Electroconvulsive therapy in major depression: current aspects

Eletroconvulsoterapia na depressão maior: aspectos atuais

Paula Barros Antunes,¹ Moacyr Alexandro Rosa,² Paulo Silva Belmonte-de-Abreu,³ Maria Inês Rodrigues Lobato, 4,5 Marcelo P. Fleck³

Abstract

Objective: The efficacy of electroconvulsive therapy in treating depressive symptoms has been established by means of innumerable studies developed along the last decades. Electroconvulsive therapy is the most effective biological treatment for depression currently available. The objective of this study was to demonstrate the role of electroconvulsive therapy in the treatment of depression and highlight present aspects related to its practice. Method: We reviewed in the literature studies on efficacy, symptom remission, predictive response factors as well as current aspects regarding quality of life, the patients' perception, mechanism of action, technique and cognitive impairment. Results: The main results found in the this revision were: 1) electroconvulsive therapy is more effective than any antidepressant medication; 2) the remission of depression with electroconvulsive therapy varies, in general, from 50 to 80%; 3) The effect of electroconvulsive therapy in brain-derived neurotrophic factor levels is still controversial; 4) electroconvulsive therapy has a positive effect in the improvement of quality of life; 5) patients submitted to electroconvulsive therapy have, in general, a positive perception about the treatment. Conclusion: Electroconvulsive therapy remains a highly efficacious treatment in treatment-resistant depression. With the improvement of its technique, electroconvulsive therapy has become an even safer and more useful procedure both for the acute phase and for the prevention of new depressive episodes.

Descriptors: Electroconvulsive therapy; Brain-derived neurotrophic factor; Depression; Quality of life; Treatment outcome

Objetivo: A eficácia da eletroconvulsoterapia em tratar sintomas depressivos está estabelecida por meio de inúmeros estudos desenvolvidos durante as últimas décadas. A eletroconvulsoterapia é o tratamento biológico mais efetivo para depressão atualmente disponível. O objetivo deste estudo foi demonstrar o papel da eletroconvulsoterapia no tratamento da depressão e destacar aspectos atuais relativos à sua prática. Método: Foram revisados na literatura estudos de eficácia, remissão de sintomas, fatores preditores de resposta, assim como aspectos atuais acerca da qualidade de vida, percepção dos pacientes, mecanismo de ação, técnica e prejuízo cognitivos. Resultados: Os principais achados desta revisão foram: 1) a eletroconvulsoterapia é mais efetiva do que qualquer medicação antidepressiva; 2) a remissão da depressão com a eletroconvulsoterapia varia, em geral, de 50 a 80%; 3) Ainda é controverso o efeito da eletroconvulsoterapia nos níveis de fator neurotrófico derivado do cérebro; 4) a eletroconvulsoterapia tem efeito positivo na melhora da qualidade de vida; 5) os pacientes submetidos a eletroconvulsoterapia, em geral, têm uma percepção positiva do tratamento. Conclusão: A eletroconvulsoterapia permanece sendo um tratamento altamente eficaz em pacientes com depressão resistente. Com o avanço da sua técnica, a eletroconvulsoterapia tornou-se um procedimento ainda mais seguro e útil tanto para a fase aguda, quanto para a prevenção de novos episódios depressivos.

Descritores: Eletroconvulsoterapia; Fator neurotrófico derivado do cérebro; Depressão; Qualidade de vida; Resultado de tratamento

- Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre (RS), Brazil
- Department of Psychiatry, Division of Brain Stimulation & Therapeutic Modulation, Columbia University e New York State Psychiatric Institute, USA
- Medical School, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre (RS), Brazil
- Program of Schizophrenia, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre (RS), Brazil
- Post-Graduate Program in Medicine: Psychiatry, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre (RS), Brazil

Correspondence

Paula Barros Antunes Avenida Nilo Peçanha, 1452/404 91330-000 Porto Alegre, RS, Brazil Phone/Fax: (+55 51) 3024-2091 E-mail: antunespaula@hotmail.com

Introduction

Major depression is commonly a chronic, recurring and debilitating disorder, which brings about much impairment to the functioning and quality of life (QOL) of patients. 1,2 Although the treatment with antidepressants is very efficacious for a great part of the patients, many of them do not respond adequately to the antidepressant treatment or do not tolerate the side-effects of the medications.3,4 Patients who do not have their symptoms fully remitted show higher recurrence risk have worse psychosocial functioning, worse QOL, and higher number of symptoms during follow-up.5-7

Electroconvulsive therapy (ECT) is a procedure which consists of the induction of convulsive crises by means of applying an electric current through the brain for therapeutic purposes. Resistance to the antidepressant medication is the main indication for ECT.8-11 Besides, ECT provides a faster response as compared to medication, which is necessary in severe situations that need emergency intervention, such as catatonia and suicide risk.12 The American Psychiatric Association has already included these situations as indication of ECT as the first choice.13

The efficacy of ECT to treat depressive symptoms has been established by means of innumerable studies developed during the last decades. According to Prudic, ECT is the most effective biological treatment currently available for depression, and no other treatment up to now has shown to be superior to ECT in the treatment of major depression in controlled studies.14

The objective of this revision is to present the role of ECT in the treatment of depression and highlight current aspects related to its practice. Thus, we established some clinically relevant items about ECT, and, next, we accomplished a review of the literature, emphasizing articles on meta-analyses, reviews, and randomized clinical trials.

Meta-analyses about the efficacy of ECT

There are three recent meta-analyses which have evidenced the superiority of ECT as compared to other treatments. Kho et al., in the year 2003, accomplished a meta-analysis which assessed the efficacy of ECT in the improvement of depressive symptoms, by analyzing 15 studies. 15 The comparison of ECT and control treatments, from baseline to post-treatment period, including all studies, has shown an effect size (ES) of 0.90 (95% CI 0.52; 1.27). It was demonstrated that ECT is significantly superior in the treatment of depression when compared to antidepressants or simulated ECT (when there is anesthetic induction, although no electric charge is applied). There was no significant difference as for ECT's efficacy or speed of action, when sinusoidal wave (nine studies) and brief pulse (10 studies) were compared, occurring an overlap in the confidence intervals. This study suggested that ECT is superior regarding the speed of action in the subgroup of patients with psychotic depression.

The UK ECT group, 16 also in 2003, performed a systematic review and meta-analysis of 73 randomized controlled clinical trials that compared the efficacy of real ECT with that of simulated ECT, also ECT versus pharmacotherapy, or even different ECT techniques in the improvement of depression, which was measured by the Hamilton Depression Rating Score (HDRS). The result of this study has shown that real ECT was significantly more efficacious than simulated ECT (six studies, 256 patients with ES -0.91 and 95%CI -1.27; -0.54) and more efficacious than pharmacotherapy (18

studies, 1.144 patients with ES -0.80 and 95% CI -1.29; -0.29). As for the technique, bilateral ECT was more effective than unilateral ECT (22 studies, 1.408 patients, ES -0.32 and 95% CI -0.46; -0.19), although it has provoked more cognitive side-effects. There were no significant difference in the distinct frequencies in which ECT was performed (one to three courses per week); however, the more frequent, the higher the cognitive impairment observed (six studies, 210 patients). The dose used also influenced the efficacy (seven studies, 342 patients): the higher the dose, the higher the efficacy, independently from the positioning of the electrodes. There was also no difference between the types of wave used, brief pulse or sinusoidal (eight studies, 296 patients).

Pagnin et al., in 2004, accomplished another meta-analysis that assessed the efficacy of ECT in depression by analyzing randomized controlled clinical trials.¹⁷ They found that real ECT had significantly higher response rates regarding simulated ECT and placebo (11 studies, 523 patients). The probability of occurring a positive response, in terms of odds ratio, was nearly five-fold with real ECT than with simulated ECR and placebo (OR = 4.77; 95% CI 2.39; 9.49). In the comparison of ECT with antidepressants in general (13 studies, 892 patients), ECT showed a significant superiority, with a four-fold probability of response as compared to antidepressants (OR = 3.72; 95% CI 2.60; 5.32). Separate comparisons of ECT versus tricyclic antidepressants (TAD), and ECT versus monoamine oxidase inhibitors antidepressants (MAOI) were also accomplished. A significantly higher efficacy of ECT regarding TAD (OR = 2.99; 95% CI 1.91; 4.71) and MAOIs (OR = 6.13; 95%CI 3.82; 9.83) was demonstrated.

The National Institute of Clinical Excellence - NICE), in its guidelines on ECT, reported that it was performed a review of 90 randomized clinical trials (RCT) about the efficacy of ECT in depression, and concluded that ECT is more beneficial than antidepressants and that real ECT is more effective than simulated ECT. Preliminary studies showed that ECT is more effective than transcranial magnetic stimulation.18

Aiming to assess the volume of publications with ECT in depression, we have searched for articles using the keywords "ECT", "depression" and "randomized clinical trials", obtaining 192 articles. By analyzing their abstracts and titles, we selected those aimed at comparing the efficacy of ECT in major depression or the evaluation of new techniques (e.g., high dose unilateral ECT x bilateral). Articles that did not deal with major depression patients were excluded.

ECT and remission of symptoms

The rate of remission of symptoms in depressed patients treated with ECT has been described in some studies. Husain et al., in the assessment of major depression patients submitted to bilateral ECT, demonstrated that 75% of the sample and 87% of patients who completed the ECT series (who received more than 10 sessions) had presented with complete remission (HRSD score lower than 10).19

Sackeim et al. assessed 290 patients with unipolar depression who had been submitted to ECT, of which 159 (54.8%) had their depressive symptoms remitted.²⁰ The efficacy of ECT in atypical depression was demonstrated in one study that compared patients with typical and atypical depression, who showed remission rates of 67.1% and 80.6%, respectively.²¹

In the Consortium for Research on ECT (CORE),22 one study with 531 patients reported that 64.2% (341/531) of the sample reached the remission of their depressive symptoms (HRSD ≤ 10). Sienaert et al. reported that of the 64 patients with major depression submitted to ECT in their study, 65.6% reached complete remission (HRSD ≤ 10).²³ In one study²⁴ with 92 depressed patients submitted to six sessions of ECT, only 15% reached remission (HRSD < 9).

New perspectives regarding the mechanisms of action of ECT

It is known that ECT affects multiple areas of the central nervous system (CNS), including neurotransmitters, hormones, neuropeptides, and neurotrophic factors.²⁵ Neurotrophines are proteins that protect the CNS, promote cellular growth, the growth of dendritic sprouts in the cellular bodies, as well as the expression of monoaminergic receptors and the stimulus for the production of monoamines.26

A specific neurotrophine that has been measured in several areas of the CNS, particularly in the hippocampus, is called brainderived neurotrophic factor (BDNF). The BDNF is a neurotrophic factor widely expressed in the CNS which has an important role in the cerebral development, in the maintenance and survival of the neuronal functions and in neuroplasticity.

There is increasing evidence that the BDNF has a crucial role in psychiatric disorders, including depression. One study showed that depressed patients have significantly lower BDNF levels when compared to controls, and that serum BDNF has a negative correlation with the severity of depression.²⁷ Such a decrease in the BDNF seems to be normalized with antidepressant pharmacological treatment.28

One study demonstrated that serum BDNF levels are lower in depressed patients than in controls and that the treatment with antidepressants, for a period of 12 weeks, increases the BDNF levels to the levels of controls.29

There are few studies which assessed the change of the BDNF in patients submitted to ECT. Marano et al., in a pilot study, reported that BDNF plasma levels significantly increased from the pre-ECT period (mean of 84.9pg/ml) in relation to the post-ECT period (mean of 141,2pg/ml) and this change was accompanied by a significant clinical improvement (decrease in HRSD scores).30 Of the 15 patients assessed in that study, 13 responded to ECT, and of these, 12 showed increase in BDNF levels. Of the two patients who did not respond to ECT, one had an increase in post-ECT BDNF levels. The same study showed an association between psychosis and percentage change of the BDNF, being higher the percentage of BDNF increase in psychotic patients.

Other study that assessed the behavior of plasma BDNF in patients with refractory major depression submitted to ECT reported that BDNF levels had significantly increased in patients who responded to ECT.31 There was a change from a pre-ECT mean of 8ng/ml to a mean of 15.1ng/ml five weeks after starting ECT, what was not found in patients who did not respond to ECT (pre-ECT mean of 11.5ng/ml to 9.4ng/ml in the fifth week post-ECT).

Bocchio-Chiaveto et al. demonstrated a significant increase in plasma BDNF levels one month after ECT course in patients with depression refractory to antidepressants.32

Other studies did not find significant changes in serum levels of BDNF in depressed patients submitted to ECT. 33,34

ECT and quality of life

Studies showed that ECT, besides improving the patients' symptoms, also improves their QOL. One study demonstrated that ECT is efficacious in the improvement of QOL, with a significant improvement in the scores of the brief WHOQOL scale after ECT sessions.35 Fisher et al. used the SF-36 QOL scale to compare depressed inpatients submitted to ECT to patients who underwent other treatments but not ECT.36 There was a significant improvement in SF-36 scores in both groups between baseline and discharge. McCall et al. evaluated 283 depressed patients, who were hospitalized in community hospitals, using also the SF-36 scale to measure their QOL. There was improvement in QOL scores immediately after ECT in 87% of the patients and 78% of the patients still showed this improvement six months after ECT.37 The improvement in their QOL was maintained during the six months after ECT in those patients who had sustained remission of depression.

Others studies that aimed to measure the QOL in patients submitted to ECT have used subscales of the instrument for psychopathology BASIS-32. McCall et al. compared depressed patients submitted to ECT to patients treated with medication alone.³⁸ In a 12-month follow-up, the degree of improvement in the scores of the subscale Daily Living and Role Functioning (DLRF) of the BASIS-32 was significantly higher in the group that was submitted to ECT. In other study with depressed patients, it was noticed a significant improvement (p < 0.0001) in the scores of the subscales DLRF and Relationship to Self and Other (RSO) of the BASIS-32 two and four weeks after ECT series.39

Perception of patients regarding ECT

Although ECT has a well established efficacy, physicians and patients still have a great resistance to its use. In the last decades, several authors have been concerned in assessing the perception of patients submitted to ECT in relation to the benefit of this treatment. Freeman et al. assessed 166 patients with mood or psychotic disorders who had been submitted to ECT.40 Of these, 57.2% reported that ECT was very useful and 59.4% would undergo again the treatment. In Hughes et al.'s study, of the 72 patients who had been submitted to ECT, 83% have reported improvement with the treatment and 81% of them would do it again.41

Two studies assessed the perception of patients who had been submitted to ECT in their adolescence⁴² and that of their parents.⁴³ Of the 26 patients assessed, 50% have reported that ECT was a useful treatment, whereas 60.7% of the 28 parents evaluated reported benefit with the treatment. Wheeldon et al. assessed 150 depressed patients submitted to ECT, and 80% of them reported that ECT was beneficial and more than 70% would undergo ECT again.44 In other study, of the 64 depressed patients who were evaluated two and four weeks after ECT, 53% and 52% were satisfied and would undergo the treatment again, respectively.⁴⁵ Brodaty et al. interviewed 80 depressed patients, of which 68.8% reported that their condition had improved.⁴⁶

One study that interviewed 36 patients submitted to ECT, using the questionnaire Patient Satisfaction Survey, demonstrated that 50% of the patients perceived that ECT improved their QOL, 47,3% reported being satisfied with the results and 61% were satisfied for having undergone ECT.47 However, only 36% would chose to undergo ECT again. Melekian et al., in the assessment of 22 depressed patients, showed that there was an improvement in the attitude regarding ECT after the treatment and most patients and family members thought that ECT was beneficial and were satisfied with the treatment. 48 This study demonstrated that satisfaction with ECT was independent from treatment outcome.

Some contradictory results in relation to the patients' perception suggest that ECT would have a favorable view by some of the physicians, but not of patients.⁴⁹ One study that compared the evaluation performed by patients and that of physicians demonstrated that the effect size of the scale filled in by patients (BASIS-32) was similar to the effect size of the scale filled in by the interviewer (BPRS), 1.01 and 1.02, respectively.35

Factors that are response predictors to ECT

In depressed patients, the factors that are response predictors to ECT are not yet well established in the literature. The presence of psychotic symptoms in a depressive picture is a predictive factor of better response to ECT. 15,50,51 The depressed patients who present with psychotic symptoms respond better to ECT than depressed patients without these symptoms. One study that compared psychotic depressed patients (n = 77) with non psychotic patients (n = 77) = 176), showed a higher remission rate of the symptoms in the psychotic group.51

The previous history of resistance to pharmacological treatment was associated in some studies with worse response to ECT;52-55 however, other studies did not find such an association. 56,57 As for the duration of the episode, some studies have demonstrated that the longer duration is associated with worse response, 53,56,58 although other study did not find any relationship between the duration of the current episode and responsiveness.⁵⁹ Daly et al. compared the use of ECT in bipolar versus unipolar depressed patients and have not evidenced differences in the response and remission rates between both groups.60

ECT techniques and response

The efficacy of ECT varies according to the technique used. Studies show that high-dose unilateral ECT (UL-ECT) has an equivalent efficacy to bifrontotemporal ECT (BT-ECT); however, low-dose UL-ECT has lower efficacy. 61,62

Sackeim et al., in a double-blind study, randomized 80 depressed patients in four groups with different electric doses and positioning of electrodes: high-dose unilateral ECT [six-fold the convulsive threshold (CT), moderate (2.5-fold the CT) and low-dose (1.5-fold the CT); and bilateral ECT, with dose 2.5-fold the CT. Patients submitted to high-dose UL ECT had a remission rate of depression equivalent to patients submitted to bilateral ECT (65%), and approximately two-fold that of patients submitted to low-dose (35%) and moderate-dose (30%) UL-ECT.63 Patients submitted to bilateral ECT showed higher impairment in the anterograde and retrograde memory within the week after randomization, when compared to any dose of UL-ECT. Two months after ECT, deficits in the retrograde memory were still higher in patients submitted to bilateral ECT.

One meta-analysis that assessed 22 studies (1,408 patients) reported that BT-ECT was moderately more effective than traditional right unilateral ECT (RUL-ECT) (not high-dose), with an effect size of 0.32.16

Although the studies show conflicting findings, the efficacy of the bifrontal positioning seems to be at least comparable to that of UL-ECT and BT-ECT, and it has been suggested that its cognitive impairment is lower than that of BT-ECT.64

One randomized study compared a group of patients submitted to bifrontal ECT(BF-ECT) to RUL-ECT and demonstrated that there was no significant difference between both groups as for the improvement of depressive symptoms, in opposition to the idea that BF-ECT would be better than traditional RUL-ECT.²⁴ In other study, which compared patients who received BF-ECT and UL-ECT, there was also no significant difference between both groups, although patients who received UL-ECT reached response/remission after lower number of sessions.²³

Other study randomized patients to three groups: moderate-dose BF-ECT (1.5 fold the CT), low-dose BT-ECT (immediately above the CT) and high-dose RUL-ECTL (five-fold the CT). 65 There was no significant difference regarding the efficacy to improve depressive symptoms (measured by the HRSD) between groups.

There are some studies that show a superior clinical efficacy of BT-ECT as compared to BF-ECT. Bakewell et al., in a retrospective study with 76 patients, compared BF-ECT to BT-ECT with doses sufficient to reach a convulsion within 30 seconds.66 Bifrontotemporal positioning was significantly more efficient, although only moderately. There was higher risk of relapse with need of hospitalization within one year in the group submitted to BF-ECT, although this group had also presented a lower rate of clinically perceived cognitive side-effects.

Other retrospective study also demonstrated that patients submitted to BT-ECT were significantly less prone to being hospitalized due do relapse of depression in comparison to BF-ECT.67

The first ECT devices produced sinusoidal pulses whereas the current devices produce brief pulses (duration of each pulse: 1-2ms) and, more recently, ultra-brief ones (duration of each pulse < 0.5ms; being common, depending on the device used, pulses of 0.25 or 0.3ms). Preliminary studies have been suggesting that right unilateral ECT with ultra-brief stimulation (RUL-UB ECT) preserves the efficacy and substantially reduces the cognitive sideeffects. Loo et al. demonstrated that RUL-UB ECT can be effective in the treatment of depression with less side-effects than standard right unilateral ECT, however, with slower effect, needing a higher number of sessions than standard ECT.⁶⁸ In other study, Loo et al. compared patients submitted to RUL-UB ECT (0.3ms) to standard right unilateral ECT (1.0ms) and demonstrated that the efficacy was equivalent in both groups, being the cognitive outcomes superior in the group submitted to RUL-UB ECT.⁶⁹

Although RUL-UB ECT apparently provokes less cognitive sideeffects, it is still a technique under investigation and needs further studies before being widely employed.

Post-ECT maintenance

Despite being very efficient in the acute treatment of depression, ECT is a treatment that is ordinarily discontinued after achieving therapeutic success. Although post-ECT relapse is high even with long-term antidepressant treatment, it is even higher if no maintenance treatment is used.^{22,70} Therefore, the maintenance treatment should be carefully chosen and individualized according to the patient's history.

Studies show that the relapse rate after six to 12 months of ECT is approximately 50% in patients who underwent ECT due to refractory depression.^{20,55,70,71}

One naturalistic study that assessed depressed patients who

showed acute remission with ECT demonstrated that, after one year, 41% of the patients have relapsed. 72 In other study, 61.6% of the patients who had acutely remitted with ECT have relapsed after six months of follow-up, being significantly higher the relapse rate in the group that used placebo.²⁰

In other study, the relapse rate within six months was 57.7% of the patients, and the relapse rate of depression (new depressive episode) within 6.8 years after ECT was 42.3%. This study showed that the group of patients who underwent maintenance treatment with antidepressants had a lower relapse rate than the group without such a treatment.⁷³

Sackeim et al. demonstrated that 64% of the patients who received adequate pre-ECT antidepressant treatment relapsed in the first post-ECT year.55

There are few studies that evidence the best alternative to be adopted after the ECT series. In one study that followed-up patients with unipolar depression after ECT course, the association of nortriptyline with lithium showed a lower relapse rate (39%) as compared to placebo (84%) and nortriptyline in monotherapy (60%).²⁰

Some studies assessed the efficacy of maintenance ECT as a treatment option after acute treatment with ECT. One recent review about maintenance ECT showed that, in patients with depressive disorders, maintenance ECT is an important treatment option, especially in those patients who responded well to acute ECT course and showed a history of relapses or recurrences during the pharmacological maintenance treatment.74

Kellner et al., in a follow-up study of patients who had been successfully submitted to ECT, compared one group which used continuation ECT (C-ECT) to other group that used maintenance pharmacotherapy.²² The group that used C-ECT showed a six-month maintenance relapse of 37.1% compared to 31.6% of patients who used medications, without statistical difference between groups.

It is still undetermined which is the best maintenance scheme with ECT. It is probable that each patient needs a specific scheme. The most common is a progressive decrease in the frequency of sessions, weekly in the beginning, fortnightly afterwards and, in the end, monthly. The total duration of the maintenance should be also individualized, but it seems that it should not be lower than six months.22

Memory deficit and ECT (recent studies)

With the decrease of the depressive symptoms obtained by ECT, the improvement in some neurocognitive functions have been observed, especially attention, concentration and general

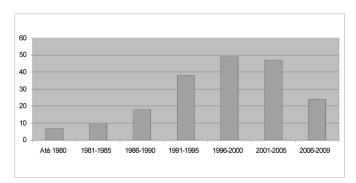


Figure 1 - Number of randomized clinical trials about ECT o depression

Source: Medline - February 17, 2009

intelligence, whereas some alteration has been observed in abstract reasoning and creativity. However, adverse cognitive effects, such as disorientation, impairment in learning, anterograde and retrograde memory, may be observed after a convulsive crisis, including that produced in ECT.75

Cognitive side-effects are the main limitation of ECT, by decreasing the patient's satisfaction and contributing with the stigma associated with the treatment.

Of the cognitive effects, memory deficit is the most important. Just after ECT course, most patients have difficulty to retain recently learned information (anterograde amnesia) and to remember events that occurred weeks or months before ECT (retrograde amnesia). 76,77 In most patients, anterograde amnesia improves rapidly after ECT (in general, within less than one month). As to retrograde amnesia, it is the most persistent collateral cognitive effect of ECT, improving during the first months after the treatment. The memory of the autobiographic information is less affected than impersonal events.78

Randomized clinical trials have shown that memory deficit is more severe with bilaterally positioned electrodes as compared to those unilaterally positioned, 62,63 and the higher the stimulus dose. 62,79

One study proved that BT- ECT provoked more severe and persistent retrograde amnesia, and higher amnesia for autobiographic events when compared to RUL-ECT.77 The use of sinusoidal stimulation was also associated with higher cognitive deficits in relation to brief pulse. In this study, old age, lower pre-morbid intellectual function and female gender were associated with higher cognitive deficits. Cognitive tests are not able to detect persistent alterations, but patients and family members should be oriented to the possibility of impairment, although temporary.13

One study showed that patients who received moderate-dose BF-ECT showed higher Mini Mental scores when compared to patients who received high-dose RUL-ECT or low-dose BT-ECT.65

Conclusion

The efficacy of ECT in depression has been well established by means of an extensive literature. The results show that the benefit goes beyond symptom improvement. There is also improvement in the patients' QOL, functioning and well-being. Besides, patients who undergo this experience are, in their majority, favorable and show positive attitudes regarding ECT. The biggest challenge is to deal with stigma, prejudice and resistance to the use of such an efficient treatment.

Disclosures

Writting group member	Employment	Research grant ¹	Other research grant or medical continuous education ²	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other ³
Paula Antunes	UFRGS	*	-	-	-	-	-
Moacyr Alexandro Rosa	Universidade de Columbia	FAPESP***	-	-	-	-	-
Paulo Belmonte- de-Abreu	НСРА	-	-	-	-	-	-
Maria Inês Rodrigues Lobato	НСРА	-	-	-	-	-	-
Marcelo P. Fleck	UFRGS HCPA	CNPq*** FIPE/HCPA*** Sixth Framework Programm: Comunidade Européia*	Bolsa de Produtividade CNPq*	-	-	Consultor temporário da Organização Mundial da Saúde	-

^{*} Modest

For more information, see Instructions for authors

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^{**} Significant

^{***} Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author. Note: UFRGS = Universidade Federal do Rio Grande do Sul; HCPA = Hospital de Cínicas de Porto Alegre; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; CNPg = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FIPE/HCPA = Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto

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