Electroconvulsive Therapy in Medication-Nonresponsive Patients With Mixed Mania and Bipolar Depression

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Background: The aim of this study was to investigate the effectiveness of electroconvulsive therapy (ECT) in medication-nonresponsive patients with mixed mania and bipolar depression.

Method: Forty-one patients with mixed mania (DSM-IV diagnosis of bipolar I disorder, most recent episode mixed) and 23 patients with bipolar depression (DSM-IV diagnosis of bipolar I disorder, most recent episode depressed) consecutively assigned to ECT treatment were included in this study. Subjects were evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS), the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impressions-Severity of Illness scale (CGI-S). Assessments were carried out the day before starting ECT, 48 hours after completion of the third session (T_1), and a week after the last session of ECT (T_2).

Results: Both groups received an equal number of ECT sessions (mean ± SD = 7.2 ± 1.7 vs. 7.3 ± 1.6). In both groups, within-group comparisons showed that there was a significant reduction in CGI-S score (mixed mania, $p < .0001$ at T_1 and T_2; bipolar depression, $p < .01$ at T_1, $p < .0001$ at T_2), MADRS total score (both groups, $p < .0001$ at T_1 and T_2), BPRS total score (mixed mania, $p < .0001$ at T_1 and T_2; bipolar depression, $p < .001$ at T_1, $p < .0001$ at T_2), and BPRS activation factor score (mixed mania, $p < .0001$ at T_1 and T_2; bipolar depression, NS at T_1, $p < .01$ at T_2). Between-group comparisons revealed that patients with mixed mania showed significantly greater decrease in MADRS score ($p < .001$) and a greater proportion of responders (CGI-S) than patients with bipolar depression at endpoint (56% [N = 23] vs. 26% [N = 6], $p = .02$). Patients with mixed mania showed a greater reduction in suicidality, as measured by MADRS score, than patients with bipolar depression ($p < .02$).

Conclusion: In our study, ECT was associated with a substantial reduction in symptomatology, in both patients with mixed mania and those with bipolar depression. However, the mixed mania group exhibited a more rapid and marked response as well as a greater reduction in suicidal ideation. Response to ECT was not influenced by the presence of delusions.

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Mixed mania is a common presentation of bipolar disorder (30%–40% of the cases).[1] Compared with bipolar depression, mixed mania is characterized by longer[2,3] and more severe episodes,[4–6] higher frequency of psychotic features,[3] Axis I comorbidity,[7] greater risk of suicide,[8] and a poorer outcome.[2,4,5,9] The treatment of mixed mania is usually based on the clinician's personal experience rather than on consensus guidelines. Antidepressants can exacerbate this condition and, in some cases, increase its chronicity.[5] Lithium is effective in only 15% to 25% of the cases.[10] It has also been reported that valproate[11,12] and/or carbamazepine,[10,13] as well as gabapentin,[14] lamotrigine,[15] clozapine,[16] and olanzapine,[17] may be effective in mixed mania. However, these findings are derived from uncontrolled studies and were not designed to directly test the efficacy of these treatments for mixed mania.

Although electroconvulsive therapy (ECT) has been found to be effective in treating mania,[18] data on its efficacy treating mixed mania are limited. Small et al.,[19] investigating the efficacy of lithium and ECT in mania, found that ECT was more effective when manic and depressive symptoms occurred simultaneously. Tundo et al.[20] investigated the efficacy of ECT in patients with mixed mania and found that 19 of 26 patients had a good response, 3 subjects had a partial response, and 4 subjects had no response. More recently, Gruber et al.[21] found that 7 medication-refractory patients with mixed mania were responsive to ECT. Devanand et al.,[22] comparing the efficacy of ECT in depressed, manic, and mixed bipolar patients, showed robust response rates in all 3 groups. However, mixed patients needed a greater number of ECT sessions and a longer hospitalization. Although explicit definitions of *treatment resistant* were not always given, it is noteworthy that the majority of these studies report on patients who had a history of not responding to more tra-

ditional treatments for bipolar disorder. The aim of the present study was to evaluate the response to ECT in patients with well-characterized treatment-resistant mixed mania and bipolar depression.

METHOD

Forty-one subjects with mixed mania (DSM-IV diagnosis of bipolar I disorder, most recent episode mixed) and 23 with bipolar depression (DSM-IV diagnosis of bipolar I disorder, most recent episode depressed) consecutively referred for ECT at the Psychiatric Unit of the Department of Psychiatry, Neurobiology, Pharmacology, and Biotechnology of the University of Pisa (Pisa, Italy) were enrolled in this naturalistic study. The diagnoses were made by 2 senior psychiatrists (A.C., L.D.) according to DSM-IV criteria.[23] All patients were nonresponders to pharmacologic treatments. For patients with mixed mania, 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. Treatment nonresponse in patients with bipolar depression was defined as persisting depressive symptoms despite 2 trials of at least 8 weeks consisting of 1 trial with mood stabilizer(s) plus a tricyclic antidepressant (TCA) (200 mg/day of imipramine or the equivalent, or the maximum tolerable dose) and 1 trial with a selective serotonin reuptake inhibitor (SSRI) (40 mg/day of fluoxetine or the equivalent) combined with mood stabilizer(s) and a TCA. A senior psychiatrist (A.C.) determined, after reviewing patients' relevant history, which patients met these treatment nonresponder criteria. All subjects gave their written informed consent to receive ECT and to participate in this study.

The patients were evaluated the day before starting ECT treatment (T_0), 48 hours after completion of the third session of ECT (T_1), and a week after the last session of ECT (T_2) using the Montgomery-Asberg Depression Rating Scale (MADRS),[24] the Brief Psychiatric Rating Scale (BPRS),[25] and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[25] In the absence of a specific scale for mania, the change in manic symptoms was approximated using the BPRS activation factor, which is composed of the items tension, mannerism, and activation.[25] These scales were administered by a psychiatrist (M.C.C.) with substantial experience in the assessment and treatment of bipolar patients.

ECT was administered 2 times a week (usually Tuesdays and Fridays). Thiopentone (3–5 mg/kg body weight), succinylcholine (0.5–0.75 mg/kg body weight), and atropine sulfate (0.65 mg) were used intravenously for anesthesia. Brief-pulse, square-wave stimuli were delivered through bilateral electrode placement using a MECTA-SR2 (MECTA Corporation, Lake Oswego, Ore.) Parameters included a pulse width ranging from 1 to 2 ms (mean = 1.3 ms), frequency ranging from 40 to 90 Hz (mean = 70 Hz), duration ranging from 0.5 to 2.0 seconds (mean = 1.5 seconds), and current ranging from 0.55 to 0.80 A (mean = 0.70 A). During the ECT sessions, patients continued to take the medications they were assigned before starting the ECT. In the bipolar depression group, 40% were taking lithium; 100%, anticonvulsants; 75%, TCAs; 25%, SSRIs; and 15%, neuroleptics. In the mixed-mania group, 40% were taking lithium; 100%, anticonvulsants; 20%, TCAs; 80%, SSRIs; and 100%, neuroleptics.

The decisions of when to terminate ECT sessions were made by the treating clinicians blinded to the rating scale data. Global response to ECT was defined a priori as a rating of "mildly ill," "borderline ill," or "not at all ill" on the CGI-S administered a week after ECT termination. In addition, a more than 50% reduction in the total MADRS score was adopted as the response criterion for depression.

Statistical Analyses

Analysis of response was carried out initially with an analysis of variance for 2 groups and 3 timepoints applied to each observation to assess main effects for group and time. Outcome analyses within group were carried out using paired-sample t test. Differences of response between the 2 groups were analyzed using t test for independent samples. The chi-square test was used to analyze categorical variables. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 9.0 (SPSS, Inc., Chicago, Ill.).

RESULTS

In both groups, the same number of ECT sessions were administered (7.2 ± 1.7 vs. 7.3 ± 1.6). There were no differences between patients with mixed mania and bipolar depression on gender distribution (male, 63% [N = 26] vs. 61% [N = 14]) and mean age (38.0 ± 11.8 years vs. 40.5 ± 14.3 years). Both mood-congruent and mood-incongruent delusions were significantly more frequent in patients with mixed mania versus bipolar depression (68% [N = 28] vs. 22% [N = 5], $\chi^2 = 10.99$, df = 1, $p < .001$). Also, comparisons between the 2 groups at baseline (T_0) indicated that there were no significant differences on CGI-S score and MADRS total score, while BPRS total and factor activation scores were significantly higher in patients with mixed mania (Table 1). At baseline, the 2 groups did not differ on severity of suicidal thoughts, as measured by the MADRS (2.9 ± 1.8 vs. 3.3 ± 1.5, t = 0.91, df = 62, p = .36).

As shown in Table 1, within-group analyses revealed that CGI-S score, MADRS score, and BPRS total score showed a progressive and significant reduction in both mixed mania and bipolar depression patients from T_0 to T_1

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Table 1. CGI-S Score, MADRS Total Score, BPRS Total Score, and BPRS Activation Factor Score Before Starting ECT (T_0), After 3 Sessions (T_1), and After Last Session (T_2) in Patients With Mixed Mania (N = 41) and Bipolar Depression (N = 23)[a]

	Within-Group Comparisons						Mixed Mania vs. Bipolar Depression (df = 1,64)
	Mixed Mania (N = 41)			Bipolar Depression (N = 23)			
Measure	Mean	SD	t Value	Mean	SD	t Value	t Value
CGI-S score[b]							
T_0	5.7	0.7	NA	5.0	0.4	NA	…
T_1	4.9	0.7	7.6*** (T_1 vs T_0)	4.6	0.7	3.1* (T_1 vs T_0)	…
T_2	3.0	1.5	79.5*** (T_2 vs T_0)	3.9	0.8	5.8*** (T_2 vs T_0)	…
MADRS total score[c]							
T_0	33.6	10.7	NA	34.7	5.3	NA	–0.05
T_1	26.3	9.8	10.9*** (T_1 vs T_0)	28.5	6.1	7.3*** (T_1 vs T_0)	–0.1
T_2	9.7	7.9	11.5*** (T_2 vs T_0)	15.1	8.0	11.3*** (T_2 vs T_0)	2.6**
BPRS total score[d]							
T_0	48.3	14.4	NA	32.5	9.7	NA	4.7**
T_1	37.2	14.7	9.2*** (T_1 vs T_0)	29.0	10.4	3.9** (T_1 vs T_0)	2.4*
T_2	23.9	18.4	11.4*** (T_2 vs T_0)	22.2	9.2	6.9*** (T_2 vs T_0)	0.4
BPRS activation score[e]							
T_0	8.5	2.6	NA	4.0	2.0	NA	7.2**
T_1	6.2	2.6	8.6*** (T_1 vs T_0)	3.6	1.6	1.6 (T_1 vs T_0)	4.4**
T_2	4.1	3.0	11.1*** (T_2 vs T_0)	2.6	1.8	3.6* (T_2 vs T_0)	2.2*

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ECT = electroconvulsive therapy, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable. Symbol: … = analysis not performed because main effect of diagnosis was not significant.
[b]Main effect of group: F = 0.17, p = .68; main effect of diagnosis: F = 61.5, p = .001.
[c]Main effect of group: F = 5.01, p = .026; main effect of diagnosis: F = 98.3, p = .0001.
[d]Main effect of group: F = 16.2, p = .0001; main effect of diagnosis: F = 22.3, p = .0001.
[e]Main effect of group: F = 61.4, p = .0001; main effect of diagnosis: F = 19.9, p = .0001.
*p < .01. **p < .001. ***p < .0001.

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and from T_0 to T_2. Furthermore, the scores on the BPRS activation factor showed a significant reduction from T_0 to T_1 and from T_0 to T_2 in the mixed mania group and from T_0 to T_2 in the bipolar depression group.

After 3 sessions (T_1), there were no significant differences between the 2 groups on the total MADRS score, whereas total BPRS and BPRS activation scores remained significantly higher in patients with mixed mania. At the end of the course of ECT (T_2), mixed mania patients had significantly lower scores on the MADRS, as compared with the bipolar depression patients. Group differences in baseline and T_1 total BPRS score disappeared at T_2; however, the activation factor score remained significantly higher in the group with mixed mania.

The proportion of responders at endpoint, defined using the CGI-S as described above, was greater in the mixed mania group than in the bipolar depression group (56% [N = 23] vs. 26% [N = 6], $\chi^2 = 5.35$, df = 1, p = .02). Response rate for depression, defined using the MADRS, was 78% (N = 32) for the mixed mania group and 52% (N = 12) for the bipolar depression group ($\chi^2 = 4.60$, df = 1, p < .05) at the end of treatment. MADRS response rate among patients with and without delusions was 36% (12/33) and 55% (17/31), respectively ($\chi^2 = 2.20$, df = 1, p = .21).

At baseline, there were no significant differences between the 2 groups in suicidality, as assessed by the MADRS. At the 2 subsequent assessments, patients with mixed mania showed a significantly greater reduction in suicidality compared with the bipolar depression group (T_1: 1.9 ± 1.4 vs. 3.0 ± 1.4, t = 3.19, df = 62, p = .002; T_2: 0.5 ± 0.9 vs. 1.9 ± 1.4, t = 2.42, p = .02).

DISCUSSION

Consistent with previous reports,[20–22] our results indicate that ECT is associated with improvement in symptoms in treatment-resistant patients with mixed mania or bipolar depression. Patients with mixed mania exhibited a greater reduction in depressive symptomatology, symptoms from the BPRS activation factor, and overall psychopathology than did patients with bipolar depression.

Although the main effect for group found with the CGI-S was small, it is noteworthy that the proportion of responders, as measured by the CGI-S, was greater in mixed mania (56%) than in bipolar depression patients (26%). In this study, the percentage of response in patients with bipolar depression was lower than that reported in the literature (around 50%).[26,27] This discrepancy may be due to our use of more stringent response criteria than have been used in previous studies. In fact, when we adopted a response criterion requiring a 50% reduction of baseline total MADRS score (as in de Montigny et al.[28]), response rates reached 78% for patients with mixed mania and 52% for patients with bipolar depression. A second possible explanation is that bipolar depression is less responsive to ECT than major depressive disorder. In light of this hypothesis, it is noteworthy

that most previous ECT studies have been conducted on subjects with major depressive disorder. Future studies should systematically explore this issue.

The presence of delusions has been reported to be a predictor of a favorable response to ECT.[29] Among our patients, those with delusions did not respond to ECT better than those without, suggesting that treatment response was not simply a reflection of a reduction in delusions. However, it is also possible that our study did not have enough statistical power to detect such a difference.

Although ECT was found to be effective in reducing suicidality in both mixed mania and bipolar depression patients, this reduction was greater and more rapid among mixed mania patients. These findings are consistent with Prudic and Sackeim's[30] conclusion that ECT exerts specific beneficial effects on suicidality. Further studies are needed to confirm whether this hypothesis is especially true for patients with mixed mania.

A major limitation of this study is that manic symptoms were not measured by means of a specific rating scale. In addition, we did not collect information about the number of other patients with mixed mania who were admitted to the psychiatric unit during the same time period and were treated differently because of ECT refusal and/or coexisting medical problems, thus limiting the generalizability of our results.

In conclusion, we found that ECT was associated with a substantial reduction in symptomatology both in patients with mixed mania and bipolar depression, with the mixed mania group exhibiting a more marked reduction in depressive symptomatology and a greater and more rapid reduction of suicidal ideation. These results add to the growing body of literature suggesting that ECT is an effective treatment for patients with mixed mania.

Drug names: atropine sulfate (Donnatal and others), carbamazepine (Tegretol and others), clozapine (Clozaril and others), fluoxetine (Prozac), gabapentin (Neurontin), lamotrigine (Lamictal), olanzapine (Zyprexa), succinylcholine (Anectine and others).

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