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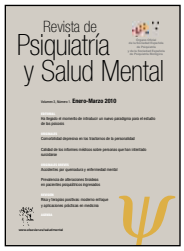

REVIEW

Effectiveness and risks of combining antipsychotic drugs with electroconvulsive treatment

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Abstract
Introduction: The simultaneous application of electroconvulsive therapy (ECT) and psychotropic drugs is based on sparse data. Despite this, and the restrictive approach of the Guidelines and Consensus is widespread in the usual care, it is widely practiced in routine clinical.
Method: We reviewed the results of search on the topic in MEDLINE, PsychINFO, EMBASE and Cochrane, and the main guidelines on the subject and analyzed for drug groups.
Results: Except some reservation with regard to classical MAOIs, antidepressants are safe and effective enhancers of the TEC. It is desirable to discontinuation of BZD whenever clinically possible before the course of ECT for risk of interference, if not possible will have to use proper technique to ensure effective incentives. It is advisable to stop or reduce the dose of lithium prior to ECT based on a cost-benefit analysis of the risk of relapse, if maintained will be adjusted lower levels and cognitive effects minimizing techniques . The combination with «classic» and «atypical» antipsychotics power positive clinical effects and the risk of combined use is low. The positive data are collected with clozapine and ECT-resistant psychosis, with little presence of effects of the decrease of seizure threshold by clozapine, and important effect of empowerment, but of limited duration.
Conclusions: Although it is strictly necessary to identify situations in terms of drugs, patient and ECT technique, and care necessary to develop tests that provide methodologically sound data, the combined use of ECT and psychotropic drugs in general presents an acceptable risk level and efficacy data by encouraging empowerment

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PALABRAS CLAVE
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Eficacia y riesgos de la combinación de psicofármacos con el tratamiento electroconvulsivo

Resumen
Introducción: La aplicación simultánea de tratamiento electroconvulsivo (TEC) y psicofármacos se sustenta en datos escasos. A pesar de ello, y de la actitud restrictiva de las guías y consensos, es de un uso generalizado en la práctica clínica.
Método: Se revisan los resultados de búsqueda sobre el tema en MEDLINE, PsychINFO, EMBASE y Cochrane, así como las principales guías sobre el tema y se analizan por grupos farmacológicos
Resultados: Salvo cierta reserva respecto a los inhibidores de la monoamino oxidasa clásicos, los antidepresivos resultan seguros y eficaces potenciadores del TEC. Resulta deseable la retirada de las benzodiacepinas siempre que sea clínicamente viable antes del curso de TEC, por riesgo de interferencia en la estimulación; si no es posible, habrá que emplear la técnica apropiada que asegure estímulos eficaces. Es recomendable interrumpir o reducir la dosis de litio previo al TEC a partir de un análisis coste-beneficio del riesgo de recaída; en caso de mantenerse, se ajustarán valores menores y técnica minimizadora de efectos cognitivos. La combinación con antipsicóticos "clásicos" y "atípicos" potencia los efectos clínicos positivos y el riesgo de uso combinado es bajo. Los datos más positivos se recogen con clozapina y TEC en psicosis resistente, con escasa presencia de efectos derivados del descenso del umbral de convulsión por clozapina, e importante efecto de potenciación, aunque de duración limitada.
Conclusiones: Aunque es preciso individualizar rigurosamente las situaciones en función de fármacos, paciente y técnica de TEC, y necesario desarrollar ensayos metodológicamente cuidados que ofrezcan datos firmes, el uso conjunto de TEC y psicofármacos presenta en general un nivel de riesgo asumible y datos de eficacia por potenciación esperanzadores.

Introduction

In today's scenario of renewed interest in electroconvulsive therapy (ECT), it is remarkable that, except in circles specifically dedicated to it, so little is done to address a common situation in clinical practice: the use of ECT and psychoactive drugs either concurrently or close together.

The criteria published by scientific societies are usually conservative, being based largely on expert consensus, on case series, and only rarely on controlled clinical trials.[1]

However, the experience of interested clinicians hints more along the lines of the scant and generally not very up-to-date reviews on the subject: there is a low risk and often even potentiation when these two resources are used concurrently, both in emergency situations when overlap is unavoidable and in acute treatment for cases resistant to monotherapy or during maintenance ECT.

Our objective was an up-to-date review on a topic that we believe to be of benefit in routine clinical practice—including the scant data available on the latest generations of antidepressants and antipsychotics.

Methodology

An exhaustive review was done on the search results for this subject in MEDLINE, PsychINFO, EMBASE, and Cochrane, as well as the most important guides on the subject.[1-5]

Results

Antidepressants

The attitude toward combining ECT and antidepressants is a good example of that possibly undue caution we mentioned. Numerous authors present data on the low risk and possible potentiation of the antidepressant effect when treatments are combined, and this would be justified at least in cases of resistance and in overlapping at the end of a round of ECT.[6] Welch[7] maintains that both tapering the antidepressant dose and combining for purposes of potentiation are appropriate, the only requirement being to avoid abrupt suspension of the drug.

However, we found that, in general, the opinion against using the two treatments together continues to prevail in careful reviews such as those by Pritchett et al[8] (1993) and Klapheke[9] (1997), and it is also the opinion of a luminary such as Abrams in his 2002 text.[10]

Regarding the guides and consensuses, the 1999 Spanish Consensus on ECT recommended that treatment already instituted with tricyclics or selective serotonin reuptake inhibitors (SSRI) not be discontinued, and that the decision be individualized in the case of the classical monoamine oxidase inhibitors (MAOI).[5] The NICE guide of April 2003[2] states that the ECT-drug therapy combination showed no superiority over ECT alone, although the duration of

the clinical trials used was insufficient. Compared with placebo, the continuation of tricyclics and/or lithium reduced the incidence of relapse in patients who had responded to ECT.

Britain's Royal College's 2005 Guide[1] concludes that the lack of large clinical trials or common outcome measures between studies limits interpretation of the available evidence. The data available suggests that therapeutic response to ECT may be enhanced by the antidepressants lithium and pindolol without great risk to patients and that there is a clear need for randomised clinical trials with pharmacological interventions during a cycle of ECT.

Reviewing the subject by pharmacological groups, more often than not the bibliography from the 1960s on the tricyclics was methodologically controversial. Generally, they were isolated cases with contradictory data on the probable benefit of using the therapies in combination, and they reported scant problematic interactions.[11]

Among those first studies, the work of Seager and Bird[12] in 1962 is worth highlighting: in a randomised, double-blind trial with a sample of 43 patients, they found no difference in response in the acute phase between the imipramine-ECT combination and ECT plus placebo.

In 1989, Nelson and Benjamin[13] compared ECT alone with ECT plus low and high doses of tricyclics. They found there was greater improvement and fewer sessions required in cases where the combined therapy was used, and they also observed very few side effects. However, more recently, Mayur et al[14] found no significant difference in terms of speed of response to ECT in patients, whether or not they discontinued tricyclic antidepressants, although the group that continued taking antidepressants had more anticholinergic side effects.

Regarding possible interactions of the tricyclics and tetracyclics with the anaesthesia scenario, we found a sprinkling of cases that reported various heart rhythm disturbances—although one must bear in mind that concomitant medications are commonly used and that the patients are elderly—as well as possible problems related to the abrupt suspension of the drug, etc.[15] On the contrary, in 1987 Glassman[16] described a certain anti-arrhythmic protective effect during ECT following the continued use of tricyclic antidepressants.

In 1987, Selvin[17] evaluated the possible cardiovascular risks of anaesthesia—arrhythmias, specifically—for patients on tricyclic therapy and found them to be low, in the case of chronic treatment, and moderate when the antidepressants had been started within a month prior to ECT.

The possible prolongation of the convulsion due to concurrent use of ECT and antidepressants is another particularly controversial subject. It is not described with the tricyclics, despite their known effect of reducing the threshold, generally. With trazodone, it is an interaction that is often encountered, although in cases with confusing or complex concomitant medication.[18-20] This effect has also been reported with bupropion.[21,22]

Regarding the classical MAOIs, there has been widespread consensus that they should not be used together with ECT due to the risks of interaction with anaesthesia,[10] and cases of hypertension and hypotension, fever, hyperreflexia, convulsions, and hepatotoxicity have routinely been described. However, in a 1985 broad, prospective study of anaesthesia with MAOI, El-Ganzouri et al[23] were less pessimistic; in fact, they found that, except for a certain increase in arterial pressure and heart rate, there were no serious problems, and they concluded that it was not necessary to discontinue the MAOI. Those were patients on chronic treatment with MAOIs; in the case of recent treatment, the response could be different.

Monaco and Delaplaine[24] also found no complications in a 1964 double-blind trial with 26 patients being treated with tranylcypromine 10 mg, and reviews by Freese[25] in 1985, Welch[7] in 1995, and Remick et al[26] in 1987 support this opinion of low risk, as well. The American Psychological Association (APA),[4] although keeping MAOIs in the "medications usually reduced or discontinued" section, considers the combination safe if certain precautions are observed.

However, overall, caution is still advised.[9,15] Of course, very few data support the isolated opinion of Muller and Nardil[27] (1961) that combining MAOIs with ECT may result in a potentiation of efficacy such that it permits acceptance of the anaesthesia risk. However, in situations where it is required and with certain precautions, it is possible to skip the two rigorous weeks of flushing.[9]

Where the debate becomes most heated, however, will be with the SSRIs. Understandably, the first data on prolonged convulsions with SSRIs was related to fluoxetine. Three cases[15] had been described in 1991—relatively few, considering the massive use of this drug—and while none of them were serious, they prompted numerous replicas and prospective studies seeking to clarify the safety of the combined therapy.

On the whole, the studies confirming some level of risk with the SSRI-ECT combination were in the minority. With fluoxetine, avoiding the combination was advised only in situations of maintenance with ECT, although this was more because of the possible risk of interaction with anaesthesia levels than because of the effect on convulsion parameters.[32]

Regarding paroxetine, Curran[33] reported a trial in 1995 comparing 7 patients receiving paroxetine 20-50 mg plus bilateral ECT with 7 controls treated with tricyclics plus ECT. In the first group, convulsions lasted an average of 38.4 seconds compared to 23.4 seconds in the second group. They reported no other effects of interest.

In 1995, Folkerts[34] reported a case of spontaneous convulsions during anaesthesia induction with methohexital, prior to the stimulus, in a patient treated with paroxetine 40 mg; although there was no data to make the association and there had been instances of spontaneous seizures with methohexital, Folkerts urged caution, in general, when combining SSRIs and ECT.

In 1996, a review by Serfaty et al,[35] looking at 30 cases with fluoxetine, 12 with paroxetine, and 1 with sertraline, showed that, in comparison with other psychoactive drugs used with the sample, SSRIs clearly prolong the convulsions (within normal limits).

There are numerous results that rule out risk in combining ECT with SSRIs. In 1989, Kellner and Bruno[28] described

2 cases of patients with plasma fluoxetine levels within therapeutic range who had no adverse effects upon receiving ECT. Harsch and Haddox[29] also reported a case in 1990 where there was no change in convulsion parameters. In 1989, Gutierrez-Esteinor and Pope[30] published a solid study on 12 patients receiving ECT and fluoxetine 20-140 mg, with 25 controls receiving ECT only, in which they found no significant difference in convulsion times. In fact, the study describes a certain trend toward shorter convulsion times in the group on high doses of fluoxetine. Zis[31] also published a prospective study in 1992 on 7 patients with depression who received placebo or fluoxetine prior to the third or fourth ECT, with no difference found in the duration of convulsions.

In a methodologically complex study in 1996, Lauritzen et al[36] compared early response and relapses in 87 patients with depression following ECT with paroxetine 30 mg, imipramine 150 mg, and placebo. Early response was better with imipramine, but relapses were much less common? when paroxetine was used for maintenance. There were no problematic effects in any of the cases.

We may recapitulate that, although there are data suggesting a certain prolongation of convulsion time with the ECT-SSRI combination, on the whole, the increases described are not problematic. Therefore, in general, maintaining SSRIs during ECT is advocated, if they are clinically necessary, because there is a low clinical risk.[7] It must also be taken into consideration that depression could worsen if antidepressants are abruptly discontinued prior to ECT.

Finally, as for the latest to appear on our market, Farah[38] reported in 1997 on the ECT-mirtazapine combination. Although there were only 2 cases, a total of only 7 treatments, and 1 of the patients was seriously polymedicated, the results were satisfactory with no complications attributable to the interaction. With escitalopram, in 2008 Masdrakis[39] reported 3 cases with no complications at a dose of 20 mg.

The data on venlafaxine are interesting. On the one hand, regarding risks with the combination, there are data consistent with cardiac changes in patients on variable doses of venlafaxine, especially in the high range.[40-44] However, in 1995, Farah and Colenda[40] reported on use of the combination in 2 elderly patients, ages 67 and 72 years, with depression resistant to tricyclics, fluoxetine, and lithium. There was a partial clinical response, but the tolerance was excellent. Bernardo et al,[41] in a study comparing venlafaxine with imipramine and chlorimipramine, found no difference in terms of the number of ECT sessions, the mean duration of the convulsion, or the average post-ECT increase in arterial pressure and concluded that the concomitant use of venlafaxine and ECT is safe.

In a very interesting, recent (2009), and well-structured study on efficacy with the potentiation, Sackeim et al[45] found that the ECT-nortriptyline combination was more effective than the ECT-placebo combination. The study reported a similar effect with the ECT-venlafaxine combination but to a somewhat lesser degree than with nortriptyline. No significant increase in adverse effects was found, although a possible worsening of the retrograde amnesia was described for venlafaxine, which was better with nortriptyline, however.

Finally, as for ECT with bupropion, Conway and Nelson[22] reported in 2001 a case of prolonged convulsions, but it was a patient medicated with lithium and venlafaxine, as well.

On the whole, except with the classical MAOIs, which are seldom used in our setting and largely questioned, the response to ECT may be potentiated with the antidepressants, especially the tricyclics. Regarding interaction in technique or increased side effects, there is a low level of cardiovascular and cognitive risk with use of the tricyclics and a slight risk of prolonged convulsions with the SSRIs. Venlafaxine (not at high doses) and mirtazapine also appear to be effective and reasonably safe potentiators. As always, combining ECT with antidepressants and the timing of its implementation must be an individualized decision based on the patient's symptoms and medical situation, including the technical capabilities of the clinical setting where it is administered.

Benzodiazepines

The benzodiazepines have an anticonvulsant effect, which is why, traditionally, it has been thought that they may interfere with the duration of ECT-provoked convulsions and even with the efficacy of the technique.[15]

Along this line, the recommendation of the 1999 Spanish Consensus on ECT was to avoid using them during ECT unless they were taken as chronic treatment.[5] The APA criteria indicate that they should be combined with ECT only if absolutely necessary,[3,4] in which case, it is suggested that the short-half-life, lorazepam-type drugs without metabolites are preferable as anxiolytics[46] and, as hypnotics, the ultrashort-acting triazolam type.[47] The 2001 APA recommendations suggest reducing or suspending benzodiazepines whenever clinically feasible prior to a course of ECT.[4]

Most of the studies we reviewed support this practice. Stromgren[48] compared 23 patients receiving benzodiazepines as hypnotics or anxiolytics with 20 controls, using unilateral ECT, and recommended that the combined use be avoided, having found a clear difference in the patients on benzodiazepines: shorter duration of convulsions, more sessions required to obtain improvement, and more ineffective sessions. The results obtained by D'Elia et al[49] in 1983 as well as Ottosson[50] and Standish-Barry et al[51] in 1985 are very similar.

In 1990, Pettinati et al[52] compared 34 patients treated with benzodiazepines plus ECT with 14 controls taking no drugs. They observed that, when unilateral ECT was applied, the use of benzodiazepines was clearly associated with ineffective convulsions and less improvement in the depression, although this was not the case when bilateral ECT was used. The study has had a major impact despite certain methodological limitations, such as the scant number of bilateral ECTs and the threshold not being determined.[11]

Klapheke[9] concluded in 1997 that benzodiazepines raise the threshold, shorten the duration of convulsions, and reduce the efficacy of unilateral ECT but indicated that one must be conservative in discontinuing them

and perhaps use sedative neuroleptics as alternatives, if necessary.

The only instance we found where it was suggested that the benzodiazepines potentiate the clinical effect of ECT was that of Petrides et al[53] in 1997, but this was about 5 cases of catatonia treated with ECT and lorazepam—not affective symptoms, as in the majority of studies.

Despite all the foregoing, combined use continues to be commonplace in daily clinical practice because it is risky to abruptly discontinue benzodiazepines due to the risk of anxiety rebound and even withdrawal, and it is problematic to postpone ECT until at least reducing the dose.[11] In this situation, given the possibility that the benzodiazepines may mean less effective ECT, discontinuing them is thought to be preferable; if that is not possible, the recommendation is that bilateral stimuli and charges that are clearly suprathreshold be used.[46]

On the whole, reduction or suspension of benzodiazepines appears to be preferable, whenever clinically feasible, prior to a course of ECT. If this is not possible, the technique will have to be adjusted to ensure effective convulsions and minimize side effects.

Lithium

The bibliography on the use of lithium during ECT continues to be contradictory. Most of the cases of interaction reported have to do with delirium situations or the risk of a prolonged effect of neuromuscular blockers during anaesthesia. They range from reports of frank neurotoxicity, such as reports associated with prolonged convulsive activity,[54] to authors who have documented the safety and beneficial effects of continuing lithium during ECT.[55-57]

In 1980, Small et al[58] presented 25 cases of ECT with concurrent use of lithium, comparing them with 25 ECT controls. With the combined treatment, deterioration in memory parameters, increased confusion, and atypical neurological changes were found. Small reviewed the subject again in 1990 and again concluded that the combined treatment must be avoided, whenever possible, but may be applied in emergency situations with rigorous monitoring of the effects.[59]

In 1990, Penney et al[60] studied 27 cases of concomitant use of lithium and ECT; 49 cases where lithium was suspended 24 hours prior to ECT or restarted 48 hours after the sessions; and 100 cases of ECT without lithium. They found only increased confusion with no other major risks, and while they did suggest caution, they did not consider it completely contraindicated. However, more recently (2005), Dolenc and Rasmussen[61] described 12 patients in whom the ECT-lithium combination was safe.

The mechanism of the interaction was not clear. It was proposed that the risk of delirium resulted from the massive shift of lithium to the intracellular space due to the opening of sodium channels caused by the convulsion.[62] Cholinergic mechanisms, a drop in the threshold with increased convulsions and, in particular, increased BBB permeability to lithium have also been implicated, although the studies showed that levels within the brain did not really increase, nor did blood levels decrease.[14]

The 1985 ECT Consensus Conference,[64] even though admitting there was no firm evidence contraindicating this combination,[10] also recommended that it be avoided, just as Abrams did in his 2002 text—despite the fact that optimistic reviews, such as the one by Rudofer et al[63] in 1987 that analysed, in particular, the pharmacokinetic interactions of lithium with ECT, found only isolated cases where anaesthesia and neuromuscular blockers were potentiated.

We can emphasize that the 1999 Spanish ECT Consensus did not consider the concomitant use of lithium and ECT contraindicated, with certain precautions related to the stimulus and the monitoring of cognitive function.[5] In 2001, the APA[4] warned of the risk of delirium with this combination and suggested suspending or reducing the dose of lithium prior to ECT, based on a cost-benefit analysis of the risk of affective relapse. For patients with a serious and recurrent affective disorder, discontinuing lithium may be ill-advised, so the decision to keep the patient on lithium must be made on a case-by-case basis, evaluating the risks of neurotoxicity against the risks of affective relapse if the medication is suspended. If need be, it could be applied by holding the last doses to reduce levels and using an ECT technique that minimizes the risk of cognitive effects.[63]

Anticonvulsants

By definition, anticonvulsants reduce the onset, proliferation, and duration of epileptic seizures.[7] A certain consensus has been reached as to anticonvulsants interfering with the duration of ECT convulsions[64] or increasing the cognitive effects which, together, affect the clinical response.[65]

Some authors (among them the APA itself in 2001)[4] advocated reducing the dose, but others said only if interference is observed so that sufficient convulsions would be obtained.[7] To maintain adequate convulsions, besides adjusting the dose of anticonvulsant, the charge administered can be increased[10] or the convulsive threshold lowered using hyperventilation.[66] There is controversy about this, however. In 2001, the APA[4] raised the issue that "adequate convulsion" was not well defined and recommended avoiding the negative impact of anticonvulsants on the threshold (provided that these were prescribed for a psychiatric indication—as mood stabilizers, for example), and Abrams warned of an increased risk of status epilepticus following an abrupt suspension of antiepileptics.

However, we do not have the data obtained from prospective trials—only from reviews of case series. Consequently, since 1997, with Zárate et al[67] in their modest series of ECT applied together with valproic and with carbamazepine, it has been accepted that the combination is not particularly toxic, when it is necessary, nor does it interfere significantly with the technique other than, with carbamazepine, the known prolongation of the effect of succinylcholine.[64] The 2007 review by Sienaert and Peuskens[68] on carbamazepine, gabapentin, lamotrigine, topiramate, and valproic also ruled out risks with the combination, but no potentiation was found, either—a hope that has been kept alive recently.[69] We do not have clearly

differentiated data with different substances—lamotrigine, as a case in point, with 2 series indicating good clinical tolerance and low interference with the technique.[65,70] Therefore, on the whole, we find that the anticonvulsants apparently do not interfere significantly with the technique, nor do they cause significant side effects, but there is also no evidence of potentiation of effect.

Antipsychotics

The use of ECT in schizophrenia is a subject still being debated. It is assumed that there is a low efficacy, overall, although prominent authors[72,73] have questioned this impression on the basis of old studies with heterogeneous samples of impaired patients. It is generally accepted that the response is quick but the effect is short-lived.[74] In recent years, ECT has been reconsidered as an option in patients with serious or refractory symptoms and even for first psychotic episodes, with promising results.[75,76]

The 2001 APA criteria[4] suggested ECT for schizophrenia, if catatonia, affective symptoms, a history of good response were present, and when the psychotic symptoms had an abrupt and/or recent onset in the present episode. Similar conclusions were reached in a 2005 Cochrane review.[77] The restrictive NICE guidelines did not consider ECT an option in the management of schizophrenia;[2] however, the Royal College's 2004 Guide[1] accepted it as a possibility in resistant schizophrenia and as first-line treatment in catatonia.

In contrast to the other groups of psychoactive drugs reviewed, we found a widespread consensus that the risk of using the antipsychotics in combination with ECT is low, and the combination even potentiates the positive clinical effects.[7] We will review both aspects: the "classical" antipsychotics and the so-called "atypicals" (to clarify the review, we maintain a distinction that is no longer tenable[78-80]).

Regarding the possible risks of combination with classical antipsychotics, the most general precaution stems from the effect of lowering the convulsive threshold. In 1993, Nobler and Sackeim[46] proposed that the dose of antipsychotics needed to be reduced during ECT to prevent possible prolonged convulsions, for it appeared to be a risk that increased with high doses. The risk seemed to be greater with phenothiazines and reserpine,[7] although these were old and contradictory studies. Although there was some data on increased morbidity and mortality with the ECT-chlorpromazine combination, in 1982 Janakiramaiah et al[81] compared ECT and chlorpromazine at various doses with CPZ alone in 60 patients and found greater efficacy with adequate doses of CPZ alone, except in speed of response, but with no data on risk. In a 1973 review of phenothiazines, Turek[82] indicated that, although the studies were methodologically questionable, there was usually low risk and greater clinical efficacy with the combination.

In terms of potentiation of the clinical effect with the combined use of typical antipsychotics and ECT, only Sarkar et al[83] presented negative data from a careful, double-blind, prospective trial with schizophrenic patients in 1994: using haloperidol 15 mg alone or in combination with 6 sessions of bilateral sinusoidal ECT, they found no short- or medium-term difference in the clinical response. Considering only the most important articles, Kong and Glatter-Gotz[84] in 1990 found good response with a low level of risk in 13 psychotics resistant to haloperidol, zuclopenthixol, fluphenazine, and droperidol alone, when ECT was added. Chanpattana et al[85] found, in 1999, that the ECT-flupentixol combination is effective in the treatment of resistant schizophrenia. These results continued to be confirmed in other trials of the group.[85-88] Although their study indicated certain methodological biases, in 2009 Ravanić et al[89] concluded that the ECT-antipsychotics combination may be used safely and effectively in treating resistant cases of schizophrenia and suggested that the new atypical drugs may be more suitable than the old ones.

We have been speaking of resistant schizophrenia, in general, and we must go on to speak about clozapine. Since the initial controversy in 1990 between no lesser figures than Meltzer[90] and Fink—the latter having proposed to the former that ECT would be more effective and less risky than clozapine in resistant schizophrenia, despite fears that may be aroused by the data on electroencephalographic abnormalities and dose-dependent, spontaneous convulsions in clozapine-treated patients—studies on combining ECT with this drug have been relatively numerous and generally positive.

In 1991, Masiar and Johns[91] reported a case of late convulsions after ECT in a psychotic patient who had received 800 mg of clozapine until 14 days prior to the ECT. The authors themselves were cautious about attributing the seizures to the combination of treatments, bearing in mind, above all, that the patient was also receiving high doses of diazepam, which had been suspended immediately prior to the ECT.

Frankenburg et al[92] (1993) reviewed 12 cases of the use of combined therapy in resistant psychosis, with an average clozapine dose of 550 mg; the clinical response was variable, with no reportable side effects. The similar cases in a correct, open, prospective trial in 2004—Kales et al, 14 cases,[93] Factor et al, 2 cases,[94] Cardwell and Nakai, 7 cases,[95] Benatov et al, 4 cases,[96] Bathia, 1 case,[97] and Kho, 10 cases[98]—showed a good percentage of favourable responses and only one case of tachycardia that persisted following ECT. In 2000, Kupchik[99] reported on 36 cases of clozapine combined with ECT; in 5 of those cases, there were cardiac arrhythmias (4 sinus tachycardia and 1 supraventricular tachycardia, in one patient treated, in turn, with caffeine), which prompted this author to suggest that cardiac arrhythmias may be a relative contraindication to administration of the combined treatment.

In 2006, Havaki-Kontaxaki[100] reviewed the most important data on the ECT-clozapine combination that had been reported up until that time and found potentiation in 67%-72% of cases, although in 22% the positive effect lasted for only 4 months; adverse effects were reported in 16% of cases.

When caffeine is added to clozapine because the ECT convulsions are not of sufficient duration (although this is a seldom-used technique), the data are contradictory: Lurie[101] reported a case of combined use with good response and no complications, but Klapheke[9] identified an increased chance of cardiac rhythm complications while Bloch et al[102]

reported an isolated case of prolonged convulsions with this combination.

As for the other so-called atypical antipsychotics, experimental data with rats on the use of risperidone (reported by the research laboratory for this drug) suggest an a priori elevation of the convulsive threshold.[103] In clinical practice, Farah et al[104] (1995) reported 10 cases of bilateral ECT together with risperidone; of these, 4 patients were described as having affective o schizoaffective symptoms and were receiving moderate doses of risperidone (6 mg on average) with unilateral or bilateral brief-pulse ECT. They found no complications and the response, in cases previously resistant to monotherapy, was favourable. Very briefly, Madhusoodanan et al[105] (1995) described a case of bipolar disorder in a 79-year-old patient who received risperidone 2 mg together with ECT with no problematic effects but no clinical benefit, either. In our setting, Alcántara et al[106] reported a case of psychotic symptoms in a patient with Parkinson's disease treated with L-dopa who received 8 ECT sessions together with risperidone 1 mg; there was good response in terms of the symptomatology and no complications.

More recently, some authors[107] pointed out that the increased efficacy of risperidone and olanzapine in combination with ECT is less than with other pharmacological potentiation strategies.

Regarding aripiprazole, Masdrakis[108] (2008) reported on 4 cases that supported its safety as concomitant treatment with ECT. All the patients benefited from the treatment and had only the minimal and transitory cognitive effects usually associated with ECT. Finally, comparing potentiation with unilateral ECT for olanzapine, risperidone and sulpiride in resistant schizophrenia, Ravanić et al[89] reported a greater effect according to the order they are listed.

On the whole, we found widespread consensus that, with "classical" antipsychotics, the combination potentiates the positive clinical effects and that the risk of using them in combination is low and related, for the most part, to the drop in convulsive threshold. The most positive data were reported with ECT and clozapine in resistant psychosis, with very few effects stemming from the clozapine-induced drop in convulsive threshold and with a significant potentiation effect, even though of limited duration. With other atypicals, there is less data available, but it indicates, in general, various degrees of potentiation and no toxicity with the combination.

Some drugs used in the ECT technique

Caffeine

As we know, caffeine is used to potentiate convulsions because the methylxanthines compete with adenosine.[7] We attempt to reduce excessively high thresholds or prolong the seizures in cases where they are short, although these two effects are sometimes independent.[109]

Since the pioneering article by Shapira et al[110] in 1987, many more have been published. In practice, intravenous caffeine sodium benzoate is generally used at a dose of 500-2000 mg immediately prior to the stimulus, with good cardiovascular and clinical tolerance, overall, even in high-risk populations.[111]

In recent times, however, the technique has been questioned for various reasons. On the one hand, in rats, lesions of the hippocampus and striatum have been described[112] that may be attributable to the combination; on the other hand, a certain annulling of the desired effect in successive sessions has been reported.[113] What has been questioned above all, however, is whether its effect is of any real clinical value[114] and whether it is necessary with the latest generation of ECT stimulators. In 1990, Coffey et al[115] conducted a double-blind study to compare caffeine-potentiated ECT with maintenance of convulsion time via stimulus adjustment; they found, in general, no difference in the evolution, cognitive effects, or side effects.

In a 2002 review of proconvulsant drugs, Datto et al[116] concluded that the strategy of modifying anaesthetic agents—using drugs such as etomidate and ketamine as well as hyperventilation—was more favourable than the strategy of using caffeine. These results were also reported in a recent (2010) trial by Bundy.[117]

Theophylline

Theophylline also prolongs ECT-induced convulsions—a fact that means assuming a certain clinical risk[118] when combining the two treatments[119,120] but also represents an alternative to caffeine, as yet relatively unexplored, for producing that effect when we desire it.[121] In 2008, Schak[122] concluded that, with an appropriate pre-treatment evaluation and certain precautions during the procedure, ECT may be administered safely to patients with chronic obstructive pulmonary disease.

Flumazenil

When ECT must be administered to patients taking benzodiazepines, one alternative that has been proposed is to "flush" the benzodiazepines with flumazenil immediately prior to ECT;[123-125] however, the dose and the ideal timing for this remain to be determined, and the risk of withdrawal has not yet been assessed.[11,126]

The 2001 APA recommendation for using flumazenil to flush benzodiazepines is that a short-acting benzodiazepine (e.g., midazolam) be administered immediately after induction of the convulsion to prevent post-ictal withdrawal effects.[4]

Potentiating drugs in psychopharmacology and ECT

L-tryptophan

It has been suggested that l-tryptophan may potentiate the antidepressant effect of ECT. In 1977, D'Elia et al[127] reported a positive result though, clinically, it was not very significant. There is evidence of a risk of increasing mnestic changes,[128] which is why the majority of authors contraindicate it.[7]

Triiodothyronine (T3) and TRH

Good results have also been reported for T3 in terms of potentiating the antidepressant effect of ECT. Specifically, better convulsion parameters, cognitive improvement post-ECT, and subjective clinical improvement have been described; however, there is not sufficient data, perhaps, to use it on a routine basis.[7,129]

Khan et al[130] describe the use of TRH at low doses (0.5 mg) administered 5 minutes after the session in patients with depression undergoing ECT treatment. In a double-blind trial, improved performance on neuropsychological batteries was observed, which suggests the possibility that cognitive damage may be reduced without modifying the convulsion time.[131] In an extension and re-analysis of the Papakostas et al study,[132] it was shown that patients whose TSH response was blocked by administration of TRH may be more susceptible to the convulsions (measured by convulsion duration), but the results of a subsequent trial[133] did not corroborate the role of TRH in modulating convulsions, at least when TRH was administered exogenously.

Conclusions

The level of risk in combining psychoactive drugs with ECT is low, overall, so that, generally speaking, the presence of these drugs should not be another factor that delays or hinders application of this technique. In addition, a certain potentiation of effect with their concomitant use has been observed on occasion.

such as in the case of the antidepressants. Except with the classical MAOIs, which are largely questioned—and bearing in mind that the data available is derived only in part from methodologically sound studies[6]—studies generally show that the therapeutic response to ECT may be potentiated by the antidepressants, especially the tricyclics. In terms of interaction in technique and increased side effects, there is a low level of cardiovascular and cognitive risk with the tricyclics and a slight risk of prolonged convulsions with the SSRIs. The latest drugs, such as venlafaxine (not at high doses) and mirtazapine also appear to be effective and reasonably safe potentiators.

Provided that it is clinically feasible, it appears that a reduction or suspension of benzodiazepines prior to the course of ECT is desirable because of the risk that convulsion times may be shorter, more sessions may be required to obtain improvement, and more sessions may be ineffective. If this is not possible, the technique will have to be adjusted to ensure effective convulsions and to reduce side effects.

On the whole, maintaining lithium treatment at therapeutic levels during ECT appears to be ill-advised due to the risk of neurotoxicity. It will be necessary to interrupt or reduce the lithium dose prior to ECT, in light of a cost-benefit analysis of the risk of a relapse of psychopathology. If the lithium is continued, it will be adjusted to lower levels, especially in the elderly, and an ECT technique that reduces the risk of cognitive effects will be used.

The indication for ECT in schizophrenia is secondary; it is generally accepted that while the response is quick, the effect is short-lived. In recent years, ECT has been reconsidered as an option in patients with serious or refractory symptoms, always in conjunction with antipsychotics.

With "classical" antipsychotics, there is a widespread consensus that the combination potentiates the positive clinical effects and that the risk of using them in combination is low and related, for the most part, to the drop in convulsive threshold.

The most abundant and positive data was reported with ECT and clozapine in resistant psychosis, with very few effects stemming from the clozapine-induced drop in convulsive threshold and with a significant potentiating effect, even though of limited duration. With other atypicals, there is less data available, but it indicates, in general, various degrees of potentiation and no toxicity with the combination.

As for other drugs, we will highlight that, with the more up-to-date ECT techniques, there is scant support for the use of caffeine; also, the use of beta blockers and, perhaps less systematically, the use of atropine probably should be considered more often. Potentiators such as TRH, l-tryptophan, and T3 are in utter disuse; it appears that the anticonvulsants do not interfere significantly with the technique, nor do they cause significant side effects, but there is also no evidence of potentiation of effect.

Although methodologically sound trials must be conducted to endorse this practice, and although the combining of ECT with psychoactive drugs as well as the timing of its implementation must be an individualized decision based on the patient's symptoms and medical situation—including the technical capabilities of the clinical setting where it is administered—we believe that, on the whole, the risk level in concomitant use of ECT and psychoactive drugs is acceptable and the data on its efficacy is promising.

Conflict of interest

The authors declare that they have no conflict of interest.

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