and neuroleptics, reaching an efficacy equal to or greater than 80% in melancholies[18].

Five out of eight controlled studies show superiority of ECT, two equality and one greater efficacy of antidepressants. Different depressive episodes have been compared in the same patients, observing a favorable response in 94% of the episodes corresponding to ECT versus 53% of those corresponding to antidepressants[19].

Combination of lithium and antidepressants seems to be an alternative treatment in efficacy but not in fastness of action[20,21].

In psychodrug resistant patients ECT continues to be effective in between 30% and 72% of the cases if the antidepressants have been administered during the correct time and with the correct doses, even though well designed and controlled prospective studies are needed[22].

Thus, ECT has been clearly shown to be effective in both bipolar and unipolar depressive disorders. However, it has also been shown to be more effective than antidepressants[23]. In spite of this, many authors continue to place ECT in the third or fourth place in their therapeutic strategy[24].

DIFFERENCES IN RESPONSE TO ECT BETWEEN BIPOLAR AND UNIPOLAR DEPRESSION

The comparison between response to ECT in unipolar and bipolar depressive patients has many methodological problems, given that the diagnosis of one entity or another is longitudinal and not cross-sectional. There does not seem to be any differences, as found by most of the authors[25-27]. This is with the exception of Black et al.[28], who observed better responses in unipolar subjects and Perris[29], who found the contrary option-bipolar patients responded better than unipolar. However, Abrams and Taylor[26] reanalyzed the data of the latter author and did not observe any significant differences when they only chose those patients who only received antidepressants.

However, in a recent study[30], a more potent and consistent effect has been found in bipolar patients, as they have a faster onset of response and require fewer treatments, regardless of the ECT used (location of the electrodes and conditions of stimulating dose), than unipolar patients. It is obvious that ECT is a potent anticonvulsive therapy, with greater anti-epileptic properties in some models than the traditional anti-epileptic drug series. This study suggests a faster onset of anti-epileptic effect in bipolar subjects in comparison with the unipolar ones. If this were the case, it could be deduced that bipolar patients show a deeper and more accumulative inhibitory response to the induction of the seizure than the unipolar patients.

Clearly, other psychopathology and/or personality factors could vary between unipolar and bipolar subjects, causing differences in the rate of clinical response.

If we compare the response of unipolar depressive and bipolar depressive episodes, the favorable response values are 70% and 69%, respectively, according to Black et al.[31].

PREDICTION OF RESPONSE TO ECT IN BIPOLAR DEPRESSION

The principal predictor of response to treatment is diagnosis[32], that should be extensive, careful and of quality for the indication to be correct[33,34].

Table 1 shows the main predictors of response to ECT in bipolar depression.

In addition, the percentage of favorable responses is subject to the type of use made of the treatment. If the stimulus applied is not controlled or limited with multiple monitoring, the ECT is considered infallible, but subject to complications[35-37], while the limited and sensible use in consonance with the monitoring results would result in it being considered safe and effective, not infallible[38,40].

ECT RESPONSE PATTERN IN BIPOLAR DEPRESSION

In the short term, improvement already begins between the third and fourth week[41,42], thus improving two weeks earlier than when antidepressive drugs are used[2,43]. As has been previously stated, the observation of a maniform response between the third and fourth electroshock is an unavoidable sign of good prognosis, The therapy should continue until the maximum improvement has been obtained, except for if significant side effects appear. In general, change to the manic phase should be avoided. If it does appear, it should be approached with the same treatment.

In the long term, patients show low mortality and better global status[2], with decreased suicide risk[8,23] and risk of phase change or initiation of rapid cycles in spite of the fact that the number of manic episodes in the decade following the introduction of ECT increased historically.

Table 1 Predictors of electroconvulsive therapy response in bipolar depression

Predictors of good response
Fully fledged symptoms of recent onset
Greater severity of the picture
Existence of psychotic symptoms[85-89]
Presence of neurotic symptoms[90]
Associated cognitive deficit[78,81,91,92]
Greater age
Agitation
Appearance of maniform response between third and fourth session of ECT[93]
Predictors of bad response
Depressive pictures initiated together with somatic diseases
Elevated number of previous depressive episodes
Long duration of previous depressive episodes[94-99]
No previous response to one or more drug therapies[100,101]
Finding of alterations in electroencephalography[102,103]
Presence of serious life events
Circadian clinical variations and second hour insomnia have little influence[104].

Between 18% and 50% of the patients who respond to therapy may have a relapse within the first six months if they do not receive any continuation treatment[44-46], above all in the first four months[47]. However, in patients treated with tricyclic antidepressants, the relapse index in the first year is 20%[48,49].

PREVENTION OF RECURRENCES

Maintenance and continuation treatment with electroconvulsive therapies are a treatment for some long evolution affective disorders, especially chronic, recurrent, pharmacoresistant ones and in patients with intolerance to the medication, non-compliant and in those with high risk of suicide even with the use of drugs. Its indication requires it to be applied in patients with a history of previous episode with complete or significant improvement. Most of the preventive efficacy tests of electroconvulsive therapy come from the prepsychopharmacological era. The most recent comparative studies between maintenance ECT and the psychodrugs are scarce and not very conclusive[50,51].

In the case of recurrent depressive episodes, the most common and studied indication, a single ECT series, shows 50% relapses in the first year. If they are patients treated with tricyclic antidepressants, the relapse index is 20%

during this same time period. In the case of maintenance electroconvulsive therapy (ECT-M), relapses reach 10%-12% of the patients[52].

A rigid schedule may be followed in which a series of 6 to 12 stimulations is followed by one weekly, another at 15 days and the following monthly for 3-6 months or a variable schedule. This depends on the patient's clinical condition, increasing the administration frequency if there are signs of recurrence.

Maintenance and continuation ECT could be underused in the treatment of bipolar disorder[53,54].

Only 3% of all the ECT used in the United States are maintenance and continuation ones.

According to that stated, the findings of one study[55] suggest that bipolar disorder patients with pharmacotherapeutic failure and/or multiple hospitalizations could be candidates for ECT-M, especially if they have a good previous response to another ECT cycle. According to this study, neither structural nor functional abnormalities in neuroimaging nor a present or past alcohol abuse predict poor response. It also suggests that the use of ECT-M as a single therapy in the treatment of pharmacoresistant patients may not be enough. Thus, the concomitant use of psychotropics is recommended. Chanpattana[56] has made a similar observation. Most of the patients included in this study have needed maintenance ECT more frequently than those recommended for unipolar patients. This suggests that the intertherapeutic intervals would not have to be greater to that of one to three weeks.

In addition, a significantly better response, defined in time for rehospitalization, for all the patients of the group treated with ECT-M was found in another study[57] conducted with 21 patients —13 depressives (unipolar and bipolar) and 8 schizoaffective— treated with ECT-M in association with pharmacotherapy, compared with 21 controls treated only with psychotropic medications.

Analyzing the subgroups, the depressive patients treated with ECT-M showed a significant decrease in the percentage of rehospitalization and its durations. In the schizoaffective subjects, a significant difference in survival time in favor of the group treated with ECT-M was observed. When the two subgroups were compared, the schizoaffective ones had a markedly lower positive response compared with the depressive subjects.

No consensus has been reached regarding how much time the patients would have to be symptom free before ending ECT-M. Abrams[58] recommends a second opinion before continuing beyond 1 year or 12 treatments.

The duration of continuation ECT (ECT-C) has also been under debate.

Some investigators[59] are in favor of a maximum of 6 months, while others recommend a minimum of 6 months. Abrams[54] has suggested indefinite ECT-C for patients associated with serious suicide attempts that are not preventable with continuation of pharmacotherapy.

Maintenance ECT requires periodic evaluations of the patient, assessing his/her mental status, cognitive function and somatic condition in general, including electrocardiogram and other complementary tests if necessary.

The pharmacotherapy that the patient receives and appearance or change in any disease suffered should also be taken into account.

The usual ECT-M program consists in weekly sessions followed by others every two weeks for a few weeks, and then going to a monthly interval until it is considered that the patient has adequate stability.

ECT TECHNIQUE IN BIPOLAR DEPRESSION

ECT attempts to provoke severe generalized tonic-clonic seizure episodes for all the series on the central nervous system from 200 to 250 seconds. To obtain this convulsion, an electron load with a certain potency is applied up to the central nervous system. When the electrical stimulus administered has depolarized a sufficient number of neurons, there is a generalized, paroxystic, gran mal seizure, whose duration should be greater than 30 seconds in electroencephalographic measure to be effective. The energy level necessary to produce this seizure is called *convulsion threshold* and may vary with different factors, such as age, number of treatments or use of anti-seizure drugs. A total of 275 to 350 milliCoulombs (mC) of electric energy are administered in each session using pulsatile current with short impulses.

The parameter that makes up the EEG amplitude during the seizure is called *seizure energy index* and should be superior to 550 instead of microvolts-second.

Bilateral application is faster and more effective, although it causes a greater number of cognitive type side effects on the contrary to the unilateral application.

The anesthetic agent used should be a rapid inductor, without interactions with ECT nor with psychodrugs. Currently, the agents used most are thiopental and methohexital, the latter one generally causes local pain, but it is associated with less arrhythmias than the former. Midazolam has also been used successfully without shortening the seizure duration. Etomidate, that affects adrenal function, if used frequently, does not increase convulsive threshold and is adequate in patients with high threshold. Ketamine can be used intramuscularly, but is associated to postictal psychosis. Profofol decreases tachycardia and hypertension,

but does not reduce the appearance of arrhythmias and increases convulsive threshold.

Muscle relaxants are useful to avoid fractures and other problems related with muscular contraction. In general, total muscle relaxation is not necessary, only that which achieves palpebral reflex loss. Succinylcholine, whose effect decreases due to the effect of the treatment itself, is generally used.

In bipolar depression, the number of treatments administered will be that in which the maximum improvement is achieved, in general between 6 and 12. This depends on the severity and chronicity of the picture, although it may reach 20. The patient's condition should be frequently reviewed, observing the percentage of improvement or appearance of side effects.

The frequency of the most usual application is generally two or three times per week, greater frequencies being faster, which are associated to a greater number of side effects.

DRUG INTERACTIONS OF ECT

It is very important to review the medication that the patient is receiving when the ECT is done due to possible interactions that may occur.

Tricyclic antidepressants

When its initiation is less than 1 month, it has been related with an increase in morbidity[60], increasing cardiovascular risk. The risk of convulsions does not seem to increase after ECT use. Association of tricyclic antidepressants and electroconvulsive therapy does not seem to improve efficacy, although it may mean less risk of early relapses after the ECT series[49,61,62].

Monoamine oxidase inhibitors

In general, its suspension is recommended 2 weeks before the onset of ECT, given the danger of hyper or hypotensive episodes, neurological alterations and hepatotoxicity, although some reviews[63,64] question its contraindication. MAOI interact with certain muscle relaxants and have been associated to a greater number of frustrated episodes[65]. Furthermore, they may interact with medications that should be used urgently during the procedure.

Selective serotonin reuptake inhibitors

This is the safest antidepressant. The association initially described between fluoxetine and epileptic status has not been subsequently corroborated, although the convulsion duration does increase[66] and the energy dose to be applied should be reduced.

Neuroleptics

Abrams[15] recommended the use of incisive neuroleptics. It does not generally have any problems at low doses, although temporal-spatial disorientation in the elderly has been described[60]. Even more, according to one study[67], ECT combined with low clozapine doses is effective both for the treatment of an acute episode and for the maintenance treatment of resistant mania. High doses have been associated to prolonged convulsions[68].

Benzodiazepines

They increase the convulsive threshold[69] and decrease convulsion time[41,70]. They should be substituted with neuroleptics or short half life benzodiazepines, such as lorezepam (maximum 3 mg/day) with a final dosage between 8 and 12 hours before the administration of ECT, should be given.

Lithium

Alteration in the permeability of the hematoencephalic barrier produced during electroconvulsive therapy has been a reason for debate. Some authors describe memory disorders and more significant confusion[71] and even delusions and other atypical neurological alterations[72]. The combination of ECT with lithium carbonate has also been associated with longer convulsive episodes. Furthermore, it may interact with certain muscle relaxants. In general, its suppression is recommendable, unless it is a maintenance ECT or pictures of mania that require it, in which we should reduce the doses and obtain lithemias in the hours close to the ECT.

Lithemia values should frequently be obtained before and during ECT. Reduction or even suppression of the dose will avoid a large part of the risk of neurotoxicity associated to the alteration of the hematoencephalic barrier[32]. However, in a retrospective series of case and control studies[73], greater frequency of appearance of neurotoxic effects was not found in the group receiving lithium and ECT regarding that which only received ECT.

Antiepileptics

Phenytoin does not increase the convulsive threshold, but decreases the response to maximum stimuli.

According to one study[74], the association of ECT with classical antiepileptics (carbamazepine and valproic acid) is safe and effective.

No significant differences were found in regards to the total number of ECT required, type of treatment (unilateral or bilateral), stimulating energy necessary in the bilateral treatments, duration of the episodes in the bilateral treatments, adverse effects (especially to the frequency and severity of the memory problems) and response to treatment. The only differences of the group in which two treatments were associated in comparison with the control group (only electroconvulsive therapy) were the greater stimulating energy necessary and the lower duration of the convulsive episodes in the unilateral ECT treatments.

Suspension of anti-epileptics may cause prolonged convulsions. In general, it is better to continue the anti-epileptic therapy, except if there are no adequate convulsions, in which case, the drug dose should be reduced.

CONTRAINDICATIONS

At present, there is no absolute contraindication for ECT[75]. The treatment indication should be done according to the benefit/risk ratio based on the existing disease.

Table 2 lists the determining factors of indicating or contraindicating the ECT.

The situations in which the risk increases clearly are those that reach ASA (American Society of Anesthesiologists) grades of anesthetic risk 4 or 5 (listed in table 3).

COMPLICATIONS AND ADVERSE EFFECTS

Cardiovascular complications

They are the most frequent and serious complications. The presence of arrhythmias is very frequent, it being favored by the presence of previous cardiovascular disease, advanced age and high ASA evaluation[76]. In this way, 30% of the healthy patients and 70% of the cardiopathic ones suffer them. Most of the times, these are reversible episodes[35] and they generally occur in the immediate postictal period[77].

Table 2 Determining factors of the decision of indicating or contraindicating ECT

Patient's condition (seriousness and duration of disease)
Threat to life
Response prior to other treatments or to ECT
Adverse events and contraindications of other treatments
Risk of no treatment

Table 3 Grades of anesthetic risk 4 or 5 to the American Society of Anesthesiologists

Space occupying brain lesions
Intracranial hypertension
Recent myocardial infarction
Recent brain hemorrhaging
Vascular malformations
Unstable aneurysms

Neuropsychiatric complications

Prolonged convulsions

These are more frequent during the first ECT session, with the concomitant use of certain drugs (theophylline, caffeine, lithium), with abstinence or suppression of others (sedatives or hypnotics and antiepileptics), in patients with previous seizure disorders or with existence of previous paroxytic activity in the EEG, in certain neurological alterations (tumors, subdural hematomas) or metabolic ones, with hyperventilation, with childhood-adolescent age and with the use of monitored multiple ECT.

Confusion

This is present in 5%-10% of the patients. It occurs in the 15-30 post-ECT minutes. It is favored by the existence of previous cognitive deterioration, stroke, elderly age, use of certain drugs (lithium, benzodiazepines and antidepressants with anticholinergic power), use of high energy doses and bilateral application[78].

Changes in vascularization of the basal ganglia and white substance during the post ECT period in these patients have been observed[79,80].

Delirium

It is the most frequent cause of suspension of electroconvulsive treatment. It occurs more frequently in bilateral application, with high energy stimuli and sinusoidal wave, and with the use of certain anesthetics (ketamine).

Cognitive disorders

In general, they are partial and have little intensity[81].

It produces anterograde or retrograde amnesias, in general recovered several weeks after the treatment[77], and almost all within the first nine months, although it may sometimes give rise to permanent deficits[82].

According to a recent 1 year long longitudinal study[83], the patients who received treatment with ECT-m during this period did not have adverse cognitive effects (memory, attention and frontal functions).

On the other hand, due to the improvement of the affective condition, more favorable performances can be observed in the neuropsychological batteries after ECT.

In fact, the existence of a previous cognitive deficit in the depressive patient seems to be an indicator of response for this treatment, it being a clear indication for dementia associated to depression or in the picture of depressive pseudodementia.

Memory loss may lessen, decreasing the total number of sessions and frequency of application, using unilateral ECT and low energy stimuli and discontinuing drugs such as lithium, benzodiazepines and antidepressants[84].

Headaches and muscle pain

They generally improve and can be prevented with rest and analgesics.

Fractures

They were produced in the pre-anesthetic period.

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