Analyses of Treatment-Emergent Mania With Olanzapine/Fluoxetine Combination in the Treatment of Bipolar Depression

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Background: Treatment-emergent mania is a potential risk when patients with bipolar disorder are treated with antidepressant agents. These subanalyses compare treatment-emergent mania rates in bipolar I depressed patients treated with olanzapine, placebo, or olanzapine/fluoxetine combination.

Method: In this 8-week, double-blind investigation, patients with bipolar I depression (DSM-IV criteria) (N = 833, baseline Montgomery-Asberg Depression Rating Scale total score ≥ 20) were randomly assigned to olanzapine (5–20 mg/day, N = 370), placebo (N = 377), or olanzapine/fluoxetine combination (6/25, 6/50, or 12/50 mg/day; N = 86). Treatment-emergent mania was evaluated with the Young Mania Rating Scale (YMRS), the Clinical Global Impressions-Bipolar Edition (CGI-BP) Severity of Mania scale, and adverse events records.

Results: Overall rates of study discontinuation due to mania were low and not significantly different among the therapy groups (p = .358). Incidence of treatment-emergent mania (defined as a YMRS score < 15 at baseline and ≥ 15 at any subsequent visit) did not differ significantly among therapy groups (olanzapine 5.7%, placebo 6.7%, olanzapine/fluoxetine combination 6.4%; p = .861). Subjects receiving olanzapine or olanzapine/fluoxetine combination had greater mean decreases in YMRS scores than those receiving placebo (p < .001 for both). Subjects receiving olanzapine or olanzapine/fluoxetine combination also had greater mean decreases in CGI-BP scores than those receiving placebo (p = .040 and p = .003, respectively).

Conclusion: These results suggest that olanzapine/fluoxetine combination does not present a greater risk of treatment-emergent mania compared to olanzapine or placebo over 8 weeks of acute treatment for bipolar I depression. Due to the cyclical nature of bipolar disorder, patients taking olanzapine/fluoxetine combination for bipolar depression should still be monitored for signs or symptoms of emerging mania.

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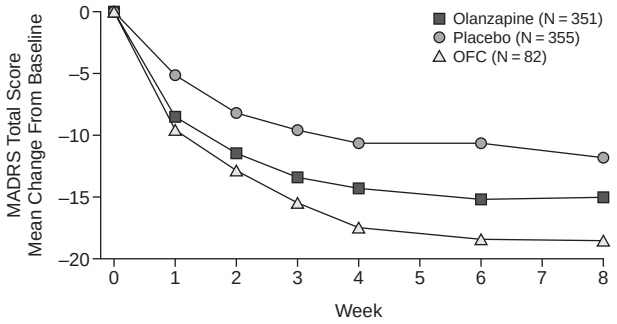
Treatment-emergent mania is a common clinical concern when treating patients with bipolar depression. Because maintenance therapies for bipolar disorder (e.g., lithium, valproate) are often less effective in the depressive phase of the illness, antidepressants are often used in combination with maintenance therapies to treat breakthrough depression.[1] Despite the greater efficacy of antidepressants in reducing depressive symptoms, patients with bipolar I disorder can rapidly switch from depression into mania, and the risk is greater in the absence of a mood stabilizer. Even one manic episode is undesirable, because mania can lead patients to engage in highly unsafe and/or financially damaging behaviors. Furthermore, each additional manic episode increases the risk of recurrence and worsens the prognosis of the disorder.[2] Mania also frequently necessitates hospitalization and is therefore expensive to treat. Clearly, there is a need for an effective treatment for bipolar depression that does not present a significant risk of switching into mania.

Although comparative data are limited, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors

Figure 1. Least-Squares Mean Change From Baseline in MADRS Scores[a,b]



[a]Sample sizes represent only those subjects who had a baseline score and at least 1 post-baseline score. Improvement in MADRS scores with olanzapine and olanzapine/fluoxetine combination was significantly greater than placebo throughout the study period ($p < .001$). Improvement in MADRS scores with olanzapine/fluoxetine combination was significantly greater than olanzapine at weeks 4–8 ($p < .02$).
[b]Reprinted with permission from Tohen et al.[15]
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination.

Table 1. Baseline Demographic Information and Patient Illness Characteristics[a]

Variable	OFC (N = 86)	Olanzapine (N = 370)	Placebo (N = 377)	p
Age, mean (SD), y	40.3 (13.0)	42.2 (12.5)	41.7 (12.4)	.910
Gender, female, %	67.4	62.4	62.6	.684
Origin, white, %	77.9	84.1	82.2	.521
Rapid cycling course, %	39.5	38.4	35.0	.817
Manic or mixed episode in past 12 mo, %	80.5	83.5	77.8	.199
Length of current depressive episode, median, d	81	63	82	.006

[a]Adapted with permission from Tohen et al.[15]
Abbreviation: OFC = olanzapine/fluoxetine combination.

(MAOIs) have been reported as having a higher risk of treatment-emergent mania than selective serotonin reuptake inhibitors (SSRIs) and bupropion.[3,4] Mania switch rates reported for TCAs have been as high as 70%,[5] but generally have been in the range of 20% to 30% in acute treatment trials.[3,4,6] Switch rates for MAOIs have varied from 35% to 50%.[4,5] Rates reported for SSRIs have generally been under 5%,[3,7] but have been as high as 12%.[4] The only randomized, double-blind clinical trial of bupropion in bipolar depression showed a treatment-emergent mania rate of 11%.[8] No significant differences in switch rates have been confirmed among the different SSRIs or bupropion.[9,10] Treatment-emergent mania rates for serotonin-norepinephrine reuptake inhibitors may be intermediate between the rates for TCAs and SSRIs. For example, Vieta et al.[11] reported a treatment-emergent mania rate of 13% for venlafaxine. Little is known regarding treatment-emergent mania rates for combination therapies, although there is evidence that the frequency and severity of antidepressant-associated switching can be reduced by concurrent use of mood stabilizers.[4] (It should be noted that none of the above-mentioned drugs is currently U.S. Food and Drug Administration [FDA]–approved for the treatment of acute bipolar depression.[6,12])

Several attempts have been made to identify patients who are at increased risk of treatment-emergent mania. Patients with bipolar I disorder have been reported as being at greater risk of antidepressant-induced switching than patients with bipolar II disorder.[9] One analysis found the best predictor of antidepressant-induced mania to be number of past manic episodes.[4] Other risk factors proposed to be predictors have included family history of mania, early onset of bipolar disorder, female gender, hypothyroidism, and history of drug-induced rapid cycling.[13] Premorbid mood state (i.e., manic rather than euthymic) immediately prior to onset of depression may also predict switching.[14]

The present subanalyses examine the incidence of treatment-emergent mania during a randomized, double-blind, placebo-controlled trial[16] of olanzapine and olanzapine/fluoxetine combination in acute bipolar depression. In that trial, olanzapine/fluoxetine combination was found to be more effective than olanzapine or placebo without increased risk of treatment-emergent mania (Figure 1). The purpose of the present analyses was to examine these data in more detail in order to determine the relative risks of mania associated with olanzapine/fluoxetine combination, olanzapine monotherapy, and placebo. Given prior research on olanzapine's efficacy in bipolar mania,[17,18] we hypothesized that olanzapine/fluoxetine combination would yield treatment-emergent mania rates similar to those for olanzapine monotherapy and placebo.

METHOD

Data for the present analyses were obtained from an 8-week randomized, double-blind, placebo-controlled trial[16] of olanzapine monotherapy and olanzapine/fluoxetine combination in the treatment of bipolar I disorder, depressed (DSM-IV criteria). Patients with bipolar depression (N = 833, baseline Montgomery-Asberg Depression Rating Scale [MADRS] total score ≥ 20) were randomly assigned to olanzapine (5 to 20 mg/day, N = 370), placebo (N = 377), or olanzapine/fluoxetine combination (6/25, 6/50, or 12/50 mg/day, N = 86). All patients from the original study[16] were included in the present analyses (i.e., patients with a history of rapid cycling or mixed episodes were not excluded). Table 1 presents baseline patient demographics and illness characteristics. The a priori 4:4:1 randomization schedule occurred because olanzapine/fluoxetine combination was included as an exploratory therapy arm. Further details of the

Table 2. Results of a Stepwise Logistic Regression Model Predicting Treatment-Emergent Mania for the Sample[a]

Variable	Coefficient	Standard Error	Wald χ^2	p	Odds Ratio	95% CI
Intercept	–3.42	0.32	112.43	< .001	…	…
Baseline YMRS score ≥ 12	1.50	0.44	11.66	< .001	4.50	1.90 to 10.68
Female gender	0.60	0.36	2.76	.10	1.82	0.90 to 3.67
Presence of psychotic features	0.86	0.38	5.08	.02	2.35	1.12 to 4.95

[a]The following baseline demographic and illness characteristics were used as possible predictors: age; race; gender; baseline body mass index; presence of melancholic features, atypical features, psychotic features, or rapid cycling; family history of bipolar disorder; length of current episode; baseline YMRS score; age at onset of bipolar disorder; number of previous depressed, manic, or mixed episodes; and number of depressed, manic, or mixed episodes in the last 12 months.
Abbreviation: YMRS = Young Mania Rating Scale.

study's methodology and primary results have been published elsewhere.[16]

Occurrence and severity of manic symptoms were measured using the Young Mania Rating Scale (YMRS),[19] the Clinical Global Impressions-Severity of Illness, Bipolar Edition (CGI-BP),[20] and the number of patients with "manic reaction" recorded spontaneously as an adverse event. Rates of study discontinuation attributed by the investigator to "induction of mania" on a patient summary form were also reviewed. The YMRS is composed of items addressing the following symptoms: elevated mood, increased motor activity/energy, increased sexual interest, decreased sleep, irritability, increased rate and amount of speech, language-thought disorder, abnormal speech content, disruptive-aggressive behavior, unkempt appearance, and loss of insight. Scores range from 0 to 60. The CGI-BP is a 3-item scale rating severity of mania, severity of depression, and overall severity of bipolar disorder. For each item, 1 of 7 levels of illness is selected: (1) normal, not ill; (2) minimally ill; (3) mildly ill; (4) moderately ill; (5) markedly ill; (6) severely ill; and (7) very severely ill. Only the CGI-BP Severity of Mania item was used in the current analyses; scores range from 1 to 7.

Treatment-emergent mania was defined a priori as a YMRS score < 15 at baseline and ≥ 15 at any subsequent visit. This cutoff of YMRS score = 15 was judged by the authors to represent a degree of manic symptoms that would be clinically noticeable. Subjects who met the criterion for treatment-emergent mania were discontinued from acute phase treatment but are included in all analyses below.

For all analyses, only subjects with a baseline and at least 1 postbaseline assessment were included. Scales were administered at baseline and at weeks 1, 2, 3, 4, 6, and 8 of treatment, and adverse events were recorded at each of these visits. All visitwise analyses employed a mixed-effects model repeated measures (MMRM) regression analysis. Treatment differences for each visit were tested with a single degree of freedom contrast based on least-squares means from the final model. Thus, all reported mean change scores reflect least-squares means. Fisher exact test was used to analyze treatment differences for categorical data. The above analyses were specified a priori.

Additional post hoc analyses included stepwise logistic regression analysis to evaluate patient demographic data to identify predictors of treatment-emergent mania. The Wald χ^2 test evaluated goodness-of-fit for all logistic regression models.

RESULTS

The mean number of previous episodes of mania (lifetime) was 14.5 (SD = 43.9) for the olanzapine group, 9.9 (SD = 16.6) for the placebo group, and 12.0 (SD = 29.4) for the olanzapine/fluoxetine combination group and did not differ significantly among treatment groups. A logistic regression revealed that number of past manic episodes was not a significant predictor of treatment-emergent mania for this sample (Wald $\chi^2 = 0.088$, $p = .77$). A subsequent stepwise logistic regression analysis utilizing a pool of 18 demographic and illness characteristic variables resulted in a significant model ($\chi^2 = 25.13$, $p < .001$) that included the following predictors of treatment-emergent mania for the sample: baseline YMRS score ≥ 12, female gender, and presence of psychotic features (Table 2).

Study Discontinuation due to Mania

Rates of study discontinuation attributed to "induction of mania" by the investigator on a patient summary form were not significantly different among the therapy groups. A total of 15 olanzapine subjects (4.1%), 24 placebo subjects (6.4%), and 4 olanzapine/fluoxetine combination subjects (4.7%) discontinued the study due to this reason (overall, $p = .358$). Of these subjects, 4 (1 olanzapine and 3 placebo subjects) required hospitalization for their manic or mixed symptoms.

Mania Reported as an Adverse Event

The percentage of patients with "manic reaction" reported as a treatment-emergent adverse event by an investigator was low and similar for the therapy groups: 4% (N = 15) for olanzapine, 5% (N = 18) for placebo, and 5% (N = 4) for olanzapine/fluoxetine combination ($p = .856$).

Young Mania Rating Scale Results

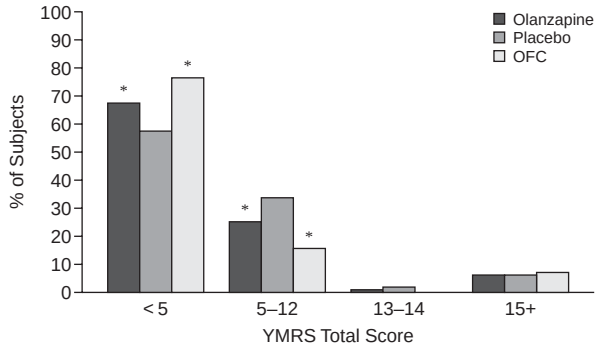
Mean baseline YMRS scores were 4.96 (SD = 4.64) for the olanzapine group, 4.85 (SD = 4.55) for the placebo

Table 3. Visitwise Least-Squares Mean Change for Young Mania Rating Scale Score

				Versus Olanzapine			Versus Placebo		
Week	Therapy	Mean ± SE	95% CI	t	df	p	t	df	p
1	Olanzapine	–0.28 ± 0.24	–0.75 to 0.18						
	Placebo	–0.07 ± 0.23	–0.52 to 0.38	–0.75	1652	.456			
	OFC	–1.51 ± 0.44	–2.37 to –0.64	–2.64	1659	.008	–3.10	1659	.002
2	Olanzapine	–0.43 ± 0.24	–0.90 to 0.05						
	Placebo	–0.28 ± 0.24	–0.74 to 0.18	–0.51	1776	.613			
	OFC	–1.13 ± 0.44	–2.01 to –0.26	–1.50	1725	.133	–1.82	1719	.069
3	Olanzapine	–0.88 ± 0.25	–1.37 to –0.40						
	Placebo	–0.17 ± 0.24	–0.65 to 0.30	–2.34	1848	.019			
	OFC	–1.30 ± 0.46	–2.20 to –0.41	–0.87	1822	.385	–2.34	1819	.020
4	Olanzapine	–1.03 ± 0.25	–1.53 to –0.54						
	Placebo	–0.18 ± 0.24	–0.66 to 0.30	–2.78	1881	.006			
	OFC	–1.47 ± 0.46	–2.38 to –0.56	–0.89	1852	.375	–2.63	1845	.009
6	Olanzapine	–1.40 ± 0.27	–1.93 to –0.87						
	Placebo	0.01 ± 0.27	–0.53 to 0.54	–4.07	2333	< .001			
	OFC	–2.08 ± 0.48	–3.03 to –1.13	–1.30	2048	.194	–3.96	2102	< .001
8	Olanzapine	–1.47 ± 0.29	–2.03 to –0.91						
	Placebo	–0.07 ± 0.31	–0.67 to 0.53	–3.66	2472	< .001			
	OFC	–2.17 ± 0.50	–3.15 to –1.19	–1.29	2103	.198	–3.77	2191	< .001

Abbreviation: OFC = olanzapine/fluoxetine combination.

Figure 2. Percentage of Subjects in YMRS Total Score Categories at Endpoint, by Therapy Group



*Significant versus placebo at p < .05.
Abbreviations: OFC = olanzapine/fluoxetine combination, YMRS = Young Mania Rating Scale.

group, and 4.96 (SD = 4.81) for the olanzapine/fluoxetine combination group and did not differ significantly across treatment groups. Incidence of YMRS-defined treatment-emergent mania (baseline YMRS score < 15 and ≥ 5 at any subsequent visit) was low and similar among the therapy groups (olanzapine, 5.7%; placebo, 6.7%; olanzapine/fluoxetine combination, 6.4%; p = .861). Of these subjects, 5 (1 olanzapine, 3 placebo, and 1 olanzapine/fluoxetine combination) required hospitalization for their manic or mixed symptoms. The mean baseline YMRS score for the olanzapine/fluoxetine combination subjects who went on to develop treatment-emergent mania during the course of the trial was 4.60, which was not significantly different from those who did not develop treatment-emergent mania (4.16, p = .78). Table 3 presents YMRS weekly mean change and statistics for pairwise comparisons. MMRM analysis of mean change data revealed a significant main effect for therapy (F = 10.78, df = 2,704; p < .001), with no significant main effect for visit (F = 1.94, df = 5,1307; p = .09) or treatment-by-visit interaction (F = 1.80, df = 10,1371; p = .06).

Figure 2 shows percentages of subjects with YMRS scores in specific ranges at endpoint, by therapy group. A Fisher exact test of overall group differences was significant, p = .003. Pairwise comparisons revealed that compared to placebo, there were significantly higher percentages of olanzapine/fluoxetine combination subjects (p = .001) and olanzapine subjects (p = .005) in the YMRS score < 5 range. In the YMRS score 5–12 range, there were significantly lower percentages of olanzapine/fluoxetine combination (p < .001) and olanzapine (p = .008) subjects. There were no significant group differences for the YMRS score 13–14 or the YMRS score 15+ ranges, and the percentages were low (i.e., < 10%).

Clinical Global Impressions-Bipolar Edition Severity of Mania Results

Mean CGI-BP Severity of Mania scores at baseline were 1.48 (SD = 0.90) for olanzapine, 1.57 (SD = 1.01) for olanzapine/fluoxetine combination, and 1.49 (SD = 0.91) for placebo and did not differ across therapy groups (p = .76). At study endpoint, mean changes were –0.11 for olanzapine, –0.26 for olanzapine/fluoxetine combination, and +0.02 for placebo. Mean decreases in CGI-BP score were statistically significantly greater for olanzapine versus placebo (p = .040) and for olanzapine/fluoxetine combination versus placebo (p = .003). Number of patients with a CGI-BP Severity of Mania score < 4 (i.e., "not ill" to "mildly ill") at baseline and ≥ 4 ("moderately ill" to "very severely ill") at any subsequent visit was

low and not significantly different among the therapy groups: 21 (6.3%) for olanzapine, 4 (5.3%) for olanzapine/fluoxetine combination, and 21 (6.3%) for the placebo group (p = 1.00).

DISCUSSION

For patients with bipolar depression, antidepressant medication carries the potential risk of mania, especially when it is prescribed in the absence of a mood stabilizer. Fluoxetine has been associated with treatment-emergent mania in some[4,21] but not all[7] reports, and rates have ranged from 0% to 12%. In the present analyses, olanzapine/fluoxetine combination had a treatment-emergent mania rate that was low (6.4%) and similar to olanzapine monotherapy (5.7%) and placebo (6.7%). No meaningful differences among the groups with regard to treatment-emergent mania were detected on examination of mean change, categorical, or adverse event data. Rates of study discontinuation due to treatment-emergent mania also did not differ among groups. It appears that when the combination is used, olanzapine may counterbalance any increased risk of mania posed by fluoxetine, allowing the olanzapine/fluoxetine combination to have low treatment-emergent mania rates, similar to olanzapine and placebo. This pattern of results was similar for the YMRS and CGI-BP. However, further research on olanzapine/fluoxetine combination in bipolar depressed patients is needed, as the present results are limited by a small sample size (N = 86) for the olanzapine/fluoxetine combination therapy arm.

The categorical YMRS approach is of interest because it places subjects into groups based on the severity level of their YMRS scores after 8 weeks of exposure to therapy. Although YMRS cutoffs are not well defined in the literature, a YMRS total score of < 5 can be considered as complete remission of mania; a YMRS score < 12 can be considered to be within normal limits; a YMRS score from 13 to 14, hypomania; and a YMRS score ≥ 15, mania. In the present analyses, at endpoint, 93% of olanzapine/fluoxetine combination subjects had YMRS scores within normal limits, with over 75% having YMRS scores less than 5. Very few subjects in any of the groups were in the hypomanic range (YMRS score 13–14), and there were no olanzapine/fluoxetine combination subjects in this range.

The analysis examining predictors of treatment-emergent mania in this sample showed that bipolar I depressed patients with an elevated baseline YMRS score were at greater risk for developing treatment-emergent mania. Specifically, subjects with a baseline YMRS score of 12 or higher had a 4.5 times increased risk of treatment-emergent mania compared to those with a baseline YMRS score of less than 12. These results suggest that patients with mixed features at the beginning of treatment should be closely monitored for signs of treatment-emergent mania during pharmacotherapy.

Limitations of the present analysis included the somewhat arbitrary choice of YMRS score = 15 as a cutoff for treatment-emergent mania. A more stringent definition would also have incorporated the DSM criteria for mania. In addition, the trial was only 8 weeks long, and it is possible that a longer period of follow-up might have revealed a greater number of manic switches. Finally, it is important to note that the present findings pertain to bipolar I depression and may or may not extend to bipolar II depression.

In conclusion, the present analyses did not indicate that acute treatment with olanzapine/fluoxetine combination presents a significant risk of treatment-emergent mania in bipolar depression compared to placebo. However, due to the cyclical nature of bipolar disorder, patients taking olanzapine/fluoxetine combination should still be monitored for signs or symptoms of emerging mania. Together with the primary results of the present study,[16] as well as previously published mania data,[17,18] these results offer additional evidence for the mood-stabilizing properties of olanzapine. Current treatment guidelines for bipolar depression endorse the use of antidepressants in combination with a mood stabilizer.[1] Thus, olanzapine/fluoxetine combination could represent a promising treatment strategy for bipolar depression based on both efficacy[16] and mania-related safety considerations.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), venlafaxine (Effexor).

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