Long-Term Olanzapine Therapy in the Treatment of Bipolar I Disorder: An Open-Label Continuation Phase Study

Todd M. Sanger, Ph.D.; Starr L. Grundy, B.Sc.Pharm.; P. Joseph Gibson, Ph.D.; Madhav A. Namjoshi, Ph.D.; Michael G. Greaney, M.S.; and Mauricio F. Tohen, M.D., Dr.P.H.

Background: Olanzapine has demonstrated efficacy in the treatment of acute mania in 2 double-blind, placebo-controlled trials. We describe the results of the open-label extension from one of these trials.

Method: In a 3-week, double-blind study of patients with DSM-IV bipolar I disorder, olanzapine was superior to placebo for the treatment of acute manic symptoms. Of the 139 patients who entered the double-blind phase of the 3-week study, 113 patients continued into the 49-week open-label extension. Efficacy measurements including the Young Mania Rating Scale (YMRS), the 21-item Hamilton Rating Scale for Depression (HAM-D-21), the Clinical Global Impressions scale-Bipolar Version, and the Positive and Negative Syndrome Scale and safety measurements including the Simpson-Angus scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale were completed throughout. The analysis considered all treatment results, starting with the first olanzapine dose. Adjunctive lithium and fluoxetine were allowed during the open-label extension.

Results: The mean length of olanzapine treatment was 6.6 months, with a mean modal dose of 13.9 mg/day. A significant mean improvement in the YMRS total score, baseline to endpoint (–18.01, $p < .001$), was observed. During treatment, 88.3% of patients experienced a remission of manic symptoms (YMRS total score ≤ 12), and only 25.5% subsequently relapsed (YMRS total score ≥ 15). Significant improvement in HAM-D-21 scores was observed ($p < .001$). Forty-one percent of patients were maintained on olanzapine monotherapy. The most common treatment-emergent adverse events reported were somnolence (46.0%), depression (38.9%), and weight gain (36.3%).

Conclusion: During up to 1 year of olanzapine therapy, either as monotherapy or in combination with lithium and/or fluoxetine, patients with bipolar disorder demonstrated significant improvement in mania and depression symptoms with a favorable safety profile. Further double-blind, controlled studies are needed to confirm these results.

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Reprint requests to: Todd M. Sanger, Ph.D., Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285.

Bipolar I disorder affects between 0.4% and 1.6% of the U.S. population.[1] It is a multiphasic, cyclic disorder characterized by periods of extreme euphoria and/or dysphoria followed by intermittent periods of mood stability. Often patients experience subsyndromal symptoms between mood episodes. The disorder also carries a high risk of relapse. Within 1 year of recovery from a mood episode, half of all patients will suffer a second episode.[2] At least 80% of patients who have an initial episode of mania will have one or more subsequent manic episodes. Unfortunately, these recurring episodes have been shown to have a cumulative deteriorative effect on patient functioning and recovery.[3] Over time, patients frequently experience disruption in employment and interpersonal relationships and have difficulty maintaining or sustaining social support. Repeated hospitalizations are common, and health care utilization costs are high, creating a significant drain on societal resources.

Unfortunately, current pharmacotherapy is less than optimal for many bipolar patients, and the need is great for therapies that are not only safe and effective during acute episodes but also demonstrate safe, prophylactic efficacy. Despite the existence of very few long-term clinical trials, current pharmacotherapy for the prophylaxis treatment of bipolar disorder includes lithium, valproate, carbamazepine, and antipsychotics. Research has shown that lithium maintenance therapy helps stabilize mood and reduces the frequency and severity of manic and depressive episodes in bipolar patients.[3] However, open, naturalistic reports over the past decade suggest more modest benefits of lithium than those observed in earlier controlled but possibly flawed studies.[4] A substantial number of patients with bipolar disorder fail to respond to

lithium prophylaxis, including those with a high frequency of prior episodes, mixed mania, comorbid personality disturbance, and rapid cycling.[2] Moreover, noncompliance associated with adverse effects (nausea, thirst, polyuria, hand tremors, problems with memory, weight gain) is common.[5] Between 50% and 60% of patients do not remain well on lithium monotherapy.[6] Anticonvulsants, such as carbamazepine and valproate, are frequently prescribed instead of lithium, especially for patients who have atypical clinical features or a rapid-cycling course and patients who are intolerant or unresponsive to lithium therapy. Unfortunately, carbamazepine has complicated pharmacokinetics and a potential for significant drug interactions, thus requiring considerable clinical attention in its application. Furthermore, significant proportions of patients fail to tolerate or respond adequately to carbamazepine. Limited evidence of the long-term prophylactic efficacy of carbamazepine, its poor patient acceptability, and its rare, although serious, hematologic side effects detract from the routine prophylactic use of this agent. Efficacy of valproate has been postulated based on open-label, longer-term clinical trials.[7,8] A recently completed randomized, double-blind, placebo-controlled 12-month trial revealed that valproate did not differ from placebo on the a priori primary outcome measure (time to recurrence of any mood episode during maintenance therapy).[9] However, in this same trial, valproate was superior to placebo on several secondary measures.[9] Common adverse effects of valproate include sedation, headache, ataxia, gastrointestinal disturbance, weight gain, and total alopecia.[10] Valproate appears to have a lower risk of blood dyscrasia than carbamazepine but can reduce platelet number and function, and it has been recommended that blood counts be monitored during treatment.[5]

Prior to the introduction and widespread use of lithium and anticonvulsants, antipsychotic agents were used to treat acute mania. The long-term efficacy of antipsychotics in bipolar disorder remains to be demonstrated in clinical trials. However, many patients with bipolar disorder are given typical antipsychotics concomitantly when their response to lithium or anticonvulsants alone proves inadequate.[11–14] Unfortunately, numerous adverse events have been associated with the use of typical antipsychotics (sedation, tremor, and memory problems), which may add to the burden of illness and influence compliance with treatment.[15] Moreover, patients with bipolar disorder, compared with patients with schizophrenia, appear to be at a greater risk for development of tardive dyskinesia and extrapyramidal symptoms (EPS).[16,17] The depressogenic effect of typical antipsychotic agents further complicates their use in management of mood disorders.[18]

Clozapine, an atypical antipsychotic, has shown efficacy in the treatment of bipolar and schizoaffective disorders.[19,20] However, clozapine has been associated with agranulocytosis in 0.8% of patients and thus requires weekly blood monitoring, which limits its routine use in clinical practice, particularly in long-term therapy. The use of risperidone as an "add-on" treatment to mood-stabilizing agents has been studied in a 3-week, double-blind, placebo-controlled trial.[21] Mood stabilizer (lithium or valproate) plus risperidone, haloperidol, or placebo were compared in this trial. There were no statistically significant differences in the percentage of patients who achieved a ≥ 50% decrease in Young Mania Rating Scale (YMRS) score from baseline to endpoint (38.8% for the placebo + mood stabilizer group, 56.9% for the haloperidol + mood stabilizer group, and 58.0% for the risperidone + mood stabilizer group). However, there was a statistically significant difference in the YMRS total score from baseline to endpoint in favor of risperidone versus placebo; it is not reported whether this was a significant finding for risperidone if compared with haloperidol. In a small-sample, 28-day, randomized, double-blind trial, risperidone has also been studied as acute monotherapy versus lithium and haloperidol.[22] In all 3 treatment groups, there was a statistically significant improvement on the YMRS, the primary efficacy variable, from baseline to endpoint and no difference among the 3 treatments. Risperidone and haloperidol did not statistically significantly differ with respect to EPS in this study.

In a retrospective case series of patients with treatment-resistant bipolar disorder in which quetiapine was added to existing treatment with mood stabilizers, 2 of 6 patients showed evidence of response (based on a moderate-to-marked improvement on the Clinical Global Impressions scale-Bipolar Version [CGI-BP]).[23] Quetiapine treatment has also been reported prospectively in 16 patients with either bipolar disorder or schizoaffective disorder for a mean duration of 10.8 weeks.[24] In this study, patients who had previously been treated with an antipsychotic and a mood-stabilizing agent had quetiapine added and the previous antipsychotic withdrawn. Patients demonstrated a statistically significant improvement from baseline to endpoint on the YMRS during that period of time.

Olanzapine, a novel antipsychotic, was found to be effective in the monotherapy treatment of acute mania, with or without psychosis, associated with bipolar I disorder in 2 double-blind trials.[25,26] In addition, olanzapine has been compared in a double-blind trial with divalproex sodium.[27] Olanzapine was statistically significantly superior to divalproex on the a priori primary efficacy measure, which was baseline to endpoint YMRS total score (–13.4 vs. –10.4, respectively; p = .028). Using a priori categorizations for response and remission, 54.4% of olanzapine-treated patients experienced a ≥ 50% reduction in YMRS score as compared with 42.3% of divalproex-treated patients (p = .058), and 47.2% of olanzapine-treated patients met remission criteria (endpoint YMRS score ≤ 12) versus 34.1% of divalproex-treated patients (p = .039). Additionally, the efficacy of olanzapine as an "add-on"

treatment to either valproate or lithium has been studied in a double-blind controlled trial.[28] In this "add-on" study, the addition of olanzapine compared with the use of valproate or lithium alone appears to provide significantly superior efficacy in the treatment of bipolar disorder. These trials further suggest that olanzapine has a favorable safety profile, particularly with respect to depressive symptoms and EPS, unlike conventional antipsychotic drugs. The 3-week double-blind monotherapy trial[25] had a 49-week open-label extension. In this article, we report the safety and efficacy results from the 49-week open-label extension phase of that study.

METHOD

Patients

All 113 patients in the 49-week extension phase initially met diagnostic criteria for bipolar I disorder, with or without psychotic features, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[29] (single manic episode, most recent episode manic, most recent episode mixed). The Structured Clinical Interview for DSM-IV–Patient Edition[30] was used for diagnostic confirmation. All subjects were hospitalized because of mania and had relatively severe symptoms, demonstrated by an initial score of at least 20 on the YMRS.[31] Male and female patients between the ages of 18 and 65 years who completed at least 1 week of double-blind therapy (olanzapine vs. placebo) during the acute-phase study were eligible to enter the extension phase of the study. Prior to study participation, written informed consent was obtained from each patient and/or the patient's authorized legal representative.

Study Design

Tohen and colleagues[25] have previously published the 3-week acute-phase study design. Patients who continued into the open-label extension study received olanzapine in a dose range of 5, 10, 15, or 20 mg/day for 49 additional weeks. Olanzapine dose on the first day of open-label treatment was 10 mg, and it could be adjusted upward or downward in increments of 5 mg/day as clinically indicated. Patients were assessed at the end of the first week, every 2 weeks for 4 weeks, and monthly thereafter. Patients were allowed to continue as either inpatients or outpatients during the extension study. Hospitalized patients who entered the study could be discharged when investigators considered it clinically appropriate. Patients requiring more than 3 weeks of hospitalization because of bipolar symptoms were discontinued from the study.

In general, concomitant medications with primary central nervous system activity were not allowed. However, when clinically appropriate, adjunctive therapy with either lithium or fluoxetine was allowed during the extension phase for control of residual and/or breakthrough affective symptoms. Investigators were encouraged to keep olanzapine as monotherapy for 3 weeks before the addition of either fluoxetine or lithium; however, no strict criteria were defined in the protocol. Benzodiazepines were permitted, but could not exceed lorazepam equivalents of 4 mg/day. Benztropine, up to a maximum dose of 2 mg/day, could be used for treatment-emergent EPS. Benztropine was not allowed to be administered prophylactically.

Assessments

Severity of illness and psychopathology were assessed using the following scales: YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21),[32] CGI-BP,[33] and Positive and Negative Syndrome Scale (PANSS).[34] The PANSS permitted consideration of 2 specific symptom domains: hostility and cognition.[35] The PANSS hostility score[35] was defined as the sum of the PANSS items for excitement, hostility, uncooperativeness, and poor impulse control. The PANSS cognitive score[35] was defined as the sum of the following PANSS items: cognitive disorganization, difficulty in abstract thinking, stereotyped thinking, tension, mannerisms and posturing, poor attention, and lack of judgment and insight. If any of the individual items that comprised a total score were missing, the total score was treated as missing. Prior to data collection, interrater reliability of the YMRS (primary efficacy measure) was established (correlation of each rater with the groupwise median score of each item ranged between 0.76 and 0.99, with a median of 0.94).

Response in mania symptoms was defined a priori as a ≥ 50% improvement from baseline in YMRS total score at any time. Symptomatic remission in mania was defined a priori as achievement of a YMRS total score of 12 or less. Symptomatic relapse in mania was defined a priori as a YMRS total score of 15 or more, following achievement of symptomatic remission in mania.

To assess the safety of long-term treatment with olanzapine, treatment-emergent adverse events and changes in vital signs, electrocardiograms (ECGs), and laboratory analytes were recorded. The severity of EPS was measured using the Simpson-Angus scale,[36] the Barnes Akathisia Scale,[37] and the Abnormal Involuntary Movement Scale (AIMS).[38]

Statistical Methods

To assess patients starting from their initial treatment with olanzapine in this study, the acute data were included with the open-label data for those patients who were treated with olanzapine during the double-blind phase and who subsequently entered the open-label phase. The last non-olanzapine observation available in the study was used as the patient's baseline score. Patients with a baseline and at least 1 postbaseline measurement were included in the analyses of change scores. Mean change from baseline to endpoint was tested for significance

Table 1. Clinical Characteristics of Patients[a]

Characteristic	Value
Length of current episode, d (N = 113)	
Mean (SD)	54.0 (51.1)
Median (range)	33.0 (7–292)
Age at onset of illness, y (N = 111)	
Mean (SD)	24.2 (8.9)
Median (range)	22.0 (10–50)
Previous no. of illness episodes (lifetime)	
Manic (N = 103)	
Mean (SD)	19.9 (31.5)
Median (range)	10.0 (0–200)
Depressive (N = 105)	
Mean (SD)	17.4 (32.5)
Median (range)	5.0 (0–175)
Mixed (N = 105)	
Mean (SD)	9.4 (30.1)
Median (range)	1.0 (0–264)

[a]Ns represent the numbers of patients reporting specific information.

Table 2. Baseline to Endpoint Change in Severity of Illness Scores: Last Observation Carried Forward[a]

		Baseline		Change From Baseline		Within-Group
Scale	N	Mean	SD	Mean	SD	p Value[b]
YMRS total	109	25.49	11.46	–18.01	13.25	< .001
HAM-D-21 total	109	12.17	7.32	–5.77	8.26	< .001
CGI-BP						
Severity of mania	110	4.24	1.26	–2.13	1.57	< .001
Severity of depression	110	1.85	1.10	0.05	1.49	.750
Severity of overall bipolar disorder	110	4.18	1.25	–1.68	1.59	< .001
PANSS						
Total	109	68.63	23.54	–21.61	22.66	< .001
Positive	109	19.41	7.86	–8.54	8.10	< .001
Negative	109	13.58	6.29	–2.62	5.67	< .001
Cognitive	109	17.66	6.96	–6.33	6.24	< .001
Hostility	109	10.65	4.79	–4.50	4.85	< .001

[a]Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version, HAM-D-21 = 21-item Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.
[b]Within-treatment group mean change was tested with the Student t test.

using the Student t test. All hypotheses were tested using a 2-sided α level of 0.05. To assess the longitudinal effects of olanzapine therapy, likelihood-based mixed-model repeated-measures analyses (SAS PROC MIXED; SAS Institute, Cary, N.C.) were conducted on the postbaseline YMRS total scores and HAM-D-21 total scores. The fixed effects included a fourth- and third-order polynomial in time for YMRS and HAM-D-21, respectively. The random effects included only an intercept and linear term in time. The time to symptomatic remission and relapse of mania was characterized using Kaplan-Meier estimated survival curves.

RESULTS

Patient and Illness Characteristics

A total of 113 patients entered into the open-label study phase. These patients had a mean length of exposure to olanzapine of 6.6 months per patient, with a mean ± SD modal dose of 13.9 ± 5.4 mg/day. Two thirds of the patients required doses of ≤ 15 mg of olanzapine per day during this open-label study. Patients' mean age was 38.6 ± 10.9 years; 51% were men and 74% were white. Eighty-two percent of patients were in an active manic episode, and 18% were in an active mixed episode; about half (54%) had psychotic features. Overall, 35% of subjects had rapid cycling. Illness characteristics for these patients at the initiation of the study are presented in Table 1.

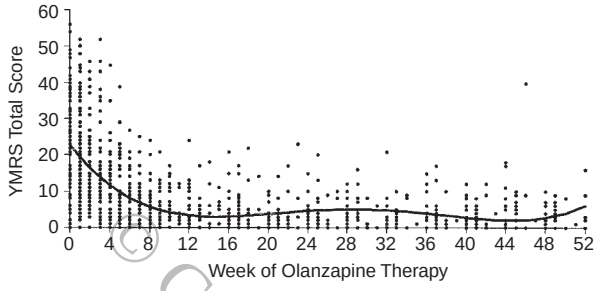
Of the 113 patients who entered the open-label phase of the study, 45 (39.8%) completed the phase. Fourteen (12.4%) of the 113 patients withdrew due to lack of efficacy, and 7 (6.2%) patients discontinued due to an adverse event: accidental injury, depression (N = 2), drug dependence, hostility, hyperglycemia, or unintended pregnancy. Discontinuation due to other reasons (patient decision, 19.5%; physician decision, 5.3%; criteria not met/noncompliance, 11.5%; lost to follow-up, 5.3%) occurred in 47 patients.

Efficacy

Manic symptoms. A significant improvement from baseline to endpoint (mean change = –18.01, $p < .001$) was seen on the primary efficacy measure, the YMRS total score. In addition, the CGI-BP severity of mania score, a secondary measure of mania, demonstrated a significant improvement from baseline to endpoint (mean change = –2.13, $p < .001$) (Table 2). The weekly improvement in YMRS total scores is presented in Figure 1 with the estimated improvement curve. Response in manic symptoms was achieved by 84.4% (92/109) of the patients during the open-label phase. Full symptomatic remission of mania was met by 88.3% (98/111) of patients. Time to symptomatic remission of mania can be seen in Figure 2. From the Kaplan-Meier curve, it is estimated that 50% of patients would remit within 11 days of treatment and 75% would remit within 21 days of treatment. Of the 94 patients who remitted and continued in the study, 24 (25.5%) subsequently relapsed into mania (9 relapses occurring within the first 15 days, 10 relapses occurring between days 16 and 170, and the last 5 relapses occurring by day 338).

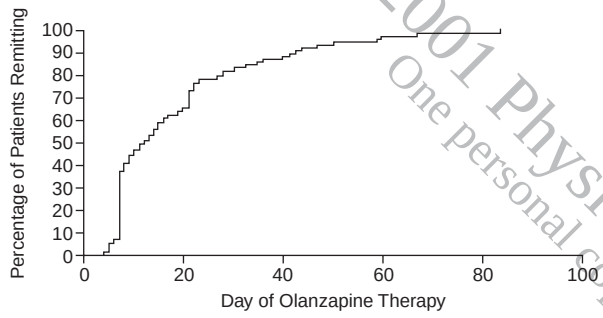
Depressive symptoms. On average, these manic subjects had moderately severe baseline depressive symptoms (mean HAM-D-21 total score = 12.17). A significant improvement from baseline to endpoint in depressive symptoms also occurred over the course of long-term olanzapine therapy (mean change in HAM-D-21 total score = –5.77, $p < .001$) (Table 2). The weekly improve-

Figure 1. Weekly YMRS Total Score With Long-Term Olanzapine Treatment[a]



[a]Abbreviation: YMRS = Young Mania Rating Scale.

Figure 2. Time to Symptomatic Remission of Mania (YMRS total score ≤ 12): Kaplan-Meier Analysis[a]

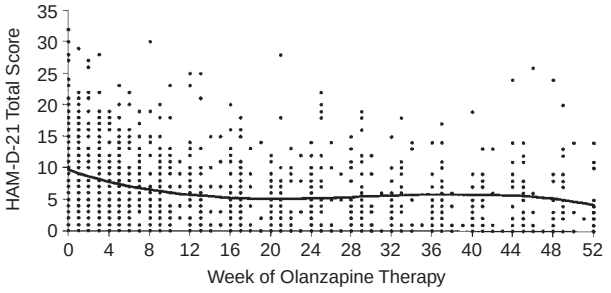


[a]Abbreviation: YMRS = Young Mania Rating Scale.

ment in HAM-D-21 total scores is presented in Figure 3 along with the estimated improvement curve. Patients with pure manic symptoms had a lower HAM-D-21 total score at baseline than those with mixed symptoms (11.85 vs. 13.55, respectively). A statistically significant greater improvement on the HAM-D-21 total score was observed in patients with pure manic symptoms versus those with mixed symptoms (–6.13 vs. –4.15, respectively; p = .013).

Other efficacy measures. Improvements were also evident in the secondary measures of efficacy, including the PANSS total, positive, negative, hostility, and cognitive scores as well as the CGI-BP overall severity of bipolar disorder score (Table 2). Except for the CGI-BP overall severity of bipolar disorder score, there was no difference in any secondary efficacy measures for patients with pure manic symptoms versus those with mixed symptoms. Patients with pure manic symptoms demonstrated statistically significant greater improvement in CGI-BP overall severity of bipolar disorder score versus those with mixed symptoms (–1.88 vs. –0.80, respectively; p = 0.36).

Figure 3. Weekly HAM-D-21 Total Score With Long-Term Olanzapine Treatment[a]



[a]Abbreviation: HAM-D-21 = 21-item Hamilton Rating Scale for Depression.

Table 3. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Patients Receiving Olanzapine Only (N = 113)

Event	%
Somnolence	46.0
Depression	38.9
Weight gain	36.3
Asthenia	27.4
Dry mouth	25.7
Increased appetite	22.1
Agitation	21.2
Headache	21.2
Pain	19.5
Rhinitis	19.5
Dizziness	18.6
Anxiety	17.7
Insomnia	17.7
Constipation	14.2
Tremor	14.2
Apathy	10.6
Nausea	10.6
Nervousness	10.6

Safety

There were no clinically significant changes observed in vital signs (including heart rate and ECG intervals) or laboratory analytes in patients treated with olanzapine during the open-label extension study. Treatment-emergent adverse events with a frequency greater than or equal to 10% are reported in Table 3. Depression, somnolence, and weight gain were the most common events. The mean ± SD weight gain over the study (mean length of treatment = 6.6 months) was 6.64 ± 8.51 kg ($p < .001$), and the range was –13.61 kg to 34.02 kg. EPS were measured using objective rating scales. Akathisia (as measured by the Barnes Akathisia Scale) and parkinsonism (as measured by the Simpson-Angus scale total score) were statistically significantly reduced in patients from baseline to endpoint (–0.23 ± 0.85 and –0.50 ± 1.84, respectively; p = .006 and p = .006). Treatment-emergent akathisia (Barnes Akathisia Scale score ≥ 2 at any postbaseline visit, given a score of < 2 at baseline) occurred in 17.9% (14/78) of patients. Treatment-emergent parkinsonism (Simpson-

Angus scale total score > 3 at any postbaseline visit, given a score of ≤ 3 at baseline) occurred in 13.6% (12/88) of patients. Dyskinesias (as measured by AIMS) reduced from baseline to endpoint (–0.09 ± 1.10), but the change was not statistically significant (p = .387). Using the Schooler-Kane criteria[39] for assessing long-term treatment-emergent dyskinetic events (defined as scores that were not present at baseline of 3 or greater in 1 body region or 2 or greater in any 2 body regions, on items 1–7, for the last 2 assessments), no patients (0 of 101 evaluated) met the criteria. After initiating olanzapine in the 4 patients who had presumptive tardive dyskinesia at baseline, based upon the Schooler-Kane criteria, all 4 no longer met the criteria for tardive dyskinesia at any time on treatment with olanzapine. Concomitant anticholinergics were necessary in only 21 patients, with a mean benztropine equivalent dose of 0.605 ± 0.559 mg/day.

Adjunctive Medication Use

At the investigator's discretion, pharmacologic management of residual and breakthrough symptoms allowed for the concomitant use of lithium, fluoxetine, and benzodiazepines. Eighty-eight patients required benzodiazepine therapy (mean dose for the patients who required benzodiazepines was 1.04 ± 1.44 mg/day). Thirty-six patients (32%) received lithium therapy at a mean dose of 786 ± 465 mg/day for a mean of 160 ± 135 days of joint therapy. Of the patients who received lithium, 44% started the lithium during the first open-label visit. Thirty-seven patients (33%) received fluoxetine therapy at a mean dose of 13.5 ± 9.3 mg/day for a mean of 179 ± 104 days of joint therapy. The use of fluoxetine was more dispersed throughout the open-label phase. Of those patients who received fluoxetine, half started fluoxetine by 7 weeks of open-label olanzapine treatment. Forty-six patients (41%) received neither lithium nor fluoxetine.

The patients receiving olanzapine and lithium had statistically significant decreases in mean YMRS total score (–14.14 ± 16.16, p < .001) and HAM-D-21 total score (–4.23 ± 6.73, p < .001) from their last visit just before starting lithium to their last combination therapy visit. For YMRS total score, the mean entry baseline (score immediately prior to the first olanzapine dose) was 29.11 ± 12.85 in comparison to a mean score on treatment with olanzapine just prior to receiving lithium of 24.51 ± 16.33. For HAM-D-21 total score, the mean entry baseline was 12.00 ± 7.01 in comparison to a mean score on treatment with olanzapine just prior to receiving lithium of 12.03 ± 6.32. Adjunctive lithium was temporally associated with several adverse events. The most common adverse events that worsened in severity or first occurred after the patient received lithium were somnolence (41.7%), weight gain (27.8%), depression (22.2%), agitation (22.2%), insomnia (19.4%), thinking abnormal (19.4%), asthenia (16.7%), rhinitis (16.7%), dry mouth (16.7%), diarrhea (16.6%), increased appetite (13.9%), nervousness (13.9%), tremor (13.9%), and hostility (13.9%).

The patients receiving both olanzapine and fluoxetine had statistically significant decreases in mean YMRS total score (–3.16 ± 7.05, p = .010) and HAM-D-21 total score (–3.78 ± 8.12, p = .007) from their last visits just before starting fluoxetine to their last combination therapy visit. For YMRS total score, the mean entry baseline (score immediately prior to the first olanzapine dose) was 25.95 ± 10.85 in comparison to a mean score on treatment with olanzapine just prior to receiving fluoxetine of 6.57 ± 6.68. For HAM-D-21 total score, the mean entry baseline was 15.22 ± 7.80 in comparison to a mean score on treatment with olanzapine just prior to receiving fluoxetine of 10.68 ± 6.09. Eleven of the 37 patients experienced increases in the YMRS total score after fluoxetine was added to the treatment. Only 3 of the patients experienced scores ≥ 15 on the YMRS (a priori definition of relapse). Importantly, at endpoint, only 1 of the 37 patients treated concomitantly with fluoxetine had a sustained significant increase in YMRS total score (YMRS total score = 21), whereas the remaining 36 patients treated concomitantly with fluoxetine had a YMRS total score of ≤ 8 at endpoint (a priori definition of remission, YMRS total score ≤ 12). The most common adverse events that worsened in severity or first occurred after the patient received fluoxetine were depression (48.6%), weight gain (21.6%), nausea (18.9%), anxiety (18.9%), thinking abnormal (18.9%), somnolence (16.2%), personality disorder (16.2%), agitation (16.2%), insomnia (13.5%), asthenia (13.5%), anorexia (13.5%), rhinitis (10.8%), pain (10.8%), nervousness (10.8%), and libido decrease (10.8%).

The patients receiving olanzapine monotherapy only (no lithium or fluoxetine) had statistically significant mean decreases in YMRS total score (–14.30 ± 12.50, p < .001) and HAM-D-21 total score (–4.56 ± 6.13, p < .001) from baseline to endpoint. The mean YMRS and HAM-D-21 total scores at baseline were 22.26 ± 11.03 and 9.91 ± 6.32, respectively. For these patients, the most common adverse events that worsened in severity or first occurred after the patient received olanzapine were agitation (39.1%), somnolence (37.0%), weight gain (30.4%), anxiety (26.1%), dry mouth (19.6%), depression (17.4%), constipation (13.0%), and insomnia (13.0%).

DISCUSSION

Perhaps because no currently available treatment is fully satisfactory, specialists in the treatment of bipolar disorder have postulated that an ideal mood stabilizer should meet widely ranging requirements. These include efficacy against mania, depressive symptoms, and psychosis; prophylactic benefits in maintenance treatment; and a favorable profile of safety, tolerability, and ease of use.[40] In 2

placebo-controlled acute treatment studies, olanzapine was an effective, safe, and tolerable treatment for bipolar mania, controlling manic symptoms without provoking depressive symptoms.[25,26] This open-label extension study revealed marked and sustained improvements for olanzapine-treated bipolar I patients. The patients in this study were at high risk for relapse; each had experienced about 50 lifetime episodes of bipolar disorder and over one third had rapid cycling (i.e., more than 4 episodes in the preceding year). Significant improvement in manic symptoms was observed at the patients' last visit as measured by the YMRS total scores. Over 84% of the patients responded to treatment, and 88% of the patients achieved symptomatic remission of their manic symptoms, most within 11 days. Of those patients whose manic symptoms remitted, approximately one fourth subsequently relapsed. A limitation of our a priori definition of remission is that we required only 1 measurement as opposed to multiple measurements over a sustained period of time to meet our remission criteria; however, it is important to note that this definition would then also increase the rate of relapse. Although it is difficult to draw conclusions from relapse rates that are not obtained in comparator trials, the rate seen in our trial is comparable to the 23% relapse rate (range, 0%–59%) reported for lithium and better than the 56% relapse rate (range, 0%–94%) reported for placebo in a meta-analytic study.[15] Although enrollment required a minimum YMRS total score of 20, no minimum depression rating was stipulated. Therefore, there was less room for demonstrating an antidepressant effect of olanzapine. Regardless, significant improvement in depressive symptoms was observed.

The olanzapine-treated patients were also observed to have statistically significantly decreased hostility as demonstrated by an improvement in the PANSS hostility score.[35] An overall decrease in hostility is of particular significance in a clinical setting, since hostile or uncooperative patients can pose a danger to other patients and staff as well as to themselves.

The olanzapine-treated patients experienced statistically significantly increased cognition during long-term treatment as demonstrated by an improvement in the PANSS cognitive score.[35] Typical antipsychotics[41,42] and lithium[43] have been associated with decreased cognition. If olanzapine does not change cognition or improves cognition, it would be of significant benefit to patients compared with currently standard treatments.

Efficacy was achieved with a favorable safety profile. Somnolence was the most commonly reported treatment-emergent adverse event, but, in some instances, may have been clinically helpful for the symptoms of mania, especially since sleep deprivation may worsen mania. Given the characteristically increased energy and decreased need for sleep in mania, some patients may have misinterpreted normalization as "somnolence." Similarly, it is possible that the estimate of treatment-emergent depression may have been somewhat inflated by misattribution of normalizing mood. In support of this speculation, depressive symptoms identified by objective ratings were reduced over the period of the study. The third most frequently reported adverse event was weight gain. Patients gained about 6 kg over 6.6 months of treatment with olanzapine on average. No patients discontinued this open-label study due to weight gain. Very few EPS and no tardive dyskinesia (per the Schooler-Kane criteria[39]) were observed in these patients over the mean of 6.6 months of exposure that each patient had. Lack of tardive dyskinesia is a significant preliminary finding in this population that has traditionally been thought to be predisposed to the development of tardive dyskinesia with antipsychotic treatment.[16,17]

The majority of patients received adjunctive lithium or fluoxetine with olanzapine at some time in the study. This study was the first long-term evaluation of olanzapine in bipolar patients and allowed investigators to add lithium or fluoxetine at any time, although they were encouraged to try olanzapine as monotherapy for 3 weeks. Given that, prior to this trial, there was little information to support the efficacy of olanzapine monotherapy for acute mania, it is not surprising that 44% of the patients who received lithium started it during the first open-treatment visit. Although it is not possible to ascertain whether patients would have improved comparably on olanzapine monotherapy, they had significant improvement in their manic and depressive scores after the addition of lithium. Not surprisingly, those patients treated with adjunctive lithium experienced increased diarrhea and thirst.

Those patients given adjunctive fluoxetine had large improvements in their psychopathology scores while on monotherapy with olanzapine prior to the addition of fluoxetine. Fluoxetine was not generally given to the patient early in the open-label phase, but was more commonly dispersed throughout the 49 weeks. After the addition of fluoxetine, patients continued to have modest improvements in their manic and depressive scores. Not surprisingly, those patients given fluoxetine had a larger incidence of depression reported (48.6%) in comparison to the overall group of patients (38.9%). However, baseline HAM-D-21 total score for patients given fluoxetine at time of the addition of fluoxetine (10.68) was lower than the mean baseline observed at study entry for all patients (12.17). It is unclear why fluoxetine was added, but it appears that fluoxetine was not added until patients experienced significant improvement in their mania scores.

Those patients who received only monotherapy olanzapine had larger improvement in both manic and depressive symptoms than those patients treated with adjunctive lithium or fluoxetine in addition to olanzapine. It is not surprising that olanzapine monotherapy performed better than adjunctive therapy, since patients who were doing well on monotherapy would be less likely to add adjunctive lithium or fluoxetine.

Although this study demonstrates the clinical potential of olanzapine in open-label long-term management of bipolar I disorder, it is not without limitations. Certainly, confirmatory double-blind, randomized, controlled studies that capture a lengthy perspective of the disease course are needed. Additionally, active-comparator data (e.g., lithium or valproate) would be useful in determining the place of olanzapine in the armamentarium of therapy. Strict initiation criteria for adjunctive treatment with lithium or fluoxetine would provide a clearer understanding of their role as adjunctive therapies.

Another limitation of our study is the low completion rate (39.8%). Very few patients withdrew from the study due to lack of efficacy (12.4%). This completion rate reflects the difficulty in the clinical management of patients with bipolar disorder in general, especially in an experimental trial with a then-unproven pharmacotherapy. In addition, the completion rate highlights the difficulty in conducting long-term research in this population.

Significant improvements were achieved in mania and depressive symptoms, and residual and/or breakthrough symptoms were well managed over almost 1 year of olanzapine therapy. Efficacy was achieved with a very favorable safety profile. Further double-blind clinical trials are needed to confirm the results from this long-term open-label study.

Drug names: benztropine (Cogentin and others), carbamazepine (Tegretol and others), clozapine (Clozaril and others), divalproex sodium (Depakote), fluoxetine (Prozac), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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