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REVIEW ARTICLE

The Role of Electroconvulsive Therapy (ECT) in Bipolar Disorder: Effectiveness in 522 Patients with Bipolar Depression, Mixed-state, Mania and Catatonic Features

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Abstract: ***Objective*:** We evaluated the effectiveness of Electroconvulsive Therapy (ECT) in the treatment of Bipolar Disorder (BD) in a large sample of bipolar patients with drug resistant depression, mania, mixed state and catatonic features.

***Method*:** 522 consecutive patients with *DSM-IV-TR* BD were evaluated prior to and after the ECT course. Responders and nonresponders were compared in subsamples of depressed and mixed patients. Descriptive analyses were reported for patients with mania and with catatonic features.

***Results*:** Of the original sample only 22 patients were excluded for the occurrence of side effects or consent withdrawal. After the ECT course, 344 (68.8%) patients were considered responders (final CGIi score ≤2) and 156 (31.2%) nonresponders. Response rates were respectively 68.1% for BD depression, 72.9% for mixed state, 75% for mania and 80.8% for catatonic features. Length of current episode and global severity of the illness were the only statistically significant predictors of nonresponse.

***Conclusion*:** ECT resulted to be an effective and safe treatment for all the phases of severe and drug-resistant BD. Positive response was observed in approximately two-thirds of the cases and in 80% of the catatonic patients. The duration of the current episode was the major predictor of nonresponse. The risk of ECT-induced mania is virtually absent and mood destabilization very unlikely. Our results clearly indicate that current algorithms for the treatment of depressive, mixed, manic and catatonic states should be modified and, at least for the most severe patients, ECT should not be considered as a "last resort".

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INTRODUCTION

Bipolar disorder (BD) is a serious and extremely recurrent illness frequently associated with cognitive and functional deterioration that poses many treatment challenges [1]. Despite a growing armamentarium of psychotropic medications, many patients with BD remain refractory to pharmacological treatment, relapses are common and morbidity and mortality remain elevated [2-9]. Because of the high rate of treatment nonresponse, the use of complex polypharmacy has increased dramatically over the years [10, 11]. Although there are several examples of "rational polypharmacy" [12, 13] and anecdotal evidence that some BD patients may benefit from certain complex regimens, the increased reliance on polypharmacy occurred in the absence of any controlled evidence. Indeed, the efficacy of combined treatment consisting of three or more medications is not demonstrated [14]. Whether "rational" or "irrational", the medication burden associated with increased use of complex polypharmacy raises several concerns including increased switches rate, rapid cycling, treatment resistance, apart from adverse side effects [13] due to drug interactions [14] and patient nonadherence [15-17]. Concern about the efficacy of current treatments for BD has been particularly marked for bipolar depression: adjunctive second-generation anti-depressants over monotherapy with mood stabilizers do not seem to bring any benefit [16]. Moreover, a recent prospective naturalistic longitudinal study [18] reported a significantly lower likelihood of recovery in BD inpatients with depressive compared to those with manic episodes.

Electroconvulsive therapy (ECT) has a unique place in the therapeutic armamentarium for BD; it has been shown useful as an acute treatment of severe depressive, manic and mixed states [19-25], in highly suicidal patients, in those

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presenting with catatonia, and in those with drugs refractory disease [26]. The limitations of pharmacotherapy indicate the need for a better definition of the role of ECT in BD. All BD treatment guidelines suggest that ECT should be applied only in pharmacotherapy-resistant or very severe cases [26-31]. Accordingly, ECT is not included as one of the first treatment options for either the manic or depressive phase, independently from the severity or the variety of clinical presentation.

However, in clinical practice, there is a broad consensus on the use of ECT in several groups of patients with severe clinical pictures, often in situations of emergency, as a first-line treatment; in such cases, ECT should be considered earlier than psychotropic medications. This is the case of patients with suicidal ideation and behavior, severe weight loss, malnutrition, dehydration and globally exhausted for protracted depressive or manic episode, [32], severe mixed state and catatonia. On the other hand, there is a significant variability among psychiatrists on the timing of referring patients affected by treatment-resistant mood disorders for ECT. Most practitioners take into account ECT only when the patient have not responded to several pharmacological treatments; such attempts may last for months or years, prolonging the patient's suffering. The length of episode seems to correlate with treatment resistance and poor outcome after ECT, a key point to discourage the use of ECT as a 'last resort' option [33].

Bipolar Depression

The studies supporting the effectiveness of ECT in severe and refractory depression have been conducted mostly in patients with major depressive disorder (MDD). ECT in BD depression is less extensively studied [19, 22]. This is rather unexpected, because literature data showed significant differences in antidepressants' efficacy between MDD and BD depression [16]. Not only depression in BD patients resulted less responsive than in MDD, but also the use of antidepressants may induce manic switching, mixed states (MS) and cycle acceleration [34, 35]. A better response to ECT was also observed in patients suffering from MDD compared with BD depression [36]. In a large sample of 130 patients (17 unipolar, 67 BP II and 46 BP I), unipolar depressive patients showed rates of remission (HAM-D <8) significantly higher (70.6%) compared to BD II (43.3%) and BD I (34.8%) [37]. In another report [38] unipolar patients showed response rates higher than BP patients, using measures of subjective evaluation. On the other hand, other Authors [39, 40, 41] did not show a different outcome in MDD and bipolar depression. In all these studies the rate of manic switch was not increased in BD depressive patients in comparison with MDD. As regard the rapidity of response to ECT, some Authors have observed a more rapid improvement in symptoms and a faster response in BD than in MDD patients, regardless of the final outcome [42, 43].

Recently, a Norwegian randomized and controlled trial [44] has compared the efficacy of ECT and pharmacological treatment in 73 subjects suffering from resistant bipolar depression. The study, conducted at seven acute-care psychiatric inpatient clinics, has showed that the acute phase of BD depression may have a better response to ECT than to pharmacological treatment. The ECT group showed significantly higher rates of response than the group that received pharmacological treatment (73.9% versus 35.0%), while as far as rates of remission are regarded, the authors did not found differences between the two groups (34.8 versus 30.0%). BP I and II patients did not differ in response to ECT.

All these studies are not directly comparable because of the differences in selection criteria and methodology, however, current available evidence consistently indicates that resistant bipolar depression tends to respond much better to ECT than to pharmacological treatment, pointing at ECT as a treatment option.

Mixed State

Mixed state (MS) indicates an affective picture in which various combinations of depressive and manic symptoms are present at the same time. With mania and depression, MS represents a major phase of bipolar disorder and, if compared with nonmixed episodes, is characterized by a more complex clinical presentation [45-47] and a less favorable response to conventional pharmacologic treatments [47-49]. Treatment of MS is a therapeutic challenge mostly for the lower response to mood stabilizers, compared to pure manic or depressive episodes, and the actual necessity of drug combination [48]. Moreover, the use of antidepressants has been reported to worsen short-term intra-episodic mood instability and mixed symptomatology in a relevant proportion of cases [35, 50-52]. On the other hand, the use of antipsychotics may induce depressive symptoms [53, 54]. The limitations of lithium salts in the treatment of MS have been widely reported [49, 55]. Anticonvulsants -valproate and carbamazepine- as well as atypical antipsychotics [56, 57], have shown a higher efficacy than lithium in the treatment of mixed mania. However, the major part of the evidence derives from clinical trials enrolling manic patients with few depressive symptoms (dysphoric mania). Clinical observations have pointed out a worse outcome for severe MS compared with both mania and depression, so that further therapeutic strategies are necessary.

Although ECT has been performed for the first time in a patient with MS with outstanding outcome [58] and has been shown to be effective in BD depression [59], the effectiveness of ECT in MS has not been thoroughly investigated. Actually, MS is often underdiagnosed, due to inadequate nosographic definition [47, 60, 61], and misdiagnosed because of its pleomorphic symptomatic presentation [62]. As a consequence, many patients with MS are included in samples of schizophrenic or manic patients treated with ECT [47]. For these biases, literature data is disappointingly limited, and most likely the use of ECT in MS treatment has not been specifically described by most of the clinical practice guidelines for the treatment of BD [22]. Several, naturalistic reports point out that ECT is an effective treatment for mixed state, with reported response rates over 50% [25]. In a retrospectively study conducted in Aarhus Psychiatric Hospital [63], a high response to ECT in a sample of 19 patients with MS has been observed. In this study, unilateral ECT was the only helpful therapy for patients treated with high doses of neuroleptics and antidepressants for prolonged

periods without effect. Others authors [64], evaluated the response to bitemporal ECT in a sample of 7 medication-resistant patients meeting Research Diagnostic Criteria (RDC) for both mania and major depression, showing a significant improvement of the severity of both depressive and manic symptoms. Despite the limitations of these small retrospective and uncontrolled reports, the results suggested that ECT may be an effective treatment for subjects whose mixed state have resistant to pharmacological treatment. In a chart review [65], the response to ECT was compared in three groups of DSM-IV bipolar patients: depressed (n = 38), manic (n = 5), and mixed (n = 10). On the basis of CGI severity evaluation, all three groups showed robust response rates: 76 % in the depressed group, 100% in manic group and 80% in mixed group. The Authors concluded that in mixed states the response to ECT is as satisfactory as that observed in bipolar depressed and manic states. This observation backs the thesis that ECT is efficacious in all the phases of Bipolar Disorder. Nonetheless, the mixed patients required a longer length of hospitalization and a higher number of ECT treatments than the depressed ones. These observations suggest that mixed states are more complex to treat and may take a longer time to respond in comparison to depressed and manic episodes. These results are in line with Ciapparelli *et al*. [66] and Medda *et al*. [67] who highlighted a significant improvement in mixed patients treated with ECT compared to depressive patients. However, MS presented more residual symptoms such as agitation and psychotic features compared with depressive patients. The methodologies used in these studies were very different and in none of them a comparison treatment was utilized in order to establish the efficacy of ECT. Hence, these observations do not provide definitive evidence for the usefulness of ECT in mixed episodes and further randomized controlled studies are warranted.

However, the forementioned observations provide evidence for the safety and efficacy of ECT in drug resistant patients. On the basis of this evidence, ECT should be considered the treatment of choice in resistant MS patients, though further management might be necessary for residual manifestations.

Mania

In acute mania, the treatments of first choice are lithium, antiepileptic mood-stabilizers and antipsychotic drugs, and ECT is considered only for drug resistant patients [68, 69]. ECT is considered as a first line treatment in patients with delirious and severe mania, associated with life-threatening physical exhaustion [70, 71].

The evidence for the use of ECT in acute mania is not as rich as that reported for depression; nevertheless, on the basis of the available literature, ECT appears efficacious in acute mania, also in drug resistant patients, with response rates ranging from 80% to over 90% [23, 72-77]. Thus, ECT should be considered a useful second line treatment for refractory mania. In addition, manic patients with rapid cycling course, unresponsive to medications, may benefit of ECT [78].

Catatonic Features

Catatonia is a neuropsychiatric syndrome characterized by motor dysregulation, associated with thought, mood and awareness abnormalities. Immobility, stupor, mutism, negativism, rigidity are the most typical symptoms [79]. On the basis of the current knowledge, catatonia appears as an independent neuropsychiatric syndrome, related to a pathophysiological end-state stereotypical reaction, finalized to ancient defensive strategies and linked to a specific pattern of activation or disinhibition of neuronal networks distributed across the SNC [80]. Since the first description [81], catatonia has been described in mood disorders, with prevalence rates ranging from 13% to 31% [82]. Among hospitalized manic patients, catatonia has been described in about the 25% and manic depressive illness has been reported in over the 50% of catatonic patients [83]. A study on patients with major depressive episode reported catatonic features (according to DSM-IV criteria) in 16 out of 79 subjects (20%) [84]. Similarly, in 99 bipolar subjects with manic or mixed episode [85], catatonia was observed in 24 out of 39 patients with mixed-mania (61%) and only 3 out of 60 patients with pure mania (5%). Generally, catatonic symptoms are considered typical of schizophrenia and, as a consequence, overlooked or misinterpreted in bipolar disorder [79, 85, 86]. Benzodiazepines and ECT are indicated for the treatment of catatonia, while antipsychotic must be avoided [87, 88]. Even if the efficacy of ECT in catatonia is widely acknowledged, only small open and retrospective studies are available in the field. Moreover, most of these observations were conducted in heterogeneous samples of patients diagnosed with varying frequencies as having schizophrenia (20%–100%) or mood disorders (0%–63%), not always on the basis of valid criteria [89-95]. In these studies, ECT resulted very effective with responses ranging from 80 to 90%; only one report showed response rate of 59% [96].

Aims of the Study

We describe the short-term outcome of a large sample of BD patients referred to the Department of Psychiatry of the University of Pisa for ECT in different phases of the illness.

All patients were resistant and or nonresponsive to pharmacological treatments. Efficacy and tolerability of ECT were systematically evaluated for depression, mixed state, mania and catatonic features. A series of comparative analyses between responders and nonresponders to ECT in different diagnostic subtypes were carried out in order to explore demographic, clinical and treatment features related to nonresponse to ECT.

METHOD

Sample

The study was naturalistic and observational and involved 522 drug-resistant BD patients, who underwent ECT between January 2006 and May 2011 at the Department of Psychiatry of the University of Pisa, a tertiary care general psychiatric hospital in Italy. Patients were ≥18-year old and met the Diagnostic and Statistical Manual of Mental

Disorders, IV-TR Edition (DSM-IV-TR) criteria for BD. The diagnoses were made by 2 senior psychiatrists (P.M., M.M.) and were confirmed by the administration of the MINI (Mini-International Neuropsychiatric Interview) (MINI), Italian version 5.0.1. 35. When inconsistencies with regard to the diagnosis emerged, all diagnostic information was reviewed for consensus agreement and, if necessary, the patients were contacted for further clarification. Our study was approved by the local Ethic Review Board of the University Hospital of Pisa (study number: 1731/2004). Informed consent for ECT is a distinct process, and its application has evolved over time. The consent process includes a careful review of the procedure itself and the possible benefits, side effects, and risks of treatment. Given the complexity of the issues and the patient acute cognitive and emotional distress, we involved family members in the process with the use of written material presentations to supplement the clinical discussion. As regards catatonic patients, the severity of illness made all subjects incapable of providing a decision, either consent or treatment refusal. Therefore, with the exception of those patients that had already been requested, it was decided to appoint a guardian, in accordance with the guidelines of our region [97]. Authorization to consent to ECT is generally not included in medical guardianship and the court must be specifically petitioned.

Definition of Resistance or Nonresponse to Pharmacological Treatments

No consensual definitions of treatment-resistant BD exist. A number of parameters should be considered in the definition, as type of phase and course of illness, number of failed adequate treatments, definition of response and number of combination treatments. In our study, as drug–resistant bipolar depression is regarded, resistance was defined on the basis of outpatient and inpatient medical records and on the reports of the patient, his/her family members, and prescribing psychiatrists. According to most widely adopted definitions, treatment nonresponse in patients with bipolar depression without psychotic symptoms was defined as a lack of response to 2 trials lasting for at least 8 weeks consisting of 1 trial with mood stabilizer(s) plus a selective serotonin reuptake inhibitor (e.g., 40 mg of fluoxetine) and 1 trial with mood stabilizer(s) plus a tricyclic antidepressant (e.g., 200 mg of imipramine). In patients with psychotic depression, an additional criterion was concomitant administration of an antipsychotic medication (e.g., 300 mg of chlorpromazine per day). In our study, the severity of medication resistance was not formally assessed, but almost all patients had failed multiple previous medication trials. In the absence of viable and shared definition of treatment resistance for bipolar depression, we adopted criteria already used by other Authors [59, 66, 98].

For patients with mixed states, nonresponse 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 symptom patterns.

Although incomplete symptomatic remission and persisting alterations of psychosocial functioning are not uncommon, mania is considered to have a more favorable response than bipolar depression. For this reason, a shared definition of treatment resistance is not reported in the literature. All our manic patients treated with ECT were clearly urgently or emergently ill and required a rapid intervention. So they showed a particularly severe manic symptomatology non responsive to multiple trials treatment with a combination of mood stabilizers, antipsychotics and benzodiazepines. As regards catatonic patients, the medical treatment algorithm for catatonia contemplates the lorazepam challenge test for the rapid resolution of acute catatonia. In our patients ECT course was proposed when the lorazepam challenge test had failed or increased dosages had not brought a rapid relief. Since our study was naturalistic, the duration of the trial with benzodiazepines and their dosages were not standardized.

Patient Evaluation

All patients were evaluated prior to ECT (baseline) and after the ECT course (final score) using the 17-item Hamilton Rating Scale for Depression (HAM-D-17) [99], the Brief Psychiatric Rating Scale (BPRS) [100], the Young Mania Rating Scale (YMRS) [101], the Mini Mental State Examination (MMSE) [102], the Clinical Global Impression scale, severity subscale (CGIs) [103] and, for catatonic patients, the Bush-Francis Catatonia Rating Scale (BFCRS) [104]. The modification of psychotic symptoms was investigated by means of BPRS psychosis cluster score: hostility, suspiciousness, hallucinations, unusual thought content, and conceptual disorganization (items 9, 10, 11, and 15; maximum score, 28). All scales were administered by a senior psychiatrist (P.M.), with more than 20 years of experience in the assessment and treatment of patients with severe BD. Responder and nonresponder groups were identified using the CGI improvement subscale (CGIi). Nonresponse was defined as a post-treatment CGIi rating ≥ 3. Responders and nonresponders were compared with depressive and mixed patients. For manic and catatonic patients, the paucity of the sample did not allow a comparison between responders and nonresponders and a descriptive analysis was conducted.

ECT Procedure

Anesthesia was induced with intravenous thiopental (2-4 mg/kg) and muscle relaxation was assured with succinylcholine (0.5-1 mg/kg). Catatonic patients with muscle damage (elevated levels of creatine-phosphokinase and/or myoglobin), at increased risk for transient hyperkalemia associated with succinylcholine, were treated with a nondepolarizingmuscle relaxant rocuronium (0.3 mg/kg IV 0.6 mg/kg) and sugammadex (4 mg/kg) was administered after the motor seizure. Studies comparing 2- versus 3-times weekly bilateral ECT suggested that ECT×2 is the more appropriate schedule for regular clinical practice unless the speed of the response is an overriding concern [105]. For this reason, in our center, we utilized a 3-times weekly schedule only for severe catatonic patients. Parameters included a pulse width of 1.0, frequency ranging from 40 to 90 Hz, duration ranging from 1.5 to 4.0 seconds, and a current of 0.8 A. Patients were ventilated with 100% oxygen until resumption of spontaneous respiration. Physiological monitoring included pulse

oximetry and an electrocardiogram. The stimulus setting was initially based on age [83] and the length of the seizures measured using an electroencephalogram (EEG), which was maintained for over 25 seconds. If the motor seizure duration decreased below 25 seconds, the stimulus setting was increased 1.5 times at the following session. The number of ECT treatments was established on the basis of the clinical observation until the treating physician had considered that a therapeutic response was obtained or until no further therapeutic benefit was expected. Concomitant psychotropic medications were permitted during the ECT course, based on the physician's decision. Only anticonvulsant medications, such as valproate or carbamazepine, were not allowed. Antidepressant and antipsychotic treatments were kept stable for at least 1 week before and during the ECT course. During the ECT course, lithium was reduced to 0.3–0.4 mEq/L and was not administered the night before ECT. In bipolar patients, benzodiazepines were allowed up to a dosage equivalent to 3 mg/die of lorazepam, as needed. As regards catatonic patients, higher doses of benzodiazepines were continued during the course of ECT in order to avoid relapses that may occur during the intervals between one session and the next one and for the suggested synergic effect of the combination of lorazepam and ECT [106]. In the present study, lorazepam occasionally shortened seizure duration below the conventional minimum (25 sec motor convulsion). In these cases, the stimulus energy was increased at the following ECT session. These shortened seizures did not appear to diminish the beneficial response. In all cases, the last dose of lorazepam was administered at least 12 hours prior to treatment. The short half-life of lorazepam and the absence of active metabolites may minimize possible antagonism of ECT [107].

Statistical Analysis

Descriptive analyses were reported in terms of mean and standard deviations for continuous variables and number and percentages for categorical ones. Comparisons between groups were performed using chi-square tests for categorical variables and Student' t- test for continuous variables (Mann-Witney or Fisher's exact test when statistical assumptions were violated). Given the exploratory nature of our studies, the significance level for each test was established at $p < .05$, 2 -tailed. For major depression and mixed state subgroups, in order to examine which demographic and clinical variables were associated with the ECT nonresponse backward stepwise logistic regressions were performed. As a threshold for the inclusion of variables in the regression analyses, we adopted an α level<.1 in univariate comparisons. All statistical analyses were performed with SPSS 20.0 version.

RESULTS

Of the 522 patients included in the present analysis, 203 patients (38.9%) met the DSM-IV criteria for current mixed episode, 8 patients (1.5%) for current manic episode, 311 patients (59.6%) for current major depressive episode (137, 26.2%, with BD-I disorder and 174, 33.33%, with BD-II disorder). From the total sample, 26 patients (4.98%) met DSM-IV-TR criteria for catatonic features; 7 (26.9%) had a Major Depressive Episode with psychotic features (4 with mood congruent and 3 with mood incongruent psychotic symptoms) and 19 (73.1%) met criteria for Mixed Episode (9 with mood congruent psychotic symptoms and 10 with mood incongruent psychotic symptoms). To be included in the outcome analysis, patients had to receive at least 3 times ECT. Of the initial 522 patients, 22 patients (6 with mixed state, 3 with BD-I and 13 with BD-II depression) were excluded because the ECT course was terminated prematurely for the occurrence of side effects or consent withdrawal (6 cognitive side effects [mainly memory loss], 2 severe headache, 5 cardiac arrhythmia, 2 respiratory complications, 5 consent withdrawal, 1 manic switch and 1 prolonged seizure). Thus, the final analysis involved 500 patients of which 197 (97%) out of 203 patients with mixed state and 295 (94.8%) out of 311 with BD depression. All the 8 patients with current manic episode and the 26 patients with catatonic features were included in the outcome analysis. As regards the response to ECT, 344 (68.8%) patients of the entire sample were considered responders (final CGIi score ≤ 2) and 156 (31.2%) nonresponders. Response rates were respectively 68.1% for BD depression, 72.9% for mixed state, 75% for mania and 80.8% for catatonic features. From the backward stepwise logistic regression the length of current episode (odds ratio [OR] = 1.028; 95% CI = 1.01 to 1.05; P = .002) and CGIs baseline total mean score (OR = 1.75; 95% CI= 1.06 to 2.89; P = .030) resulted statistically significant predictors of nonresponse. Age, age at onset, number of previous episodes, presence of psychotic features, HDRS-17, YMRS and BPRS baseline total scores, and positive lifetime comorbidity with obsessive compulsive, panic, eating and drug and alcohol use disorders were not included in the equation.

Bipolar Depression

At the end of the ECT course, 94 (31.9%) BD depressive patients were considered nonresponders and 201 (68.1%) responders. Females were more represented, with an overlapping distribution across the two groups (Table **1**). No significant differences between responders and nonresponders were observed in the number of lifetime episodes, number of hospitalizations, presence of psychotic symptoms and number of suicide attempts. The mean duration of the current episode was longer in nonresponders compared to responders (11.28 vs. 9.30 months), though without statistically significance. Chronic episodes (duration >2 years) were more represented in nonresponders compared to responders (18.1% vs. 10%; p=0.48). The BD-II subtype was significantly higher in responders than in nonresponders (59.7% vs. 43.6%, p=.01). Nonresponders showed higher rates of psychotic symptoms than responders but the difference was not statistically significant (44.7% vs. 33.3%). Lifetime rates of comorbidity with obsessive-compulsive disorder (OCD), panic, social anxiety, eating, and alcohol and drug use disorders were similar in the 2 groups. With respect to the ECT course, the mean number of ECT sessions, the electrical dose at first session and at last session, and the duration of electroencephalogram (EEG) seizure activity were overlapping in the 2 groups. Also the baseline CGIs, HDRS-17, BPRS total and psychotic cluster mean scores were not different. In contrast, the baseline YMRS mean score was significantly

Table 1. Differences in demographic, clinical course, characteristic of ECT and symptomatological scales between responders and non-responders to ECT in 295 patients with bipolar depression.

	Total (n=295)	Responders (n=201)	Non-responders (n=94)	t/χ2	p
Age (years)	49.80(13.29)	50.43 (13.57)	48.45 (12.63)	-1.13	.27
Age of onset (years)	29.50(13.99)	30.18 (13.64)	28.03(14.68)	1.2	.22
Gender, Females n (%)	177(60.0)	120 (59.7)	57(60.6)	.23	.878
Duration of current episode (months)	9.93 (11.20)	9.30 (10.74)	11.28 (12.08)	-1.41	.158
Duration of current episode >2 years	38 (12.9)	21 (10.4)	17 (18.1)	3.32	.068
Number of previous episodes	5.69 (2.83)	5.77 (3.05)	5.53 (2.33)	-.674	.501
Number of previous hospitalizations	3.87 (6.46)	4.15 (7.71)	3.26 (1.97)	-.113	.267
Suicide attempts, n (%)	.58(1.45)	.06 (1.26)	.54(.86)	-.415	.679
Bipolar Disorder type II n (%)	161 (54.6)	120 (59.7)	41 (43.6)	6.68	.01
Psychotic symptoms, n (%)	109 (36.9)	67 (33.3)	42 (44.7)	3.54	.06
Lifetime comorbidity, n (%)					
Panic Disorder / Agoraphobia	123(41.7)	90(48.8)	42(35.1)	.117	.246
Social Phobia	2(0.7)	2(1.0)	0(0.0)	.942	.332
Obsessive-Compulsive Disorder	39(13.2)	24(11.9)	15(16.0)	.901	.343
GAD	3 (1.0)	3(1.5)	0(0)	.417	.234
Anorexia nervosa	2(1.0)	2(1.0)	0(0.0)	.942	.323
Bulimia nervosa	5(1.7)	2(1.0)	3(3.2)	1.85	.173
Alcohol misuse	9(3.1)	6(3.0)	3(3.2)	.009	.923
Substance misuse	9(3.1)	4(1.4)	5(1.7)	2.40	.21
Characteristic of ECT course					
Total ECT session, mean (sd)	7.67 (2.16)	7.67 (1.99)	7.67 (2.05)	-.005	.996
Electrical dose first session, mC	169.74 (49.01)	170.37(50.94)	168.38(44.83)	-.324	.746
Electrical dose last session, mC	272.63 (111.64)	264.92(109.94)	289.13(114.04)	-.1.742	.083
EEG seizure activity, seconds (sd)	39.92(16.70)	40.63(15.99)	38.39(18.12)	-.543	.285
Symptomatological Rating Scales, mean (sd)					
CGI-Severity Baseline Final	 5.94(.61) 3.33(1.22)	 5.90(.78) 2.81(1.28	 6.03(.40) 4.44(.80)	 -1.471 -2.08	 .038 .000
Ham D Baseline Final	 23.81(4.15) 11.06(4.90)	 23.95(4.3) 9.13(3.80)	 23.51 (3.81) 15.2(4.42)	 .84 -12.13	 .40 .000
Young Mania Rating Scales Baseline Final	 7.48(5.02) 4.58(4.26)	 6.74(4.79) 3.53(3.43)	 9.08(5.15) 6.82(4.96)	 -3.73 -5.81	 .000 .000
BPRS Total Score Baseline Final	 53.39(10.67) 36.07(7.81)	 53.48(10.98) 33.13(5.46)	 53.21(10.03) 42.35(8.39)	 .205 -11.3	 .84 .000
BPRS Psychotic Cluster Baseline Final	 7.06(4.43) 5.21(2.11)	 6.82(4.30) 4.76(1.4)	 7.58(4.68) 6.18(2.91)	 -1.34 -4.49	 .182 .000

Table 2. Differences in demographic, clinical course, characteristic of ECT course and symptomatological scales between responders and non-responders to ECT in 197 patients with with mixed state.

	Total (n=197)	Responders (n=142)	Non-responders (n=55)	t/χ2	P
Age (years)	43.92 (13.00)	43.59(12.34)	44.76 (14.64)	.567	.57
Age of onset (years)	24.40 (19.29)	23.95(9.76)	25.56 (11.54)	.987	.32
Gender, Females n (%)	119 (60.4)	85(39.9)	34 (61.8)	.064	.80
Duration of current episode (months)	9.22 (11.08)	7.56(7.11)	13.49 (16.95)	3.46	.001
Duration of current episode >1 year	51 (25.9)	31 (20.4)	21 (38.1)	4.36	.037
Number of previous episodes	5.35 (3.18)	5.50 (3.14)	4.96 (3.27)	1.06	.29
Number of previous hospitalizations	3.58 (2.49)	3.60 (2.51)	3.55 (2.46)	-134	.89
Suicide attempts, n (%)	54 (27.4)	40 (28.2)	14 (25.5)	.147	.70
Psychotic features, n (%)	146 (74.1)	103 (72.5)	43 (78.2)	.66	.42
Mood-incongruent psychotic features, n (%)	50 (25.4)	35 (24.6)	15 (27.3)	.67	.71
Lifetime comorbidity. n (%)					
Panic Disorder / Agoraphobia	77(39.1)	59(41.5)	18 (32.7)	1.12	.25
Social Phobia	3(1.5)	1(0.7)	2 (3.6)	2.27	.13
Obsessive-Compulsive Disorder	29(14.7)	20(14.1)	9(16.4)	.164	.68
Anorexia nervosa	3(1.5)	2(1.4)	1 (1.8)	.044	.83
Bulimia nervosa	6(3.0)	4(2.8)	2(3.6)	.09	.76
Alcohol misuse	10(5.1)	6(4.2)	4 (7.3)	.76	.38
Substance misuse	12(6.1)	8(5.6)	4(7.3)	.18	.67
Characteristic of ECT course, mean (sd)					
Total ECT session	7.49 (2.42)	7.55 (2.02)	7.33 (3.24)	-.577	.56
Electrical dose first session, mC	149.12 (45.25)	148.65(41.83)	152.4(53.0)	.528	.598
Electrical dose last session, mC	248.03 (120.08)	248.99(122.14)	245.5 (115.6)	-.181	.856
EEG seizure activity, seconds	42.37 (19.76)	40.85(13.91)	46.27 (29.8)	1.73	.08
Symptomatological rating scales, mean (sd)					
CGI-Severity Baseline Final	 5.99 (0.60) 3.61 (1.05)	 5.61(.67) 3.23 (.92)	 6.07 (0.33) 4.60 (0.66)	 1.21 10.14	 .23 .000
Ham D Baseline Final	 22.18(4.94) 10.84(4.77)	 22.45 (4.65) 9.62(3.96)	 21.45 (5.57) 13.96 (5.26)	 -1.28 6.26	 .20 .000
Young mania Baseline Final	 16.96 (6.96) 8.65 (5.57)	 16.6(7.37) 7.33(5.02)	 17.90 (5.70) 12.07 (5.50)	 1.16 5.79	 .24 .000
BPRS Baseline Final	 61.49 (13.26) 39.91 (9.21)	 61,65(12,88) 37.21(7.15)	 61.07 (14.32) 46.85 (10.28)	 -.28 7.45	 .78 .000
BPRS Psychotic Cluster Baseline Final	 12.10 (5.92) 7.25 (3.21)	 12.19(6.19) 6.61(2.75)	 11.85 (5.17) 8.89 (3.72)	 -3.64 4.69	 .72 .000

lower in responders than nonresponders. As expected, at the end of the ECT trial, the CGIs, HDRS- 17, and BPRS and YMRS total scores were significantly lower in responders than in nonresponders.

Mixed States

After the ECT course, 55 patients (27.9%) with mixed state resulted nonresponders and 152 (72.9%) responders (Table **2**). No significant differences between the two groups were observed in age and gender distribution, number of lifetime episodes, number of hospitalizations, presence of psychotic features, mood-incongruent psychotic features and number of suicide attempts (Table **2**). The mean length of the current episode was significantly longer in the nonresponders compared to responders (13.49 vs. 7.56; P=.001) and the rate of episodes with duration >1 year was higher in nonresponders than in responders (38.1% vs. 20.4%; P=.037). Lifetime rates of comorbidity obsessive-compulsive, panic, social anxiety, eating disorders, and alcohol and drug use disorders were similar in the two groups. With respect to the ECT course, the mean number of ECT sessions, the electrical dose at first session and at last session, and the duration of electroencephalogram (EEG) seizure activity did not differ. At baseline, the HAM-D-17, YMRS, CGIs and BPRS total and psychotic cluster mean scores were not different between the two groups. As expected, at the end of the ECT course, the CGIs, HDRS-17, BPRS, YMRS totals scores were significantly lower in responders than in nonresponders. Using backward stepwise logistic regression, the length of current episode (odds ratio [OR] = 1.05; 95% CI = 1.02 to 1.08; P = .004) was the only statistically significant predictor of nonresponse.

Mania

After the ECT course 6 patients (75%) were considered responders and 2 nonresponders (25%). Table **3** shows the demographic and clinical characteristics of manic patients. The mean age were 41.0 (+11.31) and male and females gender were equally represented. The mean length of the current episode was 3.63 (± 2.20) months. The presence of psychotic symptoms was observed in 87.5% of the sample. With respect to the ECT course, the mean number of ECT sessions was 6.25 (+3. 69) and, at the end of the course, the CGIs, BPRS total, BPRS psychotic cluster and YMRS scores showed a statistically significant reduction. The rate of improvement was also substantial in CGIs, YMRS, BPRS total and psychotic scores, respectively 49.0%, 58.7%, 44.5% and 50.4%.

Catatonic Features

At the end of the ECT course, 21 patients (80. 7%) were classified as responders (CGI ≤ 3) and 5 patients (19. 3%) as nonresponders (Table **4**). Demographic and clinical characteristics of our sample are reported in Table **4**. The mean age was 49.5 (±12.52) years and female gender was largely over represented (88.5%). The mean length of the current episode was 7.12 (±3.28) months, with a mean duration of catatonic symptoms of 16.73 (±11.83) weeks. In our sample 10 patients (38.5%) had a positive personal history of catatonia and the mean number of previous mood episodes and hospitalizations were respectively 5.27 (± 2.84), and 3.19 (± 1.94). The mean number of previous suicide attempts was 0.12 (± 0.43). Seven patients (26.9%) were diagnosed as having BD depression and, in particular, 4

Table 3. Demographic features, clinical course, diagnosis and comorbidity, CGI, YMRS, BPRS total and BPRS psychotic cluster scores before and after ECT in 8 patients with manic episode.

Age (years)	41.00 (11.31)
Gender, Females n (%)	4 (50.0)
Duration of current episode (months)	3.63 (2.20)
Number of previous hospitalizations	3.13 (3.04)
Suicide attempts, n (%)	.13 (.35)
Diagnosis, n (%)	16.73 (11.83)
Manic episode without psychotic symptoms	1(12.5)
Manic episode with mood congruent psychotic symptoms	4 (50.0)
Manic episode with mood incongruent psychotic symptoms	3 (37.5)
Lifetime comorbidity. n (%)	
Panic Disorder /Agoraphobia	0 (0.00)
Social Phobia	0 (0.00)
Obsessive-Compulsive Disorder	1 (12.5)
Anorexia nervosa	0 (0.00)
Bulimia nervosa	0 (0.00)
Alcohol misuse	1(12.5)
Substance misuse	0 (0.00)
Characteristic of ECT course	
Total ECT session	6.25 (3.69)
Electrical dose first session, mC	146.00 (35.71)
Electrical dose last session, mC	259.00 (101.73)
EEG seizure activity, sec.	34.25 (14.49)
Symptomatological Rating Scales, mean (sd)	
CGI-S Baseline Final	 6.63 (.52) 4.38 (.92)[a]
YMRS Baseline Final	 42.12 (3.40) 17.38 (8.14)[b]
BPRS total score Baseline Final	 81.75 (13.23) 45.38 (11.64)[c]
BPRS psychotic cluster score Baseline Final	 16.63 (6.02) 8.25 (3.81)[d]

Baseline VS Final:
[a] t= 4.96 p=.002; [b] t= 0.30 p=.000; [c] t= 6.27 p=.000; [d] t= 4.96 p=.002.

Table 4. Demographic and clinical features, CGI, BFCRS, BPRS total and BPRS psychotic cluster scores in 26 Bipolar Disorder patients with severe catatonic features before and after ECT.

Age (years), Mean (sd)	49.50 (12.52)
Age at onset (years), Mean (sd)	28.08 (12.82)
Gender (F), n (%)	23 (88.5)
Duration of current episode (months), Mean (sd)	7.12 (3.28)
Duration of catatonic symptoms (weeks), Mean (sd)	16.73 (11.83)
Personal history of catatonia, n (%)	10 (38.5)
Number of previous mood episodes, Mean (sd)	5.27 (2.84)
Number of previous hospitalizations, Mean (sd)	3.19 (1.94)
Number of suicide attempts, Mean (sd)	0.12 (0.43)
Diagnosis, n (%)	
Bipolar depression, n (%)	7 (26.9)
1) mood congruent psychotic symptoms	4 (15.4)
2) mood incongruent psychotic symptoms	3 (11.5)
Mixed state	19 (73.1)
1) mood congruent psychotic symptoms	9 (34.6)
2) mood incongruent psychotic symptoms	10 (38.5)
Lifetime comorbidity, n (%)	
Panic Disorder/Agoraphobia	4 (15.4)
Alcohol misuse	1 (3.8)
Characteristics of ECT course	
Total ECT sessions	10.15 (3.02)
Electrical dose first session (mC)	185.9 (54.3)
Electrical dose last session (mC)	336.0 (125.7)
EEG seizure activity, seconds	34.04 (9.48)
Simptomatological Rating Scales, mean (sd)	
CGI-S Baseline Final	 6.88 (0.33) 3.73 (1.05)[a]
Bush-Francis Catatonia Rating Scale (BFCRS) Baseline Final	 32.23 (8.05) 5.77 (5.46)[b]
BPRS total score Baseline Final	 105.08 (26.06) 47.92 (21.08)[c]
BPRS psychotic cluster Baseline Final	 18.62 (5.91) 7.96 (5.09)[d]

Baseline VS Final:
[a] t= 11.68 p=.000; [b] t= 17.34 p=.000; [c] t= 11.37 p=.000; [d] t= 8.50 p=.000.

(15.4) with mood congruent psychotic symptoms and 3 (11.5%) with mood incongruent psychotic symptoms; 19 patients (73.1%) were diagnosed as having mixed state, 9 (34.6%) with mood congruent psychotic symptoms and 10 (38.4%) with mood incongruent psychotic symptoms. With respect to lifetime comorbidity, panic disorder was reported in 4 (15.4%) patients and only 1 (3.8%) showed alcohol misuse. The mean number of ECT sessions was 10. 15 ±3. 02 and, at the end of the ECT course, the mean CGIs, BFCRS, BPRS total and psychotic cluster and YMRS total scores were lowered in a statistically significant measure. BFCRS showed the largest percentage of improvement with an 82% reduction of the initial score. The rate of improvement was also substantial in CGIs, BPRS total and psychotic scores, respectively 45.8%, 54.4% and 57.2%.

DISCUSSION

In our patients, ECT resulted an effective treatment regardless of the phases of the disorder. We detected a clinically significant response in approximately two-thirds of the patients with severe and drug -resistant bipolar depression, mania and mixed state. Besides, in more than 80% of drug resistant catatonic patients, ECT resulted effective. With a proper surveillance, the treatment appeared safe and serious adverse events unlikely.

Only less than 5% of our patients interrupted the ECT course prematurely. In addition, consistently with existing literature [59, 108, 109], our data demonstrate that ECT-induced mania or depression is actually inexistent. In this perspective, long-term mood destabilization, including cycle induction or acceleration, is very unlikely [22, 110] and ECT may be considered a mood-stabilizing treatment.

To be considered a mood stabilizer, an agent ought to decrease the frequency or severity of any type of episode in BD without worsening the frequency or severity of other types of episodes [111, 112]. Some Authors have proposed a more stringent definition that requires that an agent possesses efficacy in treating both manic, mixed and depressive episodes [56] (avoiding the induction of switching into the opposite phase) and in preventing relapses and recurrences (increasing the duration of the "free" intervals). In the absence of a univocal definition, conventional mood stabilizers such as lithium and anticonvulsants represented the best candidates to achieve the above-mentioned goals, but with several disadvantages. Indeed, they show limited clinical efficacy in severe acute bipolar depressive, manic and mixed episodes, in particular in presence of psychotic, catatonic and delirious states [46]. In these patients adjunctive antidepressant and antipsychotics are routinely utilized with increased risk of acute switches and long-term destabilization. Our results suggest that in these kind of patients ECT may represent an effective and valid alternative without increasing the risk of mood destabilization.

Unfortunately, evidence on ECT in long-term prophylaxis and randomized controlled trials of continuation ECT (c-ECT) and maintenance ECT (m-ECT) in BD patients are lacking. However, on the basis of data drawn from naturalistic observations, c-ECT and m-ECT seem effective in stabilizing chronic BD patients by reducing the admission rate or the length of hospitalization [78, 113]. Case reports and open trials pointed out a significant reduction in illness morbidity among subjects suffering from rapid cycling [114]. More recently, in a retrospective study, maintenance

ECT significantly reduced the number of full hospitalization days in a sample of patients with severe BD and schizoaffective disorder, bipolar type [115]. Long-term randomized controlled trials comparing m -ECT with pharmacological treatments are warranted in order to define the efficacy and safety of ECT in preventing BPD recurrences and relapses and further research is needed to settle the necessary frequency and duration of c-ECT treatment after a successful index course of ECT.

In the present study, the length of current episode and the global severity of the symptomatology were the only predictors of nonresponse to ECT. In particular, in our patients, the duration of the depressive or mixed episode was the main predictor of nonresponse, suggesting that a long episode duration may contribute to resistance to treatments, including ECT. Unfortunately, current guidelines and consequent clinical practice look at ECT as a "last resort" treatment. Consequently, a huge amount of subjects with BD is treated for a long time with different types of antidepressants and antipsychotics, often associated, before undergoing ECT. This widespread practice may increase the risk of mood destabilization and may decrease the chance of recovery in many patients, who might have potentially responded if timely treated with ECT. In all the treatment guidelines for BD, the role of ECT is minimized and for bipolar depression and mixed states ECT is proposed as a "second-line" or "third-line" option [116]. In the light of our results, for patients with severe mixed states and catatonic features, clinical guidelines and treatment algorithms for BD should be modified. In presence of severe mixed features the use of ECT should be encouraged among the first line treatments, in particular when delirious, psychotic and suicidal symptoms are present. In these patients pharmacological treatments with antipsychotics and antidepressants are not only ineffective, but are frequently associated with complications such as chronicity, mood destabilization and suicidality. The same consideration should be done for depressive and mixed states with catatonic features non responsive to benzodiazepine, where the use of antipsychotics and mood stabilizers may exacerbate catatonic symptoms.

The nonrandom allocation and the relatively short-term course represent the main limitations of the study. Nevertheless, the systematic assessment of the clinical manifestations and outcome partially softens these flaws. Another important shortcoming is that only anticonvulsants were withdrawn before ECT treatment, whereas all other psychotropic medications were permitted, on the basis of the physician's clinical judgment. However, given that both groups were drug resistant and had been steadily taking antidepressants and antipsychotics for at least one week before and during ECT the likelihood that outcome differences may be due to pharmacological treatment is limited.

In conclusion, ECT resulted very effective for all BD acute depressive, mixed and manic episodes not responding to conventional pharmacologic management. ECT should be considered the treatment of choice in patients with severe depressive and mixed states characterized by delirious and catatonic features. Long-lasting severe depressive or mixed episodes predict a lack of response.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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