Response to ECT in depressive subtypes and mixed state

Risposta alla terapia elettroconvulsiva in sottotipi depressivi e nello stato misto

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Summary

Objectives

Available literature data suggest the efficacy of electroconvulsive therapy (ECT) in a large spectrum of depressive disorders, but the results often turn-out to be in contrast with each other. We explored differences of response to ECT in unipolar depression, bipolar depression and mixed state in a sample of patients resistant to pharmacological treatment.

Methods

130 patients (17 with major depressive disorder (UP), 67 with major depressive episode in bipolar disorder type II (BP II), 46 with major depressive episode in bipolar disorder type I (BP I) and 50 with mixed state (MS) according to the DSM-IV criteria) were included in the study and treated with bilateral ECT, on a twice-a-week schedule. The patients were assessed before (baseline) and one week after the ECT course (final score), using the Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impressions scale (CGI).

Results

The four groups (UP, BP II, BP I and MS) showed a significant improvement after the ECT course with comparable response rates in all groups. Remission rate, evaluated with the CGI and the HAM-D scales, was significantly higher in UP compared to the other 3 groups.

Conclusions

ECT should not be disregarded as an effective therapeutic option for the treatment of unipolar and bipolar depressive and mixed patients resistant to pharmacological treatment. MS and BP I tended to exhibit more residual agitation and psychotic features than UP.

Key words

Electroconvulsive therapy • Unipolar depression • Bipolar I depression • Bipolar II depression • Mixed state

Introduction

Electroconvulsive therapy (ECT) is a non-pharmacological treatment, whose efficacy has been largely proved for patients affected by severe and refractory depression [1-3]. The second edition of the guidelines of the American Psychiatric Association (APA) Task Force on Electroconvulsive Therapy [4] suggests the use of ECT in depressive patients showing lack of a response to or intolerance to antidepressant medications, a good response to previous ECT, and the need for a rapid and definitive response.

Various research studies focusing on the use of ECT have shown its efficacy in different subgroups such as patients with bipolar depression [5], mixed state [6], psychotic features [7] and suicidal ideation [8].

Major differences in response to pharmacological treatment between unipolar (UP) and bipolar (BP) depression has been reported [9]. Sachs et al. demonstrated that the use of adjunctive, standard antidepressant medication, as compared with a mood-stabilizing monotherapy, was not associated with increased efficacy [10], while there are evidences that treatment with antidepressants monotherapy turns out to be associated with manic switches, mixed state induction, and cycle acceleration [11].

The literature regarding ECT outcomes in bipolar patients were mostly provided by retrospective analyses of case series and reached contradictory conclusions. Some of the involved studies [2 11-14] showed comparable improvements in BP and UP depressive patients, while other studies [15] demonstrated better results in the UP group. Daly et al. [16 17] have shown instead more rapid clinical improvement and fewer ECT treatments in BP than in UP patients. A more recent retrospective study [18], conducted on 106 consecutive inpatients, suggests that in bipolar disorder there is a poorer subjective response to ECT than in unipolar disorder. Few evidences exist instead about the specificity of ECT treatment in bipolar I and II depression [19] and in mixed states [6 20 21]. Available data suggest that ECT may be a useful treatment for patients whose mixed states have not initially responded to psychotropic medica-

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tions [6 20 21]. Ciapparelli et al. [6] reported a better response in terms of reduction of depressive symptoms, BPRS activation factor and overall psychopathology in patients with MS compared to patients with bipolar depression. In addiction MS subjects showed a more rapid and greater reduction of suicidality. In other reports MS patients presented a higher number of days spent in hospital and a greater number of ECT treatments compared to the depressed group [21].

The aim of this study was to compare the ECT response in different depressive subgroups resistant to pharmacological treatment: unipolar, bipolar I and bipolar II. We also explored differential ECT response in patients with MS. Based on the significant body of evidence indicating the efficacy of ECT in UP depression but mixed results in BP depression and in MS, we hypothesized that UP depressive patients may present better response to ECT when compared to patients with BP depression and MS.

Methods

The study involved 180 consecutive patients with treatment resistant Major Depression or MS, who received ECT between January 2006 and December 2008 in the Department of Psychiatry of the University of Pisa. Study subjects were at least 18 years old and met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV), for a major depressive episode associated with major depressive disorder (MDD) (n = 17), BP I (n = 46) or BP II disorder (n = 67) and for a mixed episode (MS) (n = 50). Only 4 patients were rapid cyclers (2 BP II and 2 BP I); given the low number of cases, this variable was not considered in the comparative analyses.

The diagnoses were made by 2 senior psychiatrists (PM, GBC) and were confirmed by the administration of M.I.N.I. (Mini International Neuropsychiatric Interview-Italian version 5.0.1; [22] according to DSM-IV criteria. All subjects gave their written informed consent to receive ECT and to participate in this study.

All patients were non-responders to pharmacological treatment. Treatment non-response in patients with recurrent major depression without psychotic symptoms was defined as failure to respond to two different adequate monotherapy trials of medication with different pharmacological profiles (e.g. a TCA at a dose equivalent of 200 mg of imipramine for at least 4 weeks and an SSRI a dose equivalent of 40 mg of fluoxetine for at least 4 weeks). For bipolar depression despite 2 trials of at least 8 weeks consisting of 1 trial with mood stabilizers plus a TCA and 1 trial with mood stabilizer(s) plus an SSRI. In psychotic depression, an additional criterion was concomitant administration of an antipsychotic medication at the dose equivalent to at least 300 mg/die of chlorpromazine. For patients with MS non-response was defined as the presence of persisting mixed symptoms despite 1 trial of at least 16 weeks with 2 or more mood stabilizers and or typical or atypical antipsychotics and or antidepressants in variable doses depending on symptoms patterns. Antidepressants were utilized in mixed patients when depressive symptomatology was prevalent and when mood stabilizers and antypsychotichs were ineffective in controlling depression and anxiety.

The patients were evaluated prior to ECT (baseline) and a week after the ECT course (final score), using the Hamilton Rating Scale for Depression (HAM-D) [2], Young Mania Rating Scale (YMRS) [23] Brief Psychiatric Rating Scale (BPRS) [24] and the Clinical Global Improvement (CGI) [25]. The decision to terminate ECT sessions was made by the treating clinicians blinded to the diagnostic and symptomatological evaluation.

The HAM-D scores were used in two different ways for classification of response to ECT: *Response* was defined as a reduction in HAM-D score of at least 50% post-treatment compared to pre-treatment and *remission* was defined as a post-treatment HAMD scores ≤ 8 [1]. As concern CGI-Improvement subscale, *Response* was defined as a rating of 2 "much improved" or 1 "very much improved" and remission was defined as rating of 1 "very much improved" at the end of the ECT course.

In the absence of a specific scale for psychotic symptoms, the change in psychotic symptomatology was approximated using BPRS psychosis cluster score: hostility, suspiciousness, hallucinations, unusual thought content and conceptual disorganization (item 6, 9, 10, 11 and 15-maximum score 35) [2].

ECT procedure

ECT for the treatment of depression and other psychiatric disorders consists in the application of electricity to the scalp in order to induce seizure activity. ECT was performed while the patient was under general anesthesia. Patients were not typically intubated, but mask ventilation with supplemental oxygen was used with 100% oxygen until resumption of spontaneous respiration. Anesthesia was induced with intravenous thiopental (2-4 mg/kg) and succinylcholine (0.5-1 mg/kg). Bilateral ECT was delivered using a brief pulse stimulator Mecta 5000Q (Mecta Corporation, Lake Oswego, USA), on a twice-a-week schedule. Physiologic monitoring included pulse oximetry and an electrocardiogram. The electroencephalogram was also monitored during ECT to confirm seizure activity and to document seizure duration. The stimulus setting were initially based on age [13] and the length of the seizures measured by electroencephalogram (EEG) was kept above 25 seconds. If motor seizure duration fell below 25 second, the stimulus setting was raised (1.5 times) at the

next session. The number of ECT trials was established by clinical observation and continued until the treating physician considers that a therapeutic response has been obtained or that no further therapeutic benefit is to be expected. Usually termination of ECT course was considered when, after 6 treatments, the patient's symptomalogy remain unchanged after two additional treatment sessions. We preferred a twice-weekly treatment because it has been associated with less severe cognitive effects than a schedule of three time per week, and in the same degree of final clinical improvement. Concomitant psychotropic. medications were permitted during ECT course, based on doctor's choice. Only anticonvulsant medications, such as valproate or carbamazepine, were tapered or discontinued before ECT is initiated and were not used as concomitant medication during ECT treatment.

Statistical analysis

Statistical comparisons between different groups were conducted, for dimensional variables, by means of ANOVA followed by Scheffe's test and, for categorical variables, by chi-square analysis. Analyses of baseline-endpoint differences were carried out by two way ANOVA for 4 groups and 2 time points applied to baseline and final observation. Differences of response among the different groups were analysed by ANCOVA for independent samples utilizing initial scores as covariate. We conservatively set a priori level of significance at $p \leq .05$.

Results

The four groups differ in several demographic and clinical variables. The mean age was higher in UP (53.6 ± 17.2), BP II (52.8 ± 14.3) and in BP I (44.9 ± 13.9) depressives than in patients with MS (39.3 ± 13.4) ($F = 10.90$, $p = < .0001$) (Table I). The female gender was more represented in all groups: 88.2% in UP, 62.7% in BP II, 60.9% in BP I, and in MS (52.0%). The age at onset was significantly lower in MS group (23.5 ± 8.7) than in BP I group (28.5 ± 11.7), UP (32.1 ± 13.2) and BP II (33.4 ± 15.8) ($F = 6.00$, $p = .0006$). The mean number of ECT was similar in the 4 diagnostic subtypes: respectively 6.5 (± 1.7) in UP, 7.2 (± 2.3) in BP II, 7.4 (± 2.5) in BP I and 7.4 (± 2.4) in MS. Only 3 patients interrupted ECT course after 1 or 2 trials for adverse events: 1 patients with depression presented prolonged apnea after 1 session and 2 patients with MS presented respectively prolonged apnea and seizure after 1 session and postictal delirium after 2 sessions. Total number of lifetime episodes, evaluated by clinical interview, was greater in BPI (mean 6.7 ± 2.8),

TABLE I.
Demographic and clinical characteristics in unipolar, bipolar II, bipolar I depressive and MS patients treated with ECT. *Caratteristiche demografiche e cliniche in pazienti con depressione unipolare, bipolare II, bipolare I e con stato misto.*

	Unipolar n = 17	Bipolar II n = 67	Bipolar I n = 46	Mixed state n = 50	For χ^2 (df = 3)	p
Age, mean (sd)	53.6 (17.2)	52.8 (14.3)	51.0 (11.8)	39.3 (13.4)	10.90	< .0001[a]
Age at onset, mean (sd)	32.1 (13.2)	33.4 (15.8)	28.5 (11.7)	23.5 (8.7)	6.00	.0006[b]
Gender, females, n (%)	15 (88.2)	42 (62.7)	28 (60.9)	26 (52.0)	7.10	.05
Length of current episode, mean (sd)	8.6 (5.9)	8.5 (9.0)	7.1 (5.7)	5.8 (5.3)	3.43	.03[a]
Total number of episodes, mean (sd)	5.5 (3.7)	5.2 (2.8)	6.7 (2.8)	5.2 (3.0)	2.87	.04[c]
Total number of hospitalizations, mean (sd)	4.2 (4.7)	4.6 (11.8)	4.5 (2.6)	3.5 (2.0)	0.22	.88
Total number of ECT, mean (sd)	6.5 (1.7)	7.2 (2.3)	7.4 (2.5)	7.4 (2.4)	0.67	.57
Lifetime comorbidity, n (%)						
Social phobia	0 (0.0)	1 (1.5)	0 (0.0)	2 (4.0)	2.74	.43
Panic Disorder-Agoraphobia	10 (58.8)	26 (38.8)	13 (28.3)	19 (38.0)	5.01	.18
Obsessive-Compulsive Disorder	1 (5.9)	7 (10.4)	6 (13.0)	11 (22.0)	4.35	.23
Alcohol abuse	0 (0.0)	2 (3.0)	1 (2.2)	1 (2.0)	0.58	.90
Drug abuse	1 (5.9)	2 (3.0)	0 (0.0)	1 (2.0)	2.28	.52
Type of Response, n (%)						
Remission CGI-I (= 1)	12 (70.6)	30 (44.8)	19 (41.3)	17 (34.8)	9.38	.03
Response CGI-I, (≥ 2)	16 (94.1)	53 (79.1)	31 (67.4)	38 (76.0)	5.61	.29
Remission Ham D, (≥ 8)	12 (70.6)	29 (43.3)	16 (34.8)	15 (30.0)	9.83	.02
Response Ham D, (50%)	15 (88.2)	49 (73.1)	32 (69.6)	33 (66.0)	5.50	.33

[a] Scheffe test UP, BPII, BPI > MS; [b] Scheffe test UP, BPII > BPI > MS; [c] Scheffe test BPI > UP, BPII, MS.

than in UP (mean 5.5 ± 3.7), BP II (5.2 ± 2.8) and MS (5.2 ± 3.0) patients (F = 2.87, p = .04). The length of current episode was significantly lower in MS group compared to depressive subtypes (p = .03): respectively 8.6 (± 5.9) in UP, 8.5 in BP II (± 9.0), 7.1 (± 5.7) in BP I and 5.8 (± 5.3) in MS (F = 3.43, p = .03). The total number of hospitalizations was similar among the groups.

Rates for lifetime comorbidity were not statistically different among the 4 groups. We observed a lifetime comorbidity for Social Phobia in 1.5% of BP II and 4.0% of MS patients. The comorbidity for Panic Disorder was 58.8% UP group, 38.8% in BP II, 28.3% BP I and 38.0% in MS. Obsessive-Compulsive Disorder comorbidity was observed in 22.0% of MS, 13.0% of BP I, 10.4% of BIP II and 5.9% of UP. Alcohol Abuse was not reported in UP patients and was present in 3% of BP II patients, in 2.2% of BP I and 2.0% of MS patients, while Drug Abuse was present in 5.9% of UP, in 3.0% of BP II and in 2.0% of MS patients.

Response rate defined as having a final CGI severity score of 2 or less is similar in UP (n = 16, 94.1%), BP II (n = 53, 79.1%), MS (n = 38, 76.0%) and BP I (n = 31, 67.4%) patients (Table I). Remission rate, defined as having a final CGI severity score of 1, was significantly higher in the UP group (n = 12, 70.6%), while scores for other groups were similar: BPII (n = 30, 44.8%), BP I (n = 19, 41.3%) and MS (n = 17, 34.8%) (F = 9.38, p = .03). Concerning response rate defined as 50% reduction on HAM-D score, it was achieved by 88.2% of the UP group, 73.1% of BP II group, by 69.6% in BP I group and by 66.0% in MS group. Remission rate, defined as having a final HAM-D score ≤ 8, was significantly higher in the UP group (70.6%), than in BP II (43.3%), in BP I (34.8%) and in MS (30.0%) (F = 9.83, p = .02). Response rate, defined as 50% HAM-D total was similar in the 4 groups: UP I (n = 15, 88.2%), BPII (n = 49, 73.1%), BPI (n = 32, 69.6%), MS (n = 33, 66.0%).

At the end of the ECT course, CGI-S, HAM-D total, YMRS total, BPRS total and psychotic cluster scores showed a progressive reduction in all groups (Table II). At the final evaluation UP patients reported significantly lower mean scores (n = 2.2 ± 0.9) on CGIS than the other groups (F = 3.92, p = .01). On the contrary, MS reported significantly higher scores on YMRS (n = 8.3 ± 5.5) and BPRS psychotic cluster (n = 8.5 ± 3.7) in comparison with the other 3 groups (F = 15.51, p = < .0001) (F = 6.01, p = .001). In addition, BPI (n = 36.4 ± 11.2) and MS (n = 38.4 ± 9.0) showed significantly worse outcomes at the final evaluation of BPRS total compared to UP and BPII groups (F = 15.41, p = < .0001) (Table II).

TABLE II.
CGI, Ham-D, Young Mania, BPRS, BPRS psychotic cluster score in unipolar, bipolar II, bipolar I depressive and MS patients treated with ECT. *Punteggio della CGI, dell'Ham-D, della YMRS, della BPRS e del cluster psicotico della BPRS in pazienti trattati con terapia elettroconvulsiva affetti da depressione unipolare, bipolare II, bipolare I o da stato misto.*

	Unipolar n = 17	Bipolar II n = 67	Bipolar I n = 46	Mixed state n = 50	F	p
CGI-Severity, mean (sd)[a]						
Baseline	5.5 (0.7)	5.7 (0.6)	5.8 (1.1)	5.9 (0.6)	.94	.42
Final	2.2 (0.9)	2.9 (1.3)	3.2 (1.4)	3.4 (1.0)	3.92	.01
Ham D, mean (sd)[b]						
Baseline	26.5 (7.4)	25.6 (4.0)	25.0 (5.4)	22.3 (5.9)	4.71	.003
Final	7.3 (4.1)	10.1 (5.5)	10.7 (4.9)	10.2 (5.1)	1.84	.14
Young mania, mean (sd)[c]						
Baseline	4.1 (3.6)	5.7 (4.3)	8.0 (6.6)	17.5 (7.8)	44.32	< .0001
Final	1.9 (3.7)	3.0 (3.3)	4.1 (5.4)	8.3 (5.5)	15.51	< .0001*
BPRS total, mean (sd)[d]						
Baseline	54.8 (15.3)	51.8 (8.5)	56.7 (14.8)	64.1 (15.2)	23.98	< .0001
Final	32.1 (6.3)	32.8 (5.6)	36.4 (11.2)	38.4 (9.0)	15.41	< .0001**
BPRS psychotic cluster, mean (sd)[e]						
Baseline	7.5 (4.1)	7.1 (3.4)	9.9 (6.8)	15.1 (6.6)	20.76	< .0001
Final	5.5 (1.5)	5.5 (1.1)	7.1 (3.9)	8.5 (3.7)	6.01	.001*

* p < .05 (UP, BPII < BPI < MS); ** p > .01 (UP, BPII < BPI, MS). Repeated measures ANOVA. [a] Effect of group: F = 4.12, p = 0.02; effect of time: F = 3 883.76, p < 0.0001; interaction group/time: F = 1.64, p = 0.35; [b] Effect of group: F = 0.53, p = 0.75; effect of time: F = 496,47, p < 0.0001; interaction group/time: F = 4.44, p = 0.019; [c] Effect of group: F = 9.34, p = 0.001; effect of time: F = 52.10, p < 0.0001; interaction group/time: F = 1.12, p = 0.39; [d] Effect of group: F = 3.37, p = 0.04; effect of time: F = 118.69, p = 0.0001; interaction group/time: F = 0.68, p = 0.27; [e] Effect of group: F = 10.63, p = 0.001; effect of time: F = 45.65, p = 0.0001; interaction group/time: F = 3.32, p = 0.036.

Discussion

Only few studies have focused on differenting ECT response between UP and BP depression, and only one compared BP I with BP II [19]. However, the distinction between bipolar depression and MS may have an important clinical and prognostic impact that might influence response to ECT. We found a powerful and consistent effect of ECT across all diagnostic subtypes. In accordance with previous literature [25 26], patients with MS are younger and reported earlier onset when compared to patients with depression, while there are no differences in terms of number of treatments among UP, BPII, BPI and MS patients. Although available literature indicates that chronic course is more common in MS than in bipolar depression, in our sample the duration of current episode was shorter in MS than in the other 3 groups. However, we selected a sample of patients resistant to treatment medication and it is possible that our depressive patients were more chronic and severe than those included in other samples of patients with bipolar depression.

BP I showed a greater number of affective episodes compared with UP, BPII and MS patients and a higher number of hospitalizations in comparison with MS, suggesting a more cycling course.

In term of response, we found different outcomes comparing UP, BPII and BPI and MS patients. UP reported the best response and symptomatic improvement following the ECT course. Among depressive subtypes, BP I were less responsive than both UP and BPII, showing more residual symptomatology and less complete response.

As reported in other studies, MS obtained higher scores on Young Mania, BPRS total and BPRS psychotic cluster than depressive groups, followed by BPI I group that reported more manic and psychotic features than UP and BPII. The global severity of the clinical presentation, explored by CGI-S, was similar at baseline among 4 groups, but was significantly different at final, with the worst outcomes obtained by MS patients. At baseline, the severity of the depressive symptomatology, derived from HAM-D total score, was significantly higher in UP group, but was similar in the 4 groups at the end of the ECT course. Previous reports observed a relationship between length of depressive episode and poor response to ECT [27-30]. We observed that the length of the current episode differed significantly among the 4 groups, with the shortest value in MS patients.

A study performed on BP and UP patients treated with ECT reported better and more rapid ECT response in BP patients than in UP, suggesting a faster improvement intrinsic to BP [1], while another one reported similar response rates in BP and UP patients [2]. In our study, no differences in terms of number of treatments were found among the 4 subtypes. A recent large retrospective study [3], reported tough that, while UP patients showed a response in subjective and objective measures, in BP patients was observed an improvement only in the subjective measures, in spite of an improvement in clinician rated measures. In our study, based only on objective measures, all patients showed a marked response to ECT, but BP and MS patients presented more residual symptomatology, which may account for a worse outcome, utilizing subjective measures.

In contrast to the observation of a scarce response of MS to pharmacologic treatments such as lithium [31-33], in the present study we observed in MS group a rate of response to ECT similar to those reported in our bipolar I patients with depression, although with worse results in terms of remission compared to the other 3 groups.

Clearly, our study has several limitations such as the lack of a control group, sample size, no random allocation, no blinding, and short-term follow-up. In our sample, however, the likelihood of placebo effect or spontaneous remissions having a significant influence on the results is quite low, since all patients had a previous clinical history of a severe disorder, with a long-standing continuous course, that was resistant to standard pharmacological treatments. Another limitation concerns the low number of UP patients included in the study. UP reported better outcomes than BP I, MS and, to a less extent, BP II, both using categorical outcome measures such as remission and response, or quantitative measures such as Ham-D, YMRS, BPRS and CGI mean scores. The fact that all the measures are consistent reduces the possibility of chance finding. In addition, only 3 patients interrupted ECT course for adverse events, indicating that the procedure was safe and well tolerated in the great majority of the cases.

In conclusion, ECT should be considered an effective treatment for depressive and MS patients resistant to psychotropic medications. Nevertheless, while the unipolar showed a better response with significant clinical outcomes, MS presented more residual manic symptomatology compared to the other depressive groups. Moreover BPI and MS tended to exhibit residual psychotic features. Further research is needed to increase the evidence of acute ECT efficacy in MS, its long-term safety and its role in combination treatments.

Funding Sources

The study is supported by Azienda Ospedaliero-Universitaria Pisana and by the Department of Psychiatry Neurobiology Pharmacology e Biotechnology, University of Pisa, Italy.

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