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Treatment of Bipolar I Rapid Cycling Patients During Dysphoric Mania with Olanzapine

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The simultaneous presentation of manic and depressive symptoms in the same patient is fairly common. The terms *dysphoric, mixed,* and *depressive mania* have been used as equivalents to mixed states. Pharmacotherapy is less effective in this group of patients. The aim of this study is to determine the effectiveness and safety of olanzapine as an add-on therapy in patients with bipolar disorder with a rapid cycling course during a dysphoric mania episode.

Thirteen patients treated with mood stabilizers for at least 1 year and diagnosed with a mixed episode were included in an open trial. All had at least 4 episodes in the last year. Patients with organic diseases, including altered thyroid function, were excluded from the research. Patients were evaluated at inclusion and at day 28. Response was defined as a decrease of 50% in the Young Mania Rating Scale and the Hamilton Rating Scale for Depression concomitant with a Clinical Global Impression improvement of 1 or 2.

All patients completed the study. The doses of olanzapine were 16.15 ± 5.82 mg/day. There was a reduction in the manic and depressive symptoms in all patients. Ten of the 13 patients were considered to have responded to the treatment according to the response definition. Adverse effects included somnolence (23.08%) and weight gain (0.81 ± 1.96 kg in women, 2.20 ± 2.28 kg in men).

Our results suggest that olanzapine combined with mood stabilizers is safe and effective in the treatment of the manic and the depressive symptoms of dysphoric mania with a rapid cycling course. (J Clin Psychopharmacol 2002;22:450–454)

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The simultaneous presentation of depressive and manic symptoms in the same patient is fairly common. The terms *dysphoric*, *mixed*, and *depressive mania* have been used as equivalents to mixed states.[1] At least 30% to 40% of all manic states are probably dysphoric.[1–5] Pharmacotherapy in general may be less effective for patients in mixed states.[2, 6] These patients respond better to treatment combinations of lithium, valproate, and carbamazepine or to electroconvulsive therapy.[7] Although rapid cycling more often arises from a bipolar II rather than a bipolar I base,[8] mixed states are overrepresented in some studies of rapid cycling patients when bipolar I individuals are included.[9, 10]

Antidepressants have been shown to exacerbate rapid cycling in some patients[5, 11] and to worsen the course of mixed patients.[2] Atypical antipsychotics can be useful in rapid cycling patients and in mixed states. Clozapine has been shown to improve the course of rapid cycling patients.[12] Also, in a recent study, Vieta and colleagues[9] found that in a series of rapid cycling bipolar I and II patients in which five had mixed features, four of the five experienced a decrease in the number of episodes after risperidone was added to the previous treatment.[9]

Recent reports indicate that olanzapine is at least as effective as lithium[13] and superior to placebo[14, 15] in the treatment of the acute mania in both pure and mixed patients. Although mixed patients have worse outcome than pure manic patients, presenting more relapses and incomplete remissions,[2] there are no trials specifically designed to study bipolar mixed patients with a rapid cycling course.

Olanzapine is an atypical antipsychotic with demonstrated efficacy in mixed bipolar patients in a placebo-controlled trial.[15] Therefore, we evaluated the use of olanzapine in bipolar mixed patients with a rapid cycling course. We present here an open trial on the efficacy and safety of olanzapine adjunctive therapy in bipolar patients with a rapid cycling course during a mixed episode.

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Methods

We included inpatients treated in the first episode psychosis and bipolar disorder program of the department of psychiatry of a general hospital from November 1999 to October 2000. The included diagnosis was bipolar disorder with a rapid cycling course, defined as having at least 4 affective episodes in the last year. Inclusion criteria were treatment with mood stabilizers for at least 1 year and a mixed index episode diagnosed by the Cincinatti criteria extracted from DSM-IV,[2] following the recommendations of Akiskal and associates[4] and Goldberg.[16] Two depressive symptoms of DSM IV were used for the diagnosis according to these criteria. Patients were diagnosed using the Structured Clinical Interview With Psychotic Screens for DSM-IV. They were also evaluated with the 21-item Hamilton Depression Rating Scale (HAM-D), the Young Mania Rating Scale (YMRS), and the Clinical Global Impression (CGI) scale at baseline and at day 28. A significant medical condition, including altered thyroid function, was an exclusion criterion. Patients that were treated with antidepressants within 2 months before entering the study were also excluded. All patients were taking typical antipsychotic drugs, which were withdrawn the day before entering the study. Results of thyroid function tests had to be within normal ranges. After study entry, mood stabilizer dose was not modified. Olanzapine was administered in doses between 10 and 30 mg/day. Written informed consent was given by all included patients.

Response was defined as a decrease on the YMRS and HAM-D score of more than 50% from baseline to day 28 with a CGI improvement score of 1 (very much improved) or 2 (much improved). Concomitant adverse events were recorded. The weight of the patients were recorded at inclusion and at day 28.

Statistical analysis was performed using the SPSS statistical package (Chicago, IL). The two-tailed paired *t*-test was used to compare manic and depressive symptoms at admission and on day 28. Statistical significance levels were set at $p \leq 0.05$.

Results

During the course of the study, 14 patients (nine women and five men) reached the inclusion criteria. Thirteen (eight women and five men) agreed to participate in the study. Their mean age was 39.15 ± 10.15 years. All patients completed the 4 weeks of the study. As shown in Table 1, most of the patients were treated previously with valproate (N = 9) alone or in combination with other mood stabilizers.

Olanzapine was administered in the previously indicated doses. The average dose was 16.15 ± 5.82 mg/day. Adverse effects included somnolence (N = 3, 23.08%) and weight gain (0.81 ± 1.96 kg in women, 2.86 ± 2.20 in men).

In relation to the severity of illness at baseline, the mean Young Mania Scale score was 29.61 ± 8.17 and the mean Hamilton Depression Scale score was 21.15 ± 5.56 before treatment. Table 2 summarizes the results of the treatment efficacy assessments. There was a reduction in the scores of these scales in all patients included in the study. The mean YMRS was 3.15 ± 2.96 and the HAM-D was 4.765 ± 3.83 at day 28. There were significant differences in the euphoric symptoms measured by YMRS at admission and at day 28 ($t = 10.126$, $p < 0.001$) (Fig. 1) and in the depressive symptoms measured by HAM-D between baseline and endpoint ($t = 15.738$, $p < 0.001$) (Fig. 2). Considering the *a priori* definition of response as a decrease of 50% in YMRS and HAM-D along with a CGI improvement subscale of 1 or 2, 10 of the 13 patients (76.9%) were considered to have responded to the treatment (Table 2).

TABLE 1. Treatments and adverse events*

Patient	Concomittant medication	Dose of olanzapine, mg	Weight change, kg	Blood levels (Vp and CBZ, μg/mL; Li, mEq/L)
1	Valproate	15	0.0	Vp, 70
2	Valproate	20	0.0	Vp, 84
3	Valproate	15	2.0	Vp, 78
4	Valproate	10	4.0	Vp, 94
5	Valproate and lithium	10	2.0	Vp, 70; Li, 0.8
6	Valproate and lithium	20	0.0	Vp, 85; Li, 1.1
7	Valproate	10	4.0	Vp, 90
8	Valproate and lithium	20	5.0	Vp, 85; Li, 1.0
9	Lithium and carbamazepine	10	−2.0	Li, 1.0; CBZ, 10
10	Valproate	30	2.5	Vp, 75
11	Valproate	15	0.0	Vp, 90
12	Valproate	20	1.0	Vp, 75
13	Valproate	15	−1.0	Vp, 75

*CBZ, carbamazepine; Li, lithium salts; Vp, valproate

TABLE 2. Characteristics of sample*

Patient	Gender	Age, yr	YMRS admission	YMRS day 28	HAM-D admission	HAM-D day 28	CGI improvement, day 28
1	Male	37	28	3	14	0	2
2	Female	57	44	0	17	2	1
3	Male	52	41	5	14	3	2
4	Female	42	28	3	28	10	3
5	Female	33	33	5	22	8	2
6	Female	35	25	4	23	10	3
7	Male	42	22	3	13	2	2
8	Male	26	18	11	23	6	3
9	Female	46	39	4	25	3	1
10	Female	31	31	0	19	0	1
11	Male	25	21	0	25	8	2
12	Female	32	22	2	31	9	2
13	Female	51	33	1	21	1	1

*CGI, Clinical Global Impression; HAM-D, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

Discussion

Our study of mixed bipolar patients with a rapid cycling course showed a significant reduction in manic and depressive symptoms after open-label treatment with olanzapine added to mood stabilizers. In fact, all patients improved in manic and depressive symptoms. Ten had sufficient improvement to be considered treatment responders. Of note, studies have suggested that mixed bipolar patients with a rapid cycling course are especially prone to maintain depressive symptoms when treated with antipsychotics, as these compounds tend to increase the duration of depressive symptoms in bipolar patients.[17] Additionally, the course of illness becomes worse when antidepressants are used; therefore, antidepressants may increase the number of cycles in rapid cycling patients and increase the severity of mixed bipolar patients.[5] The present study was designed to assess worsening of depressive and manic symptoms with the YMRS, the HAM-D, and the CGI. The majority of double-blind clinical trials of mania measure improvements in YMRS as the principal assessment of efficacy, and the decrease of CGI and HAM-D are secondary objectives in those clinical trials. The combination of decrease of HAM-D, decrease of YMRS, and CGI improvement subscale of 2 or less provides a more comprehensive impression of the efficacy of the compound studied.

Our findings suggest that olanzapine added to mood stabilizers is effective in the treatment of mixed mania in patients with a rapid cycling course. Although there are no previous reports of treatment of dysphoric mania with a rapid cycling course, other studies support the efficacy of olanzapine in mixed mania. Tohen and associates[15] reported that mixed patients treated with olanzapine improved significantly more than those treated with placebo in manic symptoms. They also reported that manic patients with higher HAM-D scores treated with olanzapine improved more than patients treated with placebo. There are also four previous reports in the literature of olanzapine effectiveness in mixed episodes.[1, 18–20]

In the present study, no clinically significant adverse effects were observed, and there were no dropouts due to adverse events. However, seven patients gained weight during the trial. Olanzapine has been reported to increase

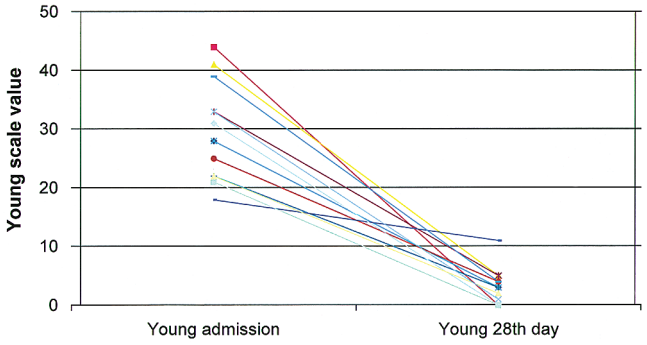

FIG. 1. Euphoric symptoms measured by Young Mania Rating Scale at admission and at day 28. (A) Young Mania Rating Scale. (B) Time in days.

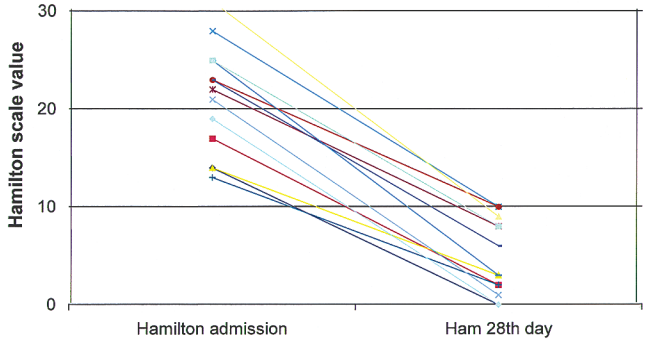

FIG. 2. Depressive symptoms measured by Hamilton Depression Rating Scale between baseline and endpoint. (A) Hamilton Depression Rating Scale. (B) Time in days.

weight.[15] Mood stabilizers such as valproate and lithium have also been associated with weight gain. Altered appetite and weight gain are also possible symptoms of mixed mania.[2]

Mixed mania is probably not only a juxtaposition of manic and depressive symptoms but also a more severe form of bipolar disorder. Mixed patients are more frequently women, have more episodes than those with pure mania, tend to have a chronic course more frequently, and have more risk of suicide.[2] Typical antipsychotics have been reported to reduce manic phases but increase the number and duration of depressive phases in bipolar patients treated with antipsychotics.[17] In fact, classical antipsychotics often complicate the diagnostic process in mixed states; when prescribed to reduce hyperactivity, they could produce affective blunting, leading to misdiagnosis with schizophrenia.[4] The antieuphoric action of antipsychotics may be related to the effect upon D_2 receptors.[21] If this is the case, then the effect observed with olanzapine may be the result of a similar mechanism, because olanzapine is able to block the D_2 receptors.[22] By contrast, olanzapine has also showed an antidepressant-like effect. In this regard, olanzapine appears to have some pharmacological actions that may help explain its antidepressant effects. Olanzapine binds to 5-HT_{2A} receptors.[22] Chronic treatment with olanzapine decreases 5-HT_{2A} receptors in the frontal cortex[23] without significant alterations in D_2 receptors. The effect of olanzapine on 5-HT_{2A} receptors is a property shared with most antidepressants. In fact, treatment with antidepressants is invariably accompanied by the down-regulation of the 5-HT_{2A} receptors.[24] However, in the case of lithium, there are studies that have reported down-regulation,[25] up-regulation,[26] and no change,[27, 28] depending on the drug regimen and the biochemical ligand used. Thus, the effects of lithium on 5-HT_{2A} receptor appear to be complex. In contrast, it has recently been demonstrated that olanzapine and clozapine facilitate noradrenergic transmission in the frontal cortex, meditated by β-adrenergic receptors.[29] This biochemical action may be accompanied by an antidepressive effect.[30]

Conclusions

Although the exact mechanism of action is unclear, atypical antipsychotic drugs, olanzapine in particular, may have not only antipsychotic effects but also thymoleptic effects on rapidly cycling bipolar patients[31, 32] and also in mixed states.

To our knowledge this is the first study of olanzapine treatment in dysphoric mania with a rapid cycling course. Our preliminary observations have some methodological limitations. The main limitation is the open nature of the treatment; therefore, we cannot rule out the possibility that nonspecific, placebo-like effects might have accounted for the changes in manic and depressive symptom severity observed in our patients. These findings need to be replicated in controlled trials. Our findings suggest that olanzapine appears to be effective as an add-on treatment in the manic and depressive symptoms of mixed mania with a rapid cycling course.

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