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Research report

Olanzapine in treatment-resistant bipolar disorder

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Abstract

Background: We evaluated the response to olanzapine in 14 consecutive patients with bipolar I disorder who were inadequately responsive to standard psychotropic agents. *Methods:* Fourteen patients with bipolar I disorder by DSM-IV criteria experiencing persistent affective symptoms inadequately responsive to at least one standard mood stabilizer were treated with open-label olanzapine by one of the authors. Response was assessed with the Clinical Global Impression Scale modified for use in bipolar disorder (CGI-BP). *Results:* The 14 patients received olanzapine at a mean (SD dosage of 14.1±7.2 (range 5–30) mg/day for a mean±SD of 101.4 + 56.3 (range 30–217) days of treatment. Of the 14 patients, 8 (57%) displayed much or very much overall improvement in their illness. In general, olanzapine was well tolerated. The most common side effects were sedation, tremor, dry mouth, and appetite stimulation with weight gain. *Limitations:* Data were obtained nonblindly and without a randomized control group, and olanzapine was added to ongoing psychotropic regimens. *Conclusion:* Olanzapine may have antimanic and mood-stabilizing effects in some patients with bipolar disorder, and is generally well tolerated. Controlled studies of olanzapine in bipolar disorder appear warranted.

Keywords: Olanzapine; Bipolar disorder

1. Introduction

Substantial clinical data suggest that the atypical antipsychotic clozapine may be effective in the acute and prophylactic treatment of some patients with bipolar disorder, including some patients inade-

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quately responsive to treatment with mood stabilizers, electroconvulsive therapy, and conventional antipsychotics (Calabrese et al., 1996; Frye et al., in press; Suppes et al., 1996; Zarate et al., 1995). The new atypical antipsychotic olanzapine has a pharmacologic and electrophysiologic profile similar to that of clozapine (Frye et al., in press; Keck and McElroy, 1996). Moreover, clinical studies suggest that olanzapine may have mood-stabilizing properties in patients with schizoaffective disorder, bipolar type (Tohen et al., 1997). However, experience with olanzapine in patients with bipolar disorder is limited, and the possible utility of an atypical antipsychotic agent in this illness would be of considerable importance in light of the high risk of tardive dyskinesia in bipolar patients.

To investigate the efficacy, tolerability, and safety of olanzapine in bipolar disorder, we reviewed the response of patients with bipolar disorder who received treatment with olanzapine at our centers for persistent affective symptoms inadequately responsive to standard psychotropic agents.

2. Methods

Patients with bipolar I disorder by DSM-IV (American Psychiatric Association, 1994) criteria who were participating in the Stanley Foundation Bipolar Network naturalistic follow-up study (Post, 1997) and who received treatment with olanzapine for at least 1 week were included in the study. Patients were excluded if olanzapine was begun when they were euthymic or within 2 weeks before or after any other major changes in their medication regimens. All patients provided verbal informed consent to receive a clinical trial of olanzapine. Response to olanzapine was rated with the Clinical Global Impression Scale (Guy, 1976) modified for bipolar disorder (CGI-BP) (Spearing et al., in press) at two points in time: response of affective state at time of olanzapine initiation was assessed after 1 month of treatment with olanzapine; and overall response of illness was assessed at the patient's last evaluation while receiving olanzapine. All raters were standardized in their use of the CGI-BP (Spearing et al., in press). Side effects to olanzapine were assessed by clinical evaluation.

3. Results

Fourteen consecutive patients with bipolar I disorder treated with olanzapine and meeting the inclusion criteria were identified. Eight (57%) patients were evaluated prospectively and six (43%) were evaluated retrospectively. All 14 patients displayed persistent affective symptoms that had not responded to standard psychotropic agents and which impaired their functioning at the time of olanzapine administration. Specifically, 12 (86%) patients were manic, hypomanic, or mixed, and 2 (14%) were depressed. Eight (57%) patients also displayed psychotic features, and 12 (86%) met the DSM-IV criteria for rapid cycling. One patient had received prior treatment with one mood stabilizer, two patients with two mood stabilizers, and 11 patients with three mood stabilizers. Thirteen patients had received prior treatment with an antipsychotic other than olanzapine. Of note, olanzapine was added to pre-existing psychotropic regimens in all but one patient. These medications were lithium ($N = 4$); valplroate ($N = 12$); carbamazepine ($N = 2$); gabapentin ($N = 3$); antidepressants (including one patient on tranylcypramine) ($N = 3$); trifluoperazine ($N = 1$); clozapine ($N = 1$), thyroid medication ($N = 8$); and benzodiazepines ($N = 3$).

Olanzapine was begun in all patients at 5–10 mg/day, usually given all at one dose at night. Olanzapine doses were subsequently increased by 5–10 mg/day every 7–14 days according to patient response and side effects to a maximum dose of 30 mg/day.

At their last evaluation, the 14 patients had received a mean±S.D. (range) dose of olanzapine of 14.1±7.2 (5–30) mg/day for a mean±S.D. (range) duration of 101.4±56.3 (30–217) days. As shown in Table 1, of these 14 patients, 9 (64%) were rated as much ($N = 6$) or very much ($N = 3$) improved after 1 month of treatment with a mean±S.D. (range) olanzapine dose of 13.6±6.0 (5–20) mg/day. At their last evaluation, 8 (57%) of the 14 patients were rated as much ($N = 6$) or very much ($N = 2$) improved, after a mean±S.D. (range) of 117.4±46.8 (57–217) days of treatment with a mean±S.D. (range) olanzapine dose of 15.2±6.7 (7.5–30) mg/day.

Of the 12 patients who received olanzapine initiated for manic, hypomanic, or mixed symptoms,

Table 1
Response to olanzapine in 14 patients with treatment-refractory bipolar disorder[a]

Affective state[b]	Patients N	Response, N (%)					
		Much or very much improved		Minimal or no change		Much or very much worsened	
		One month	Last eval	One month	Last eval	One month	Last eval
Manic, hypomanic, or mixed	12	8 (67)	7 (58)	4 (33)	3 (25)	0	2 (17)[c]
Depressed	2	1 (50)	1 (50)	1 (50)	0	0	1 (50)[d]
Total	14	9 (64)	8 (57)[f]	5 (36)	3 (21)[f]	0	3 (21)[f]

[a]Eight patients had psychotic features and 12 patients were rapid cyclers.
[b]At time of initial olanzapine administration.
[c]Both patients worsened by becoming persistently depressed.
[d]This patient, who initially displayed a very much improved response at 1 month, committed suicide 38 days later; however, he had not made follow-up appointments and it was unknown whether or not he had been taking olanzapine at the time of his suicide.
[e]The mean±SD (range) olanzapine dose and duration of treatment in these eight patients were 15.9±6.8 (7.5–30) mg/day and 136.0±18 (57–217) days, respectively.
[f]The mean±SD (range) olanzapine dose and duration of treatment in the five patients rated with minimal or no change ($N = 3$) or much or very much worsened ($N = 2$) were 11.7±6.2 (5–25) mg/day and 72.4±65.5 (30–188) days, respectively.

8 (67%) displayed much or very much improvement in these symptoms after 1 month of treatment with a mean±S.D. (range) olanzapine dose of 11.9±6.5 (5–20) mg/day, whereas 4 (33%) showed a minimal or no change with a mean±S.D. (range) dose of 11.3±6.3 (5–20) mg/day. At their last evaluation, 7 (57%) of these 12 patients showed much or very much improvement in their overall illness after a mean±S.D. (range) of 110.3±28.2 (57–150) days of treatment with a mean±S.D. (range) olanzapine dose of 16.1±7.3 (7.5–30) mg/day; 3 (25%) showed minimal or no change after a mean±S.D. (range) of 96.7±79.8 (40–188) days of treatment with a mean±S.D. (range) dose of 13.3±10.4 (range 5–25) mg/day; and 2 (17%) were much or very much worsened (both due to development of depressive symptoms) after a mean±S.D. of 36.0±8.4 (range 30–42) days of treatment with a mean±S.D. (range) dose of 10.0±7.1 (range 5–15) mg/day. Of note, the presence of psychotic symptoms was not associated with response to olanzapine in these 12 patients: 3 (50%) and 3 (50%) of the 6 patients with psychotic features were rated as much or very much improved after 1 month and at their last evaluation, respectively, compared with 5 (83%) and 4 (67%) of the 6 patients without psychotic features, respectively.

Of the two patients who received olanzapine while acutely depressed (both of whom had psychotic features), one displayed very much improvement in depressive and psychotic symptoms after 1 month of treatment on 10 mg/day. However, this patient did not make follow up appointments, and committed suicide 38 days later. It is unknown whether or not he was taking olanzapine at the time of his suicide. By contrast, the other patient went on to display very much improvement in her depressive and psychotic symptoms and in her overall illness on 15 mg/day of olanzapine, which she had maintained after a total of 217 days of treatment and which permitted discontinuation of valproate. Of note, concomitant mood stabilizers or antipsychotics were reduced in dose or discontinued in two other responders.

Olanzapine was generally well tolerated. One patient, however, discontinued the drug due to bad dreams. Reported side effects in descending order of frequency were: sedation ($N = 5$), tremor ($N = 2$), dry mouth ($N = 2$), increased hunger/weight gain ($N = 2$), restlessness ($N = 1$), swollen hands ($N = 1$), nausea ($N = 1$), headache ($N = 1$), and bad dreams ($N = 1$). Of note, no patients developed extrapyramidal symptoms or required concomitant anti-parkinsonian agents.

4. Discussion

Of 14 patients with treatment-resistant bipolar I disorder who received open-label treatment with

olanzapine for a mean of 101.4 days, 8 (57%) were rated as displaying much or very much improvement in their overall illness. Twelve of these patients met the DSM-IV criteria for rapid cycling. Also, although numbers are too small for valid comparisons, patients with manic symptoms without psychotic features responded as frequently to olanzapine as those with psychotic features. These findings suggest that olanzapine, like clozapine, may have antimanic and mood-stabilizing properties in some patients with bipolar disorder.

These preliminary observations are limited by several methodologic shortcomings. Most importantly, data were obtained nonblindly and without a randomized control group. Thus, the possibility that the observed favorable response to olanzapine was in fact due to placebo response, rater or patient bias, or spontaneous remission cannot be excluded. Second, in all but one patient, olanzapine was added to ongoing psychotropic regimens. It is therefore uncertain whether the observed mood-stabilizing response after olanzapine addition was due to olanzapine alone, a late response to concurrently administered mood stabilizers, or a synergistic response to olanzapine and concurrently administered psychotropics. Third, although clinical evaluations did not reveal any extrapyramidal side effects, formal rating scales for these signs and symptoms were not routinely used. Thus, it is possible that extrapyramidal side effects occurred that were undetected or misdiagnosed. These findings must therefore be regarded as highly provisional, pending outcome of controlled trials.

However, even when these limitations are considered, the response observed in 8 (57%) of 14 patients with treatment-refractory bipolar disorder, 12 of whom met the DSM-IV criteria for rapid cycling and all of whom were followed up for an average of 3 months, is promising. Further studies of olanzapine in bipolar disorder therefore appear warranted. These should include double-blind, placebo controlled studies of olanzapine monotherapy and add on therapy in the acute and prophylactic treatment of mania and depression, as well as controlled trials comparing the efficacy and side effect profile of olanzapine with standard mood stabilizers and typical antipsychotics. If proven to have antimanic or mood-stabilizing properties in controlled trials, olanzapine's benign pharmacokinetic and side-effect profile relative to typical antipsychotics and lack of need for regular blood monitoring relative to the atypical antipsychotic clozapine would make it an extremely useful addition to the therapeutic armamentarium for bipolar disorder.

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