See commentaries by Kellner et al and Murru p1190

Electroconvulsive Therapy in 197 Patients With a Severe, Drug-Resistant Bipolar Mixed State: Treatment Outcome and Predictors of Response

Pierpaolo Medda, MD; Cristina Toni, MD; Michela Giorgi Mariani, MD; Luigi De Simone, MD; Mauro Mauri, MD; and Giulio Perugi, MD

ABSTRACT

Objective: We prospectively evaluated the short-term outcome and the predictors of response to electroconvulsive therapy (ECT) in a large sample of patients with a bipolar mixed state.

Method: From January 2006 to May 2011, we performed an analysis using data obtained from 197 of 203 consecutive patients with a bipolar mixed state, according to *DSM-IV-TR* diagnostic criteria, who were treated with ECT at the Department of Psychiatry of the University of Pisa. All patients were evaluated prior to and after the ECT course using the Hamilton Depression Rating Scale-17 (HDRS-17), Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impressions (CGI) scale. The CGI subscale "global improvement" and final HDRS-17 and YMRS total scores were used to identify nonresponder, responder, and remitter groups.

Results: At the end of the ECT course, 55 patients (27.9%) were considered nonresponders, 82 responders (41.6%), and 60 remitters (30.5%). As expected, at the end of the ECT trial, the CGI-Severity scale (CGI-S; $P < .0001$), HDRS-17 ($P < .0001$), and BPRS ($P < .0001$) scores were significantly lower in remitters than in responders and nonresponders. Using backward stepwise logistic regression, the length of current episode, lifetime comorbidity of obsessive-compulsive disorder, and baseline YMRS total mean score were statistically significant predictors of nonresponse versus remission ($P < .0001$).

Conclusions: Less than 30% of the patients included in the study were nonresponders to ECT. Long-lasting mixed episode with excitatory symptoms and lifetime comorbidity of obsessive-compulsive disorder significantly predicted a lack of complete remission.

J Clin Psychiatry 2015;76(9):1168–1173
dx.doi.org/10.4088/JCP.14m09181

Submitted: April 4, 2014; accepted July 14, 2014.
Online ahead of print: April 14, 2015.
Corresponding author: Giulio Perugi, MD, Clinica Psichiatrica, Dipartimento di Medicina Clinica e Sperimentale, University of Pisa, Via Roma 67, 56100, Pisa, Italy (giulio.perugi@med.unipi.it).

Mixed state refers to an affective condition in which various combinations of depressive and manic symptoms are simultaneously present. Together with mania and depression, mixed state represents a major phase of bipolar disorder and, if compared with nonmixed episodes, is characterized by a more complex clinical presentation[1–3] and a less favorable response to conventional pharmacologic treatments.[4–7]

With regard to clinical features, mixed state is characterized by longer and more severe episodes,[8–12] higher frequency of psychotic features[8] and Axis I comorbidity,[13] greater[2] risk of suicide,[14] and poorer outcome[9–11,15] when compared with major depression.

Treatment of mixed state is a therapeutic challenge mostly because this condition has been associated with a poorer response to mood stabilizers and a greater need for drug combination compared to pure manic or depressive episodes.[7] Moreover, the use of antidepressants has been reported to worsen short-term intraepisodic mood instability and mixed symptomatology in a relevant proportion of bipolar patients, other than to increase the risk of manic switches and long-term cycle acceleration.[16–21] However, the use of antipsychotics for the treatment of mixed state may precipitate or induce depressive symptoms.[22,23]

Although electroconvulsive therapy (ECT) has been performed for the first time in a patient with mixed state with outstanding outcome[24] and has been shown to be effective in treating BD depression,[25] the effectiveness of ECT in mixed-state treatment has not been extensively studied for different reasons. Mixed state is often underdiagnosed due to inadequate diagnostic delimitation[2,8,26] and misdiagnosed because of its pleomorphic symptomatic presentation.[2,27,28] Consequently, many patients with a mixed state are included in samples of schizophrenic or manic patients treated with ECT.[2] For these biases, literature data have been disappointingly limited, and most likely, due to the limited evidence available, the use of ECT in mixed-state treatment has not been specifically described by most of the clinical practice guidelines for the treatment of bipolar disorder.[29]

In a retrospective study in Aarhus Psychiatric Hospital,[30] a high response to ECT in a sample of 19 patients with manic-depressive mixed states has been observed. Gruber et al[31] reported a significant reduction in depressive and manic symptoms in a case series of mixed-state patients treated with ECT. Other studies,[32] which compared the response to ECT in mixed state, bipolar depression, and mania, showed robust response rates in all groups: 80% in the mixed group, 100% in the manic group, and 76% in the depressed group. Nevertheless, the mixed group showed a higher number of days in the hospital and of ECT trials compared to the other 2 groups. Ciapparelli et al[33] reported a response rate of 56% for mixed mania and 26% for bipolar depression. In our recent study,[34] we evaluated the ECT response in a sample of bipolar I patients, in which 46 patients exhibited depression and 50 patients demonstrated a mixed state. The response rate was similar in bipolar depression and mixed state (67.4% and 76.0%, respectively), and no difference was found in the remission rate between depression (41.3%) and mixed state (34.8%). However, at the end of the ECT course, mixed state

Clinical Points

- Bitemporal electroconvulsive therapy is effective in approximately 70% of patients with a severe bipolar mixed state who do not respond to conventional pharmacologic management.
- Long-lasting mixed episodes with a prevalence of excitement symptoms, associated with OCD lifetime comorbidity, can predict a lack of complete remission.
- The use of electroconvulsive therapy in bipolar mixed episodes is not specifically described in most current treatment guidelines. Consequently, a large number mixed state patients are treated for long periods of time with complex drug combinations, increasing the likelihood that this worldwide practice may decrease the chance of recovery, at least in some patients, who could have potentially responded to ECT if treated in a timely manner.

may present more residual agitation and psychotic features compared with depressive patients.

In the present study, we describe the short-term outcome of a large sample of patients with bipolar mixed state, which is resistant to pharmacotherapy, who were treated with ECT; we also explore the potential effect of different clinical features on the response to ECT.

METHOD

Patients who received 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, were screened for inclusion in the present study. Of a total number of 562 patients, 203 patients (36.1%) met the *DSM-IV* criteria for current mixed episode, 8 patients (1.4%) for current manic episode, and 351 patients (62.5%) for current major depressive episode (137 bipolar I patients [39.0%], 174 bipolar II patients [49.6%], and 40 patients [11.4%] with major depressive disorder). The diagnoses were made by 2 senior psychiatrists (P.M., M.M.) and were confirmed by the administration of the 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.

To be included in the present outcome analysis, patients had to receive at least 3 treatments of ECT. Of the initial 203 patients with mixed state, 6 patients were excluded because the ECT course was terminated prematurely (1 severe confusion, 1 severe headache, 2 cardiac arrhythmia, 1 respiratory complications, and 1 consent withdrawal). Thus, the final analysis involved 197 consecutive patients with a drug-resistant mixed state. Study subjects were 18 years or older and provided their written informed consent to receive ECT and to participate in the study. Our study is naturalistic, observational, and noncomparative. Electroconvulsive therapy course and systematic evaluation were conducted under conditions of routine clinical practice. The study was approved by the local Ethic Review Board of the University Hospital of Pisa (study number: 1731/2004).

Information used to establish treatment resistance was based on a review of outpatient and inpatient medical records and on the reports of the patient, his/her family members, and prescribing psychiatrists. In the absence of a viable and shared definition of treatment resistance for mixed state, treatment 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 the symptom patterns. In our study, the severity of medication resistance was not formally assessed, but nearly all patients had failed multiple prior medication trials.

All patients were evaluated prior to ECT (baseline) and a week after the ECT course (final score) using the Hamilton Depression Rating Scale-17 items (HDRS-17)[36]; Young Mania Rating Scale (YMRS)[37]; Brief Psychiatric Rating Scale (BPRS)[38]; and Clinical Global Impressions (CGI), -Severity (CGI-S), and -Improvement (CGI-I) scales.[39] The variation in psychotic symptomatology was investigated using the BPRS psychosis cluster score: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization (items 9, 10, 11, and 15; maximum score, 28). All scales were administered by a psychiatrist (P.M.) with substantial experience in the assessment and treatment of bipolar patients.

For the present study, the CGI-I and final HDRS-17 and YMRS total scores were used to identify nonresponder, responder, and remitter groups. A *nonresponse* was defined as a post-treatment CGI-I rating ≥ 3; *response* as a CGI-I rating 2, "much improved"; and *remission* as a CGI-I rating 1, "very much improved," a final HDRS-17 total score ≤ 10,[40] and YMRS total scores ≤ 12.[41]

ECT Procedure

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, New York) on a twice-a-week schedule. 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.[42] 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[43] 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

Table 1. Differences in Demographic, Clinical Course, and Symptomatological Scales Between Nonresponders, Responders, and Remitters to ECT Treatment in 197 Patients

Characteristic	Nonresponders (n = 55)	Responders (n = 82)	Remitters (n = 60)	Analysis F/χ^2	Analysis *P* Value
Age, mean (SD), y	44.76 (14.64)	42.88 (12.11)	44.55 (12.69)	0.45	.642
Age at onset, mean (SD), y	25.56 (11.54)	23.43 (10.28)	24.67 (9.05)	0.74	.480
Gender, females, n (%)	34 (61.8)	47 (57.3)	38 (63.3)	0.59	.745
Duration of current episode, mean (SD), mo	13.49 (16.95)	8.60 (8.01)	6.15 (5.41)	6.92	.001[a]
Number of previous episodes, mean (SD)	4.96 (3.27)	5.07 (2.66)	6.08 (3.64)	2.35	.098
Number of previous hospitalizations, mean (SD)	3.55 (2.46)	3.49 (2.50)	3.75 (2.55)	0.20	.820
Suicide attempts, n (%)	14 (25.5)	18 (22.0)	22 (36.7)	3.91	.141
Psychotic symptoms, n (%)	43 (78.2)	60 (73.2)	43 (71.7)	0.77	.705
Lifetime comorbidity, n (%)					
Panic disorder/agoraphobia	18 (32.7)	34 (41.5)	25 (41.7)	1.30	.523
Social phobia	2 (3.6)	0 (0.0)	1 (1.7)	2.92	.233
Obsessive-compulsive disorder	9 (16.4)	18 (22.0)	2 (3.3)	9.73	.008[b]
Anorexia nervosa	1 (1.8)	1 (1.2)	1 (1.7)	0.09	.956
Bulimia nervosa	2 (3.6)	0 (0.0)	4 (6.7)	5.31	.070
Alcohol misuse	4 (7.3)	4 (4.9)	2 (3.3)	0.94	.626
Substance misuse	4 (7.3)	4 (4.9)	4 (6.7)	0.38	.827
Characteristic of ECT course, mean (SD)					
Total ECT session	7.33 (3.24)	7.51 (1.20)	7.60 (2.07)	0.19	.83
Electrical dose first session, mC	152.4 (53.0)	145.6 (40.3)	152.9 (43.8)	0.59	.55
Electrical dose last session, mC	245.5 (115.6)	243.8 (122.5)	256.1 (122.4)	0.20	.82
EEG seizure activity, s	46.3 (29.8)	40.6 (14.3)	41.2 (13.5)	1.51	.22

[a]Scheffe *F* test: nonresponders > responders, remitters.
[b]Adjusted residuals: responders, nonresponders > remitters.
Abbreviation: ECT = electroconvulsive therapy.

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 as concomitant medications during ECT treatment.

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. Benzodiazepines were allowed up to a dosage equivalent to 3 mg/d of lorazepam, as needed.

Statistical Analysis

Comparisons between groups were performed using χ^2 tests for categorical variables and ANOVA for continuous variables (Kruskal-Wallis test when ANOVA statistical assumptions were violated). Given the exploratory nature of our study, the significance level for each test was established at $P < .05$, 2-tailed. Significant differences obtained using the χ^2 and Kruskal-Wallis tests were followed by the Dunn test, and significant differences produced by ANOVA were followed by the Scheffé *F* test. To examine which demographic and clinical variables were associated with the ECT nonresponse, response, and remission, 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. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS-20.0).

RESULTS

At the end of the ECT course, 55 patients (27.9%) were considered nonresponders, 82 patients (41.6%) were responders, and 60 patients (30.5%) were remitters.

Table 1 shows comparisons of the demographic and clinical characteristics between nonresponders, responders, and remitters. The mean age and age at onset were similar in the 3 groups. Females were more represented in our sample, with a similar distribution across the different groups. No significant differences among the 3 groups were observed in the number of lifetime episodes, number of hospitalizations, and number of suicide attempts. The presence of psychotic symptoms was very common in our sample, but it did not show a different distribution in the 3 groups. The mean length of the current episode was significantly longer in the nonresponders compared to responders and remitters (13.49 vs 8.60 and 6.15; $P = .001$)

Lifetime rates of comorbidity with panic disorder, social anxiety, eating disorders, and alcohol and drug use disorders were similar in the 3 groups. Lifetime comorbidity with obsessive-compulsive disorder (OCD) was more common in responders and in nonresponders than in remitters (Table 1).

With respect to the ECT course (Table 1), the mean number of ECT sessions, the electrical dose at first session and at last session, and the duration of electroencephalogram seizure activity were similar in the 3 groups.

Comparisons between the 3 groups with respect to CGI-S, HDRS-17, YMRS, and BPRS total and psychotic cluster mean scores at baseline and at the final evaluation

Table 2. Comparisons of CGI-S, HDRS-17, YMRS, BPRS, BPRS Psychotic Cluster Baseline and Final Mean (SD) Scores in Nonresponder, Responder, and Remitter Patients Treated With ECT

Variable	Total (N = 197)	Nonresponders (n = 55)	Responders (n = 82)	Remitters (n = 60)	*F*	*P* Value
CGI-S						
Baseline	5.99 (0.60)	6.07 (0.33)	5.94 (0.81)	5.98 (0.43)	0.83	.439
Final	3.61 (1.05)	4.60 (0.66)	3.68 (0.66)	2.60 (0.85)	110.58	.0001[a]
HDRS-17						
Baseline	22.18 (4.94)	21.45 (5.57)	21.83 (4.63)	23.32 (4.59)	2.43	.091
Final	10.84 (4.77)	13.96 (5.26)	11.06 (3.65)	7.67 (3.54)	33.55	.0001[a]
YMRS						
Baseline	16.96 (6.96)	17.90 (5.70)	17.59 (6.63)	15.27 (8.15)	2.64	.074
Final	8.65 (5.57)	12.07 (5.50)	8.98 (5.07)	5.08 (4.01)	29.44	.0001[a]
BPRS total						
Baseline	61.49 (13.26)	61.07 (14.32)	59.80 (11.54)	64.18 (14.23)	1.95	.146
Final	39.91 (9.21)	46.85 (10.28)	39.84 (5.86)	33.63 (7.25)	41.95	.0001[a]
BPRS psychotic cluster						
Baseline	12.10 (5.92)	11.85 (5.17)	11.76 (5.82)	12.80 (6.69)	0.60	.548
Final	7.25 (3.21)	8.89 (3.72)	7.30 (3.05)	5.68 (1.94)	16.64	.0001[a]

[a]Scheffe *F* test: nonresponders > responders > remitters.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity, ECT = electroconvulsive therapy, HDRS-17 = Hamilton Depression Rating Scale-17, YMRS = Young Mania Rating Scale.

Table 3. Comparison of Individual BPRS Items at Baseline Between Nonresponder, Responder, and Remitter Patients Treated With ECT[a]

Item	Total (N = 197)	Nonresponders (n = 55)	Responders (n = 82)	Remitters (n = 60)	*P* Value
Somatic concerns	1.70 (1.43)	1.62 (1.50)	1.66 (1.43)	1.83 (1.38)	.224
Anxiety	4.44 (.91)	4.38 (.99)	4.49 (.79)	4.43 (1.0)	.843
Depression	4.91 (1.40)	4.80 (1.48)	4.78 (1.32)	5.20 (1.40)	.029[b]
Suicidality	2.73 (1.47)	2.73 (1.34)	2.51 (1.46)	3.03 (1.57)	.106
Guilt	3.27 (1.67)	3.02 (1.63)	3.00 (1.62)	3.87 (1.65)	.002[b]
Hostility	1.54 (1.11)	1.44 (1.01)	1.54 (1.02)	1.65 (1.31)	.766
Elevated mood	1.57 (1.28)	1.47 (1.26)	1.76 (1.34)	1.42 (1.21)	.072
Grandiosity	1.46 (1.12)	1.56 (1.27)	1.50 (1.08)	1.30 (1.03)	.219
Suspiciousness	3.34 (1.68)	3.31 (1.50)	3.17 (1.62)	3.60 (1.88)	.348
Hallucinations	2.79 (2.04)	2.64 (1.91)	2.73 (2.03)	3.00 (2.19)	.614
Unusual thought content	3.97 (1.97)	4.18 (1.90)	3.88 (1.93)	3.90 (2.09)	.605
Bizarre behavior	2.08 (1.55)	2.29 (1.57)	1.90 (1.46)	2.13 (1.64)	.194
Self-neglect	3.54 (1.18)	3.60 (1.21)	3.40 (1.14)	3.68 (1.19)	.230
Disorientation	1.49 (1.18)	1.36 (1.08)	1.41 (1.08)	1.72 (1.37)	.142
Conceptual disorganization	2.01 (0.70)	1.73 (1.57)	1.98 (1.63)	2.30 (1.87)	.204
Blunted affect	2.93 (1.59)	3.24 (1.50)	2.88 (1.57)	2.72 (1.66)	.210
Emotional withdrawal	2.20 (1.63)	2.56 (1.72)	1.88 (1.49)	2.30 (1.68)	.057
Motor retardation	1.86 (1.26)	1.65 (1.08)	1.90 (1.21)	2.00 (1.46)	.431
Tension	3.89 (1.12)	3.65 (1.11)	3.76 (1.15)	4.28 (.98)	.003[b]
Uncooperativeness	1.45 (1.10)	1.47 (1.17)	1.43 (1.02)	1.47 (1.16)	.948
Excitement	2.06 (1.42)	1.93 (1.46)	2.24 (1.40)	1.92 (1.40)	.214
Distractibility	2.89 (1.53)	2.93 (1.54)	2.85 (1.48)	2.92 (1.63)	.966
Motor hyperactivity	2.16 (1.48)	2.24 (1.54)	2.06 (1.50)	2.22 (1.42)	.679
Mannerisms and posturing	1.21 (.81)	1.27 (.89)	1.10 (.62)	1.30 (.94)	.152

[a]Values are expressed as mean (SD).
[b]Kruskal-Wallis test: remitters > nonresponders, responders.

are reported in Table 2. At baseline, the HDRS-17 mean scores were higher among remitters than responders and nonresponders. In contrast, the baseline YMRS mean score was lower in remitters than in responders and nonresponders. The baseline CGI-S and BPRS total and psychotic cluster mean scores were not different between the 3 groups. As expected, at the end of the ECT trial, the CGI-S, HDRS-17, and BPRS total scores were significantly lower in remitters than in responders and nonresponders. In these scales, remitters reported lower scores than nonresponders.

Comparisons of the BPRS items at basal evaluation showed that items 3-depression, 5-guilt, and 19-tension were significantly higher in remitters than in responders and nonresponders (Table 3).

Using backward stepwise logistic regression, the length of current episode (odds ratio [OR] = 0.935; 95% CI = 0.88 to 0.99; *P* = .016), OCD lifetime comorbidity (OR = 0.16; 95% CI = 0.031 to 0.83; *P* = .029), and baseline YMRS total mean score (OR = 0.95; 95% CI = 0.90 to 1.00; *P* = .085) were statistically significant predictors of nonresponse versus remission. (The number of previous episodes, HDRS-17 baseline total score, and positive lifetime comorbidity with bulimia nervosa resulted in variables that were not included in the equation.)

DISCUSSION

In our sample of patients with severe and drug-resistant mixed state treated with an acute course of ECT, we observed high rates of response with less than 30% of patients categorized as nonresponders. These results are similar to findings obtained in other studies[31,32,34]; in only 1 study, a lower rate of response (50%) was reported.[33] However, the low percentage of complete remission (30%) should not be considered as a failure. Indeed, considering that our sample mainly consisted of severely ill patients as suggested by the length of the index episode and the high percentage of psychotic symptoms, even a partial response may represent a meaningful difference in a patient's life in the absence of a complete remission.[44]

In our sample, a nonresponse was associated with a longer duration of the current episode, lifetime comorbidity with OCD, and higher baseline YMRS scores. The duration of the episode was the most consistent predictor of nonresponse to ECT according to previous reports in major depressive disorder (MDD), in which a longer duration of depression was associated with a lower response rate to ECT.[45–47] It is likely that, similar to depression, the exposure to longer episode duration may contribute to resistance to treatments, including ECT.

The low rate of lifetime OCD comorbidity observed in remitters is most likely related to the comorbidity observed in bipolar disorder with OCD, which is associated with increased severity, poor outcome, and residual affective symptoms.[48] However, the high rates of OCD comorbidity in the responder group suggest that ECT may also represent a useful therapeutic tool in the clinical management of bipolar disorder in comorbidity with OCD. In these patients, psychopharmacologic treatment is particularly complicated: treatment with a high dose of serotonergic antidepressants (clomipramine or a selective serotonin reuptake inhibitor) has been associated with the induction of hostile mood and aggressive behaviors,[49,50] and the utilization of atypical antipsychotic may exacerbate OCD symptoms.[51]

The higher baseline YMRS score in the nonresponder group confirms the findings of our previous studies on ECT in MDD-resistance[47,52] and suggests that ECT has a predominantly antidepressant effect compared to an antimanic effect. This hypothesis is supported by higher BPRS depressive scores in remitters compared to responders and nonresponders.

In this sample of patients with a mixed state, the presence/absence of psychotic symptoms did not affect the response to ECT treatment. The current literature on this issue is still controversial: several studies have reported a higher response in delusional compared to nondelusional patients with depression[53–55]; however, other studies did not find any difference.[47,56,57] In our recent study of a sample of unipolar and bipolar patients with major depressive episode,[52] we observed that the absence of thought-content disorder was related to a more favorable outcome, which was consistent with results obtained by de Vreede et al.[58]

The present study has several limitations, including nonrandom allocation and a relatively short-term course. However, the systematic evaluation of clinical features and outcome partially reduces these shortcomings. Another important limitation is that only anticonvulsants were withdrawn prior to ECT treatment, whereas all other psychotropic medications were permitted on the basis of the physician's clinical judgment. However, the likelihood that differences in outcome may be attributed to pharmacologic treatment is reduced by the fact that both groups were considered drug-resistant and received stable antidepressant and antipsychotic treatment regimens for at least 1 week before and during the ECT course. Finally, the presence of rapid cycling was not directly evaluated in our sample. Given the nature of our tertiary care unit, this subgroup of patients might be overrepresented, which could pose as a major confounder. However, in contrast to the duration of the current episode, the number of previous episodes was not associated with response or remission.

In conclusion, ECT should be considered the treatment of choice in mixed state patients who are not responding to conventional pharmacologic management. The short duration of the current episode, prevalence of depressive symptoms, and absence of OCD comorbidity appear to be associated with a complete remission in our sample. In contrast, long-lasting mixed episodes with a prevalence of excitement symptoms, which are associated with OCD lifetime comorbidity, can predict a lack of complete remission.

Proper identification of a mixed state has critical implications for clinical practice as mixed states might be confused with a number of other psychiatric disorders, including unipolar agitated depression, delusional depression, schizophrenia, borderline personality disorder, and organic mental disorders.[2] It would be important to distinguish mixed states from these conditions such that treatments (eg, antidepressants) that might worsen their symptomatology would be avoided, while treatments that might be particularly effective (eg, mood stabilizers and ECT) would not be underutilized. Unfortunately, in most current guidelines, the use of ECT to treat mixed episodes is not specifically described, and consequently clinical practice views ECT as a "last resort" treatment. As a result, a large number of mixed bipolar patients are treated for long periods of time with complex drug combinations prior to receiving ECT. Thus, it is likely that this worldwide practice may decrease the chance of recovery, at least in some mixed state patients, who could have potentially responded to ECT if treated in a timely manner.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clomipramine (Anafranil and others), lithium (Lithobid and others), lorazepam (Ativan and others).

Author affiliations: Department of Clinical and Experimental Medicine, University of Pisa (Drs Medda, Mariani, De Simone, Mauri, and Perugi); Institute of Behavioral Science "G. De Lisio," Carrara-Pisa (Drs Toni and Perugi); and Unit of Anesthesiology 3, Azienda Ospedaliero-Universitaria Pisana (Dr De Simone), Italy.

Potential conflicts of interest: None reported.

Funding/support: None reported.

REFERENCES

1. Perugi G, Medda P, Reis J, et al. Clinical subtypes of severe bipolar mixed states. *J Affect Disord*. 2013;151(3):1076–1082.
2. Swann AC, Lafer B, Perugi G, et al. Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness, and diagnosis. *Am J Psychiatry*. 2013;170(1):31–42.
3. Pacchiarotti I, Mazzarini L, Kotzalidis GD, et al. Mania and depression: mixed, not stirred. *J Affect Disord*. 2011;133(1–2):105–113.
4. Swann AC, Bowden CL, Morris D, et al. Depression during mania: treatment response to lithium or divalproex. *Arch Gen Psychiatry*. 1997;54(1):37–42.
5. Himmelhoch JM, Garfinkel ME. Sources of lithium resistance in mixed mania. *Psychopharmacol Bull*. 1986;22(3):613–620.
6. Duffy A, Alda M, Kutcher S, et al. A prospective study of the offspring of bipolar parents responsive and nonresponsive to lithium treatment. *J Clin Psychiatry*. 2002;63(12):1171–1178.
7. Krüger S, Trevor Young L, Bräunig P. Pharmacotherapy of bipolar mixed states. *Bipolar Disord*. 2005;7(3):205–215.
8. Perugi G, Akiskal HS, Micheli C, et al. Clinical characterization of depressive mixed state in bipolar-I patients: Pisa-San Diego collaboration. *J Affect Disord*. 2001;67(1–3):105–114.
9. Cohen S, Khan A, Robison J. Significance of mixed features in acute mania. *Compr Psychiatry*. 1988;29(4):421–426.
10. Keller MB, Lavori PW, Coryell W, et al. Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. *JAMA*. 1986;255(22):3138–3142.
11. Prien RF, Himmelhoch JM, Kupfer DJ. Treatment of mixed mania. *J Affect Disord*. 1988;15(1):9–15.
12. Post RM, Rubinow DR, Uhde TW, et al. Dysphoric mania: clinical and biological correlates. *Arch Gen Psychiatry*. 1989;46(4):353–358.
13. McElroy SL, Strakowski SM, Keck PE Jr, et al. Differences and similarities in mixed and pure mania. *Compr Psychiatry*. 1995;36(3):187–194.
14. Dilsaver SC, Chen YW, Swann AC, et al. Suicidality in patients with pure and depressive mania. *Am J Psychiatry*. 1994;151(9):1312–1315.
15. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry*. 1990;47(12):1106–1111.
16. Post RM, Leverich GS, Nolen WA, et al; Stanley Foundation Bipolar Network. A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. *Bipolar Disord*. 2003;5(6):396–406.
17. Ghaemi SN, Wingo AP, Filkowski MA, et al. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. *Acta Psychiatr Scand*. 2008;118(5):347–356.
18. Ghaemi SN, Hsu DJ, Soldani F, et al. Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord*. 2003;5(6):421–433.
19. Goldberg JF, Harrow M, Whiteside JE. Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am J Psychiatry*. 2001;158(8):1265–1270.
20. Post RM, Nolen WA, Kupka RW, et al. The Stanley Foundation Bipolar Network, 1: rationale and methods. *Br J Psychiatry suppl*. 2001;41(41):s169–s176.
21. Ghaemi SN. Treatment of rapid-cycling bipolar disorder: are antidepressants mood destabilizers? *Am J Psychiatry*. 2008;165(3):300–302.
22. Ahlfors UG, Baastrup PC, Dencker SJ, et al. Flupenthixol decanoate in recurrent manic-depressive illness: comparison with lithium. *Acta Psychiatr Scand*. 1981;64(3):226–237.
23. Nelson LA, Swartz CM. Melancholic symptoms during concurrent olanzapine and fluoxetine. *Ann Clin Psychiatry*. 2000;12(3):167–170.
24. Shorter E, Healy E. *Shock Therapy: A History of Electroconvulsive Therapy in Mental Illness*. New Brunswick, NJ: Rutgers University Press; 2007.
25. Bailine S, Fink M, Knapp R, et al. Electroconvulsive therapy is equally effective in unipolar and bipolar depression. *Acta Psychiatr Scand*. 2010;121(6):431–436.
26. Koukopoulos A, Sani G. *DSM-5* criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr Scand*. 2014;129(1):4–16.
27. Angst J, Azorin JM, Bowden CL, et al; BRIDGE Study Group. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. *Arch Gen Psychiatry*. 2011;68(8):791–798.
28. Perugi G, Medda P, Swann AC, et al. Phenomenological subtypes of severe bipolar mixed states: a factor analytic study. *Compr Psychiatry*. 2014;55(4):799–806.
29. Loo C, Katalinic N, Mitchell PB, et al. Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. *J Affect Disord*. 2011;132(1–2):1–13.
30. Strömgren LS. Electroconvulsive therapy in Aarhus, Denmark, in 1984: its application in nondepressive disorders. *Convuls Ther*. 1988;4(4):306–313.
31. Gruber NP, Dilsaver SC, Shoaib AM, et al. ECT in mixed affective states: a case series. *J ECT*. 2000;16(2):183–188.
32. Devanand DP, Polanco P, Cruz R, et al. The efficacy of ECT in mixed affective states. *J ECT*. 2000;16(1):32–37.
33. Ciapparelli A, Dell'Osso L, Tundo A, et al. Electroconvulsive therapy in medication-nonresponsive patients with mixed mania and bipolar depression. *J Clin Psychiatry*. 2001;62(7):552–555.
34. Medda P, Perugi G, Zanello S, et al. Comparative response to electroconvulsive therapy in medication-resistant bipolar I patients with depression and mixed state. *J ECT*. 2010;26(2):82–86.
35. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
36. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
37. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
38. Overall JEGD. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10(3):799–812.
39. Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology*. US Dept Health, Education and Welfare Publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.
40. Sackeim HA, Dillingham EM, Prudic J, et al. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. *Arch Gen Psychiatry*. 2009;66(7):729–737.
41. Tohen M, Jacobs TG, Grundy SL, et al; The Olanzipine HGGW Study Group. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2000;57(9):841–849.
42. Shapira B, Tubi N, Lerer B. Balancing speed of response to ECT in major depression and adverse cognitive effects: role of treatment schedule. *J ECT*. 2000;16(2):97–109.
43. Petrides G, Fink M. The "half-age" stimulation strategy for ECT dosing. *Convuls Ther*. 1996;12(3):138–146.
44. McCall WV. Is remission a necessary and sufficient definition of success in electroconvulsive therapy? part 1. *J ECT*. 2013;29(4):257.
45. Dombrovski AY, Mulsant BH, Haskett RF, et al. Predictors of remission after electroconvulsive therapy in unipolar major depression. *J Clin Psychiatry*. 2005;66(8):1043–1049.
46. Kho KH, Zwinderman AH, Blansjaar BA. Predictors for the efficacy of electroconvulsive therapy: chart review of a naturalistic study. *J Clin Psychiatry*. 2005;66(7):894–899.
47. Perugi G, Medda P, Zanello S, et al. Episode length and mixed features as predictors of ECT nonresponse in patients with medication-resistant major depression. *Brain Stimulat*. 2012;5(1):18–24.
48. Perugi G, Toni C, Frare F, et al. Obsessive-compulsive-bipolar comorbidity: a systematic exploration of clinical features and treatment outcome. *J Clin Psychiatry*. 2002;63(12):1129–1134.
49. Vieta E, Bernardo M. Antidepressant-induced mania in obsessive-compulsive disorder. *Am J Psychiatry*. 1992;149(9):1282–1283.
50. Tondo L, Vázquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. *Acta Psychiatr Scand*. 2010;121(6):404–414.
51. Baker RW, Chengappa KN, Baird JW, et al. Emergence of obsessive compulsive symptoms during treatment with clozapine. *J Clin Psychiatry*. 1992;53(12):439–442.
52. Medda P, Mauri M, Toni C, et al. Predictors of remission in 208 drug-resistant depressive patients treated with electroconvulsive therapy. *J ECT*. 2014;30(4):292–297.
53. Petrides G, Fink M, Husain MM, et al. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J ECT*. 2001;17(4):244–253.
54. Buchan H, Johnstone E, McPherson K, et al. Who benefits from electroconvulsive therapy? combined results of the Leicester and Northwick Park trials. *Br J Psychiatry*. 1992;160(3):355–359.
55. Birkenhäger TK, Pluijms EM, Lucius SA. ECT response in delusional versus non-delusional depressed inpatients. *J Affect Disord*. 2003;74(2):191–195.
56. Prudic J, Haskett RF, Mulsant B, et al. Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry*. 1996;153(8):985–992.
57. O'Connor MK, Knapp R, Husain M, et al. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. report. *Am J Geriatr Psychiatry*. 2001;9(4):382–390.
58. de Vreede IM, Burger H, van Vliet IM. Prediction of response to ECT with routinely collected data in major depression. *J Affect Disord*. 2005;86(2–3):323–327.