

Efficacy of Olanzapine and Olanzapine-Fluoxetine Combination in the Treatment of Bipolar I Depression

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Background: Despite the longer duration of the depressive phase in bipolar disorder and the frequent clinical use of antidepressants combined with antipsychotics or mood stabilizers, relatively few controlled studies have examined treatment strategies for bipolar depression.

Objective: To examine the use of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression.

Design: Double-blind, 8-week, randomized controlled trial.

Setting: Eighty-four sites (inpatient and outpatient) in 13 countries.

Patients: A total of 833 randomized adults with bipolar I depression with a Montgomery-Åsberg Depression Rating Scale (MADRS) score of at least 20.

Intervention: Patients were randomly assigned to receive placebo (n=377); olanzapine, 5 to 20 mg/d (n=370); or olanzapine-fluoxetine combination, 6 and 25, 6 and 50, or 12 and 50 mg/d (n=86).

Main Outcome Measure: Changes in MADRS total scores using mixed-effects model repeated-measures analyses.

Results: During all 8 study weeks, the olanzapine and olanzapine-fluoxetine groups showed statistically significant improvement in depressive symptoms vs the placebo group ($P < .001$ for all). The olanzapine-fluoxetine group also showed statistically greater improvement than the olanzapine group at weeks 4 through 8. At week 8, MADRS total scores were lower than at baseline by 11.9, 15.0, and 18.5 points in the placebo, olanzapine, and olanzapine-fluoxetine groups, respectively. Remission criteria were met by 24.5% (87/355) of the placebo group, 32.8% (115/351) of the olanzapine group, and 48.8% (40/82) of the olanzapine-fluoxetine group. Treatment-emergent mania (Young Mania Rating Scale score < 15 at baseline and ≥ 15 subsequently) did not differ among groups (placebo, 6.7% [23/345]; olanzapine, 5.7% [19/335]; and olanzapine-fluoxetine, 6.4% [5/78]). Adverse events for olanzapine-fluoxetine therapy were similar to those for olanzapine therapy but also included higher rates of nausea and diarrhea.

Conclusions: Olanzapine is more effective than placebo, and combined olanzapine-fluoxetine is more effective than olanzapine and placebo in the treatment of bipolar I depression without increased risk of developing manic symptoms.

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BIPOLAR DEPRESSION, or the depressive phase of bipolar disorder, represents a difficult-to-treat and disabling form of depression. However, relative to its impact, an insufficient number of studies have explored its treatment. Studies indicate that patients with bipolar disorder spend more time in and take longer to recover from the depressive phase than the manic phase. Judd et al¹ reported that patients with bipolar disorder experience depressive symptoms more than 3 times longer than they experience manic symptoms. Keller et al,² using a naturalistic study design, found that the median time to recovery from the

depressive phase was 9 weeks but from the manic phase was 5 weeks and that 22% of patients in the depressive phase but only 7% in the manic phase remained ill for at least 1 year. Moreover, Hlastala et al,³ in a controlled study of maintenance therapies, found that the median time to full remission was 16.8 weeks for a manic episode but 40.0 weeks for a depressive episode. In addition to being longer and more persistent, the depressive phase of bipolar disorder is associated with higher rates of morbidity and mortality. Dilts et al⁴ reported the relative risk of suicidality among patients with bipolar depression to be 34.9 times greater than that among patients with pure mania. Depres-

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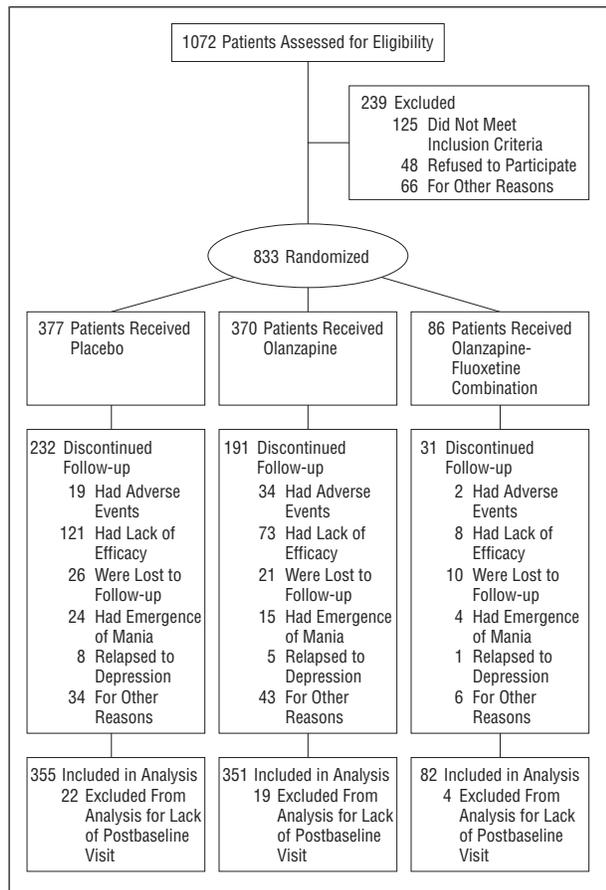


Figure 1. Flow diagram of patient progress through phases of the study.

sive symptoms have also been found to be a strong predictor of disability in patients with bipolar disorder.⁵

Nevertheless, despite the clear clinical and public health implications of these findings, treatment of bipolar depression remains an understudied area, as clinicians and researchers have historically focused more on treatment of mania.⁶ Although a wide range of mood-stabilizing medications is available, treatment options for bipolar depression remain more limited, and no medication has been formally approved for this indication. At present, the 2002 treatment guidelines from the American Psychiatric Association recommend either lithium or lamotrigine as first-line treatment.⁷ Although reviews^{8,9} of clinical trials have concluded that there is evidence of lithium's acute efficacy for bipolar depression, patients in those clinical trials frequently did not achieve a full response.¹⁰ Anticonvulsants such as lamotrigine and valproate sodium have also been used to treat bipolar depression.^{11,12} However, although Calabrese and colleagues¹¹ reported the antidepressant efficacy of lamotrigine therapy in a placebo-controlled trial of patients with bipolar depression, lamotrigine requires a slow upward titration to avoid the risk of rash.^{11,13} Other common treatments include the adjunctive use of antidepressants with a mood stabilizer. However, some antidepressants, particularly tricyclics, are problematic for their potential to induce mania or hypomania or to accelerate cycling.^{14,15} Thus, alternative effective and safe treatment options are needed.

Olanzapine has demonstrated efficacy in the treatment of acute bipolar mania¹⁶⁻¹⁸ and has been found to improve depressive symptoms in patients with schizophrenia.¹⁹ The present study was thus designed to test the antidepressant efficacy of olanzapine in treating the depressive phase of bipolar I disorder. For exploratory purposes, a small group of patients was treated with olanzapine combined with the selective serotonin reuptake inhibitor fluoxetine. The olanzapine-fluoxetine combination was previously found to be effective in a small sample of patients with treatment-resistant unipolar depression.²⁰ The present study represents the first controlled trial, to our knowledge, of an atypical antipsychotic agent alone or combined with an antidepressant for the treatment of bipolar depression.

METHODS

STUDY DESIGN

The primary objective of this 8-week, randomized, double-blind, parallel study was to compare the efficacy and safety of olanzapine monotherapy and placebo in the treatment of bipolar I disorder, depressed. An olanzapine-fluoxetine combination treatment arm was also included concurrently for exploratory purposes. Qualified patients who completed a 2- to 14-day screening and washout period were therefore randomized in a 4:4:1 allocation, as specified in the protocol, to receive olanzapine, 5 to 20 mg/d (n=370); placebo (n=377); or olanzapine-fluoxetine combination, 6 and 25, 6 and 50, or 12 and 50 mg/d (n=86) in a flexible dosing schedule. Olanzapine monotherapy was initiated at 5 mg and could be adjusted upward in increments of 5 mg/d. Olanzapine-fluoxetine combination therapy was initiated at 6 and 25 mg/d but could be administered at 6 and 50 or 12 and 50 mg/d after at least 1 day at each dose. No other dose combinations were allowed. Combination dosing was based on the positive findings from a study²⁰ of patients with treatment-resistant depression. Olanzapine and fluoxetine were administered as separate capsules, taken together once daily in the evening. Patients receiving placebo or olanzapine monotherapy also received 2 pills per day. Randomization was stratified by site and used a blinded voice response system. All clinical and statistical investigators, site personnel, and patients were blinded to treatment.

Patients were permitted adjunctive use of benzodiazepines (up to 2 mg of lorazepam equivalents per day) throughout the screening and acute therapy phases of the study. Anticholinergic therapy (benztropine mesylate or biperiden, ≤6 mg/d, or trihexyphenidyl, ≤12 mg/d) was permitted throughout the study for treatment of extrapyramidal symptoms but not for prophylaxis. Use of other psychotropic drugs was not permitted, and all such medication was tapered during the 2- to 14-day screening period at the discretion of the investigator and was completed at least 1 day before randomization.

PATIENTS

All patients were 18 years or older and met DSM-IV²¹ criteria for bipolar I disorder, depressed. A total of 1072 patients were recruited from the inpatient and outpatient services of 84 study sites in 13 countries between June 1, 2000, and December 31, 2001 (Figure 1). Diagnosis was confirmed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Patient Version.²² Patients were required to have a Montgomery-Åsberg Depression Rating Scale (MADRS)²³ total score of at least 20 at the screening visit and at the time of

Table 1. Patient and Illness Characteristics at Baseline

Characteristic	Placebo Group (n = 377)	Olanzapine Group (n = 370)	OFC Group (n = 86)	Total (N = 833)	P Value
Age, mean (SD), y	41.7 (12.4)	42.2 (12.5)	40.3 (13.0)	41.8 (12.5)	.91*
Women, %	62.6	62.4	67.4	63.0	.68
White, %	82.2	84.1	77.9	82.6	.52
Inpatients, %	13.3	13.8	9.3	13.1	.57
Psychotic features, %	12.7	13.5	7.0	12.5	.25
Melancholic features, %	67.9	66.5	62.8	66.7	.68
Atypical features, %	7.7	9.2	7.0	8.3	.89
Rapid cycling course, %†	35.0	38.4	39.5	37.0	.82
Manic or mixed episode in the past 12 mo, %‡	77.8	83.5	80.5	80.7	.20
Length of current depressive episode, median, d	82	63	81	73	.006§

Abbreviation: OFC, olanzapine-fluoxetine combination.

* $F_{2,809} = 0.1$.

†Rapid cycling was defined as more than 4 mood episodes (depressive, manic, or mixed) in the past 12 months.

‡Based on available data (placebo group, n = 302; olanzapine group, n = 310; and OFC group, n = 66).

§ $\chi^2_2 = 10.38$.

randomization. Patients were also required to have a history of at least 1 previous manic or mixed episode of sufficient severity to require treatment with a mood stabilizer or an antipsychotic agent. Exclusion criteria included a history of alcohol or substance dependence within the previous 3 months, suicidal behavior within the previous 3 months, or an unstable or untreated medical disorder. For safety reasons, any patient with worsening of manic symptoms, as verified by a score of 15 or greater on the Young Mania Rating Scale (YMRS)²⁴ during weeks 1 to 3 of treatment, was discontinued from the study. Before participation, all patients provided written informed consent; the study was approved by the institutional review board at each site.

ASSESSMENTS

Clinical visits were conducted at baseline and at weeks 1, 2, 3, 4, 6, and 8. The protocol-defined primary measure of efficacy was the change in MADRS total score from baseline to week 8. Secondary efficacy measures included the Clinical Global Impressions Bipolar Version–Severity of Depression scale (CGI-BP-S),²⁵ the YMRS, and the Hamilton Anxiety Rating scale (HAM-A).²⁶ Rates of and time to response and remission were also assessed. Response was defined as 50% or greater improvement in the MADRS total score from baseline to an end point and completion of at least 4 weeks of study. Remission was defined as a MADRS total score of 12 or less at an end point and completion of at least 4 weeks of study.

Screening included a standard history and physical examination, psychiatric examination, laboratory profile, and electrocardiogram. Adverse events were recorded at each visit and were coded using the *Coding Symbol for Thesaurus of Adverse Reaction Terms*.²⁷ Extrapyramidal symptoms were assessed using the Simpson-Angus Rating Scale²⁸ and the Abnormal Involuntary Movement Scale.²⁹ Adverse events or abnormal values that originally occurred or worsened in severity during double-blind therapy were considered treatment emergent.

STATISTICAL ANALYSIS

All analyses were conducted on an intent-to-treat basis and were performed using statistical software (SAS version 6.09; SAS Institute Inc, Cary, NC). Treatment effects were tested at a 2-tailed α level of .05. Interaction effects were tested at a 2-tailed α level of .10. As specified a priori, analysis of the primary measure of efficacy was performed using a mixed-effects model repeated-measures (MMRM) method, which has been shown to provide

highly accurate modeling of treatment outcome while accounting for nonrandom missing data (ie, patient dropout).^{30,31} Initially, an unstructured covariance matrix was used to model within-patient error. Independent factors included in this model were treatment, investigator, treatment \times investigator interaction, visit, and treatment \times visit interaction, with the treatment \times investigator interaction excluded if not statistically significant. Next, the best-fit covariance structure for each analysis was determined using a maximum Schwartz's Bayesian criterion and is reported in the tables. Possible structures included autoregressive, banded Toeplitz, compound symmetric with or without heterogeneous variances, spatial power, and unstructured. Treatment differences for each visit were tested using a single *df* contrast, based on least squares means from the final model. Inference from the repeated-measures analyses was based on the restricted maximum likelihood solution and on approximated F tests and t tests using *df*s estimated by Satterthwaite's approximation. The MADRS items and secondary efficacy measures were similarly analyzed, except for the HAM-A, which used an analysis of variance (ANOVA) model due to assessments being taken only at baseline and an end point on that measure. Thus, all reported MADRS, MADRS item, CGI-BP-S, and YMRS mean change scores represent least squares means. The MMRM analyses were performed using the SAS PROC MIXED procedure, version 6.09 (SAS Institute Inc, Cary, NC).

The ANOVA models were also used to evaluate safety data, using mean change from baseline to end point based on a last-observation-carried-forward strategy. These models included terms for treatment and country plus treatment \times country interaction if statistically significant. The Kruskal-Wallis test was used to analyze baseline length of the current episode because of the presence of outliers. The Fisher exact test was used to analyze treatment differences for categorical patient and illness characteristics. Odds ratios (and 95% confidence intervals [CI]) characterize group differences in clinical response. Kaplan-Meier analysis and the log-rank test were used to compare treatment groups for time-to-event data.

RESULTS

PATIENTS

A total of 833 patients were enrolled and randomized to treatment groups. The baseline characteristics of each group are given in **Table 1**. All of the groups were mod-

Table 2. Patient Disposition

Variable	Placebo Group (n = 377)	Olanzapine Group (n = 370)	OFC Group (n = 86)	P Value		
				Placebo vs Olanzapine	Placebo vs OFC	OFC vs Olanzapine
Weeks completed, No. (%)						
2	317 (84.1)	304 (82.2)	76 (88.4)	NA	NA	NA
4	200 (53.1)	233 (63.0)	65 (75.6)	NA	NA	NA
8	145 (38.5)	179 (48.4)	55 (64.0)	.006	.001	.01
Discontinued treatment, No. (%)						
Adverse events	19 (5.0)	34 (9.2)	2 (2.3)	.03	.39	.04
Lack of efficacy	121 (32.1)	73 (19.7)	8 (9.3)	.001	.001	.03
Lost to follow-up	26 (6.9)	21 (5.7)	10 (11.6)	.55	.18	.06
Emergence of mania	24 (6.4)	15 (4.1)	4 (4.7)	.19	.80	.77
Relapse to depression	8 (2.1)	5 (1.4)	1 (1.2)	.58	>.99	>.99
Other reasons	34 (9.0)	43 (11.6)	6 (7.0)	.28	.67	.25
Subtotal	232 (61.5)	191 (51.6)	31 (36.0)			
Time to discontinuation, median (mean ± SE), d*	41 (43.1 ± 1.2)	56 (45.8 ± 1.2)	65 (53.2 ± 2.3)	.02	<.001	.006

Abbreviations: NA, not applicable; OFC, olanzapine-fluoxetine combination.

*Time to discontinuation uses Kaplan-Meier survival analysis, with curves compared using the log-rank test.

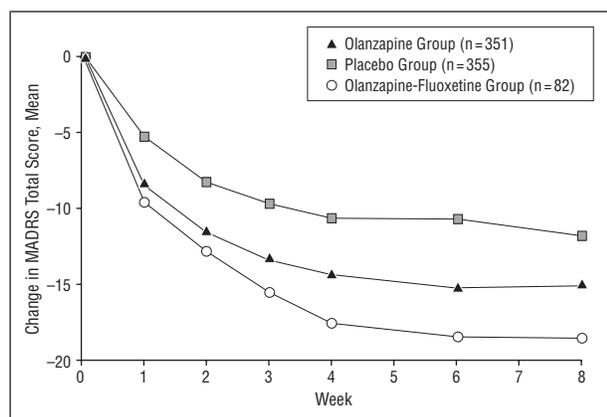


Figure 2. Least squares mean change in Montgomery-Åsberg Depression Rating Scale (MADRS) total scores during the 8-week study. Improvement in MADRS scores with use of olanzapine and the olanzapine-fluoxetine combination was significantly greater than with use of placebo throughout the study ($P < .001$). Improvement in MADRS scores with use of olanzapine-fluoxetine combination was significantly greater than with use of olanzapine at weeks 4 to 8 ($P < .02$).

erately to severely depressed, with baseline mean MADRS scores of 31.3, 32.6, and 30.8 for the placebo, olanzapine, and olanzapine-fluoxetine groups, respectively. Length of current depressive episode was statistically significantly shorter for the olanzapine group.

Mean modal drug dose for the olanzapine monotherapy group was 9.7 mg/d. Mean drug dose for the combination group was 7.4 mg/d for olanzapine and 39.3 mg/d for fluoxetine. The percentage of patients who used benzodiazepines at least once during the study was not statistically significantly different among groups (placebo group, 43.5%; olanzapine group, 43.0%; olanzapine-fluoxetine group, 36.0%; overall $P = .44$).

PATIENT DISPOSITION

Rates of study completion and reasons for discontinuation are reported in **Table 2**. Patients taking olanzapine-fluoxetine had the highest rates of completion (64.0%)

and were less likely to discontinue due to lack of efficacy or adverse events. The most frequent adverse event resulting in discontinuation from the olanzapine monotherapy group was somnolence. There were no differences among groups in the rate of discontinuation due to emergence of mania. Three patients (all in the placebo group) died during the study: 1 was a homicide victim and 2 committed suicide.

Times to study discontinuation are also reported in **Table 2**. Median estimated times to discontinuation for any reason were 41, 56, and 65 days for the placebo, olanzapine, and olanzapine-fluoxetine groups, respectively, with patients in the placebo group discontinuing significantly earlier than those in the olanzapine group (log-rank test $\chi^2_1 = 5.06$; $P = .02$) or the olanzapine-fluoxetine group (log-rank test $\chi^2_1 = 17.02$; $P < .001$) and with those in the olanzapine group discontinuing earlier than those in the olanzapine-fluoxetine group (log-rank test $\chi^2_1 = 7.68$; $P = .006$).

EFFICACY

Mean \pm SD baseline MADRS scores ranged from 30.8 \pm 6.1 to 32.6 \pm 6.2. The MMRM analyses of visitwise mean changes in MADRS scores are depicted in **Figure 2**. There were significant main effects for treatment ($F_{2,806} = 25.14$; $P < .001$) and for visit ($F_{5,1036} = 55.91$; $P < .001$), with no significant treatment \times visit interaction ($F_{10,1044} = 1.01$; $P = .43$). Between-group comparisons for visitwise MADRS mean change scores are given in **Table 3**. Starting as early as week 1 and continuing throughout the study, the olanzapine and olanzapine-fluoxetine groups demonstrated significantly greater mean improvements in MADRS total scores than those receiving placebo. Starting at week 4 and continuing to week 8, the olanzapine-fluoxetine group also demonstrated significantly greater mean improvement in MADRS total scores than the olanzapine monotherapy group. The therapeutic effect sizes for olanzapine and olanzapine-fluoxetine were 0.32 and 0.68, respectively. Due to the differences among groups in epi-

Table 3. Visitwise MADRS Mean Change Scores (MMRM Analysis)*

Treatment Group	Change in MADRS Score, Mean ± SE (95% CI)	vs Placebo			vs Olanzapine		
		t Test	df	P Value	t Test	df	P Value
Week 1							
Placebo	-5.2 ± 0.5 (-6.2 to -4.2)	NA	NA	NA	NA	NA	NA
Olanzapine	-8.5 ± 0.5 (-9.5 to -7.5)	-5.19	896	<.001	NA	NA	NA
OFC	-9.6 ± 0.9 (-11.5 to -7.8)	-4.27	896	<.001	-1.09	896	.28
Week 2							
Placebo	-8.3 ± 0.6 (-9.4 to -7.1)	NA	NA	NA	NA	NA	NA
Olanzapine	-11.5 ± 0.6 (-12.6 to -10.3)	-4.42	858	<.001	NA	NA	NA
OFC	-12.8 ± 1.1 (-14.9 to -10.7)	-3.92	841	<.001	-1.17	843	.24
Week 3							
Placebo	-9.6 ± 0.6 (-10.8 to -8.5)	NA	NA	NA	NA	NA	NA
Olanzapine	-13.3 ± 0.6 (-14.5 to -12.2)	-4.77	819	<.001	NA	NA	NA
OFC	-15.5 ± 1.1 (-17.7 to -13.3)	-4.71	808	<.001	-1.74	810	.08
Week 4							
Placebo	-10.7 ± 0.6 (-11.9 to -9.5)	NA	NA	NA	NA	NA	NA
Olanzapine	-14.3 ± 0.6 (-15.5 to -13.0)	-4.36	807	<.001	NA	NA	NA
OFC	-17.5 ± 1.2 (-19.9 to -15.2)	-5.21	794	<.001	-2.49	797	.01
Week 6							
Placebo	-10.7 ± 0.7 (-12.1 to -9.4)	NA	NA	NA	NA	NA	NA
Olanzapine	-15.1 ± 0.7 (-16.5 to -13.8)	-4.89	726	<.001	NA	NA	NA
OFC	-18.5 ± 1.3 (-21.0 to -16.0)	-5.56	696	<.001	-2.41	689	.02
Week 8							
Placebo	-11.9 ± 0.8 (-13.4 to -10.4)	NA	NA	NA	NA	NA	NA
Olanzapine	-15.0 ± 0.7 (-16.4 to -13.6)	-3.13	596	.002	NA	NA	NA
OFC	-18.5 ± 1.3 (-21.1 to -16.0)	-4.53	577	<.001	-2.46	571	.01

Abbreviations: CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model repeated-measures; NA, not applicable; OFC, olanzapine-fluoxetine combination.

*Baseline MADRS scores, mean ± SE: placebo group, 31.3 ± 0.3; olanzapine group, 32.6 ± 0.3; OFC group, 30.8 ± 0.7. The MMRM analysis used a heterogeneous banded Toeplitz structure for the within-patient error covariance structure.

sode length, this variable was subsequently entered into the MMRM model. After adjustment for episode length, week 8 MADRS mean ± SE change scores were -11.9 ± 0.8, -15.0 ± 0.7, and -18.6 ± 1.3 for the placebo, olanzapine, and olanzapine-fluoxetine groups, respectively. Because episode length was not a significant predictor of MADRS change score in this model ($F_{1,864} = 0.06$; $P = .81$) and resulted in negligible adjustment to the scores, Table 3 reports the MADRS mean change scores without this adjustment.

The response rate for the olanzapine group was 39.0% (137/351), which was significantly higher than the rate for the placebo group of 30.4% (108/355; $P = .02$; odds ratio, 1.46; 95% CI, 1.07-2.00). The response rate for the olanzapine-fluoxetine group was 56.1% (46/82), which was significantly higher than that for the placebo ($P < .001$; odds ratio, 2.92; 95% CI, 1.79-4.80) and olanzapine ($P = .006$; odds ratio, 2.00; 95% CI, 1.23-3.26) groups. Median times to response for the placebo, olanzapine, and olanzapine-fluoxetine groups were 59, 55, and 21 days, respectively (**Figure 3**). Time to response was significantly shorter for the olanzapine group compared with the placebo group (log-rank test $\chi^2_1 = 6.62$; $P = .01$) and shorter still for the olanzapine-fluoxetine group compared with the placebo (log-rank test $\chi^2_1 = 23.78$; $P < .001$) and olanzapine (log-rank test $\chi^2_1 = 7.93$; $P = .005$) groups.

The remission rate for the olanzapine group was 32.8% (115/351), which was significantly higher than the rate for the placebo group of 24.5% (87/355; $P = .02$). The remission rate for the olanzapine-fluoxetine group was

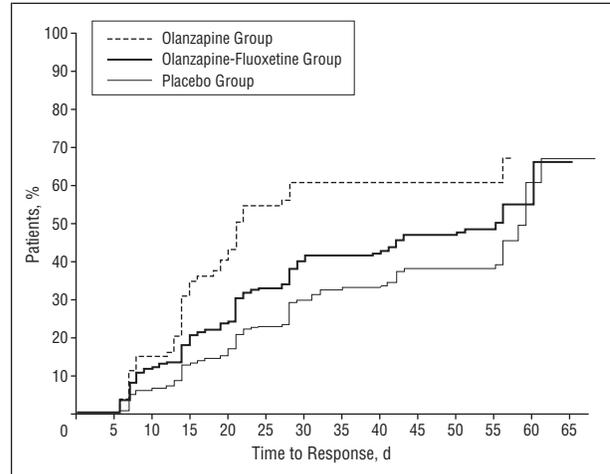


Figure 3. Kaplan-Meier estimates of time to response. Response is defined as a decrease in Montgomery-Åsberg Depression Rating Scale total score of 50% or more after at least 4 weeks of treatment. Median time to response for the olanzapine group (55 days) was significantly earlier compared with the placebo group (59 days). Median time to response for the combined olanzapine-fluoxetine combination group (21 days) was significantly earlier than for the olanzapine and placebo groups.

48.8% (40/82), which was significantly higher than that for the placebo ($P < .001$) and olanzapine ($P = .007$) groups. Median estimated times to remission for the placebo, olanzapine, and combination groups were 59, 57, and 42 days, respectively. Time to remission was significantly shorter for the olanzapine group compared with the placebo group

Table 4. Change in MADRS Item Scores Between Baseline and Week 8 (MMRM Analysis)*

Item and Treatment Group	Baseline Score, Mean ± SE	Change in Item Score, Mean ± SE (95% CI)	vs Placebo			vs Olanzapine		
			t Test	df	P Value	t Test	df	P Value
1. Apparent sadness								
Placebo	3.5 ± 0.1	-1.3 ± 0.1 (-1.5 to -1.1)	NA	NA	NA	NA	NA	NA
Olanzapine	3.8 ± 0.1	-1.5 ± 0.1 (-1.7 to -1.3)	-1.74	2439	.08	NA	NA	NA
OFC	3.6 ± 0.1	-2.1 ± 0.2 (-2.4 to -1.7)	-3.69	2122	<.001	-2.56	2034	.01
2. Reported sadness								
Placebo	4.0 ± 0.1	-1.5 ± 0.1 (-1.8 to -1.3)	NA	NA	NA	NA	NA	NA
Olanzapine	4.1 ± 0.1	-1.8 ± 0.1 (-2.0 to -1.5)	-1.48	550	.14	NA	NA	NA
OFC	3.8 ± 0.1	-2.2 ± 0.2 (-2.6 to -1.8)	-2.98	537	.003	-2.01	532	.045
3. Inner tension								
Placebo	3.3 ± 0.1	-1.0 ± 0.1 (-1.2 to -0.8)	NA	NA	NA	NA	NA	NA
Olanzapine	3.4 ± 0.1	-1.4 ± 0.1 (-1.5 to -1.2)	-2.56	2522	.01	NA	NA	NA
OFC	3.2 ± 0.1	-1.7 ± 0.2 (-2.0 to -1.4)	-3.46	2240	<.001	-1.75	2153	.08
4. Reduced sleep								
Placebo	3.1 ± 0.1	-1.3 ± 0.1 (-1.6 to -1.0)	NA	NA	NA	NA	NA	NA
Olanzapine	3.2 ± 0.1	-2.0 ± 0.1 (-2.3 to -1.8)	-4.05	2298	<.001	NA	NA	NA
OFC	3.2 ± 0.2	-2.3 ± 0.2 (-2.8 to -1.9)	-3.83	1986	<.001	-1.12	1903	.26
5. Reduced appetite								
Placebo	1.8 ± 0.1	-0.7 ± 0.1 (-1.0 to -0.5)	NA	NA	NA	NA	NA	NA
Olanzapine	2.0 ± 0.1	-1.4 ± 0.1 (-1.6 to -1.1)	-3.98	1938	<.001	NA	NA	NA
OFC	1.6 ± 0.2	-1.2 ± 0.2 (-1.7 to -0.8)	-2.09	1643	.04	0.55	1577	.58
6. Concentration difficulties								
Placebo	3.4 ± 0.1	-1.4 ± 0.1 (-1.7 to -1.2)	NA	NA	NA	NA	NA	NA
Olanzapine	3.4 ± 0.1	-1.7 ± 0.1 (-1.9 to -1.5)	-1.59	554	.11	NA	NA	NA
OFC	3.3 ± 0.1	-1.6 ± 0.2 (-2.0 to -1.2)	-0.72	538	.47	0.36	533	.72
7. Lassitude								
Placebo	3.5 ± 0.1	-1.5 ± 0.1 (-1.7 to -1.2)	NA	NA	NA	NA	NA	NA
Olanzapine	3.5 ± 0.1	-1.5 ± 0.1 (-1.7 to -1.2)	-0.01	2388	.99	NA	NA	NA
OFC	3.7 ± 0.1	-2.1 ± 0.2 (-2.5 to -1.6)	-2.48	2063	.01	-2.51	1976	.01
8. Inability to feel								
Placebo	3.6 ± 0.1	-1.6 ± 0.1 (-1.9 to -1.4)	NA	NA	NA	NA	NA	NA
Olanzapine	3.6 ± 0.1	-1.6 ± 0.1 (-1.9 to -1.4)	-0.13	2469	.90	NA	NA	NA
OFC	3.5 ± 0.1	-2.3 ± 0.2 (-2.7 to -1.9)	-3.13	2157	.002	-3.10	2069	.002
9. Pessimistic thoughts								
Placebo	3.3 ± 0.1	-1.3 ± 0.1 (-1.5 to -1.1)	NA	NA	NA	NA	NA	NA
Olanzapine	3.3 ± 0.1	-1.4 ± 0.1 (-1.6 to -1.2)	-1.07	2471	.29	NA	NA	NA
OFC	3.2 ± 0.1	-2.0 ± 0.2 (-2.3 to -1.6)	-3.35	2140	<.001	-2.67	2050	.008
10. Suicidal thoughts								
Placebo	1.9 ± 0.1	-0.9 ± 0.1 (-1.1 to -0.7)	NA	NA	NA	NA	NA	NA
Olanzapine	2.0 ± 0.1	-1.1 ± 0.1 (-1.3 to -0.9)	-1.68	2149	.09	NA	NA	NA
OFC	1.8 ± 0.1	-1.2 ± 0.2 (-1.5 to -0.9)	-1.69	1830	.09	-0.57	1753	.57

Abbreviations: CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model repeated-measures; NA, not applicable; OFC, olanzapine-fluoxetine combination.

*The MMRM analysis used a banded Toeplitz structure for the within-patient error covariance structure based on maximum Schwartz's Bayesian criterion for items 1, 3, 4, 5, 7, 8, 9, and 10 and a heterogeneous banded Toeplitz structure for the within-patient error covariance structure based on maximum Schwartz's Bayesian criterion for items 2 and 6.

(log-rank test $\chi^2_1=5.05$; $P=.02$) and again significantly shorter for the olanzapine-fluoxetine group compared with the placebo (log-rank test $\chi^2_1=17.95$; $P<.001$) and olanzapine (log-rank test $\chi^2_1=6.01$; $P=.01$) groups.

Analyses of the individual MADRS items are given in **Table 4**. The olanzapine and olanzapine-fluoxetine groups showed statistically significant improvements on inner tension, reduced sleep, and reduced appetite compared with the placebo group. In addition, the olanzapine-fluoxetine group showed statistically significant improvement on core mood items, including apparent sadness, reported sadness, lassitude, inability to feel, and pessimistic thoughts, compared with the olanzapine and placebo groups.

Analyses of the secondary measures of efficacy are given in **Table 5**. The olanzapine group showed greater

mean improvement on the CGI-BP-S than the placebo group, and the olanzapine-fluoxetine group showed greater mean improvement than the placebo and olanzapine groups. In addition, the olanzapine and olanzapine-fluoxetine groups showed greater mean improvement on the HAM-A than the placebo group but were not significantly different from each other.

TREATMENT-EMERGENT MANIA

Treatment-emergent mania was defined as a YMRS score less than 15 at baseline and 15 or greater at any time thereafter. In all 3 groups, the incidence of treatment-emergent mania was low, and there were no statistically significant differences among groups ($P=.86$). Rates of treatment-emergent mania were 6.7% (23/345) for the

Table 5. Change in Scores From Baseline for Secondary Measures of Efficacy

Item and Treatment Group	Patients, No.	Mean ± SD Baseline Score	Change in Score, Mean ± SE (95% CI)	vs Placebo			vs Olanzapine		
				t Test	df	P Value	t Test	df	P Value
YMRS*									
Placebo	355	4.8 ± 4.6	-0.1 ± 0.3 (-0.8 to 0.6)	NA	NA	NA	NA	NA	NA
Olanzapine	351	5.0 ± 4.8	-1.4 ± 0.3 (-2.0 to -0.8)	-3.04	2170	.002	NA	NA	NA
OFC	82	5.0 ± 4.8	-1.9 ± 0.6 (-3.0 to -0.8)	-2.91	1868	.004	-0.88	1791	.38
CGI-BP-S*									
Placebo	355	4.8 ± 0.8	-1.2 ± 0.1 (-1.4 to -1.0)	NA	NA	NA	NA	NA	NA
Olanzapine	351	4.9 ± 0.8	-1.6 ± 0.1 (-1.8 to -1.4)	-2.90	575	.004	NA	NA	NA
OFC	82	4.8 ± 0.7	-2.2 ± 0.2 (-2.5 to -1.8)	-4.49	559	<.001	-2.57	553	.01
HAM-A†									
Placebo	315	16.7 ± 0.4	-3.5 ± 0.4 (-4.4 to -2.7)	NA	NA	NA	NA	NA	NA
Olanzapine	309	17.1 ± 0.4	-5.5 ± 0.4 (-6.4 to -4.6)	F = 31.1	1,685	.002	NA	NA	NA
OFC	71	15.8 ± 1.0	-7.0 ± 1.0 (-9.0 to -4.9)	F = 11.3	1,685	<.001	F = 2.0	1,685	.16

Abbreviations: CI, confidence interval; CGI-BP-S, Clinical Global Impressions Bipolar Version–Severity of Depression; HAM-A, Hamilton Anxiety Rating Scale; NA, not applicable; YMRS, Young Mania Rating Scale.

*Analyses use mixed-effects model repeated-measures (MMRM) and report mean change at week 8. The MMRM analysis used a banded Toeplitz structure for the YMRS and a heterogeneous banded Toeplitz for the CGI-BP-S for the within-patient error covariance structure based on maximum Schwartz's Bayesian Criterion for each.

†These data were collected at baseline and end point only; therefore, analyses use analysis of variance and report mean change at the patient's end point.

Table 6. Treatment-Emergent Adverse Events Reported by 10% or More of Patients in Any Group

Adverse Event	Patients, %			P Value		
	Olanzapine Group (n = 370)	OFC Group (n = 86)	Placebo Group (n = 377)	Olanzapine vs Placebo	OFC vs Placebo	Olanzapine vs OFC
Somnolence	28.1	20.9	12.5	<.001	.06	.22
Weight gain	17.3	17.4	2.7	<.001	<.001	>.99
Increased appetite	13.5	12.8	5.0	<.001	.01	>.99
Headache	12.4	14.0	18.6	.03	.35	.72
Dry mouth	11.1	16.3	6.1	.02	.004	.20
Nervousness	10.5	9.3	8.0	.26	.66	.84
Asthenia	9.7	12.8	3.2	<.001	<.001	.43
Insomnia	8.4	9.3	15.1	.005	.23	.83
Diarrhea	6.5	18.6	6.6	>.99	.001	.001
Nausea	4.3	11.6	8.8	.02	.41	.02

Abbreviation: OFC, olanzapine-fluoxetine combination.

placebo group, 5.7% (19/335) for the olanzapine group, and 6.4% (5/78) for the olanzapine-fluoxetine group. Mean change scores on the YMRS are reported in Table 5. Mean mania scores decreased significantly in the olanzapine and olanzapine-fluoxetine groups compared with the placebo group, with no significant difference between the olanzapine and olanzapine-fluoxetine groups.

SAFETY

Adverse events that emerged during the study or that were present at baseline and then worsened in severity were considered treatment emergent. **Table 6** lists treatment-emergent adverse events reported by 10% or more of patients in any treatment group. The adverse event profile for olanzapine-fluoxetine combination therapy was similar to that for olanzapine monotherapy but also included statistically significantly higher rates of nausea and diarrhea.

Mean change in and emergence of extrapyramidal symptoms were low, with no statistically significant differences across treatment groups. The percentage of pa-

tients who used anticholinergic medications at least once during the trial was statistically significantly greater in the olanzapine-fluoxetine group (8.1% [7/86]) compared with the olanzapine group (2.8% [10/360]; $P = .03$) but not the placebo group (3.7% [14/377]; $P = .09$).

Mean ± SD weight gain was higher in treated patients than in those who received placebo (olanzapine vs placebo: 2.59 ± 3.24 kg vs -0.47 ± 2.62 kg, $F_{1,774} = 194.36$, $P < .001$; olanzapine-fluoxetine vs placebo: 2.79 ± 3.23 kg vs -0.47 ± 2.62 kg, $F_{1,774} = 80.87$, $P < .001$). Weight gain was not significantly different between the olanzapine and olanzapine-fluoxetine groups ($F_{1,774} = 0.16$; $P = .69$). In addition, the percentage of patients who had a potentially clinically significant change in weight, defined as a 7% or greater increase from baseline, was significantly greater for the olanzapine (18.7% [65/347]) and olanzapine-fluoxetine (19.5% [16/82]) groups compared with the placebo group (0.3% [1/355]) ($P < .001$ for all) but did not differ between the olanzapine and olanzapine-fluoxetine groups ($P = .88$). In the olanzapine-fluoxetine group, 7.3% (6/82) of the patients had potentially clinically relevant orthostatic hypo-

tension, defined as a 30 mm Hg or greater decrease in systolic blood pressure from supine to standing. This percentage was significantly greater than that in the placebo (1.4% [5/352]; $P=.008$) and olanzapine (1.4% [5/346]; $P=.009$) groups. In addition, 4.9% (4/82) of the olanzapine-fluoxetine group had a potentially clinically relevant increase in high supine systolic blood pressure (≥ 180 mm Hg with an increase ≥ 20 mm Hg); this percentage was significantly greater than that in the olanzapine group (0.6% [2/349]; $P=.01$) but not that in the placebo group (1.7% [6/354]; $P=.10$). There were no clinically relevant QT prolongations. Only 2 women (1 in the placebo group and 1 in the olanzapine group) had treatment-emergent QTc intervals of 470 milliseconds or greater, and no men had treatment-emergent QTc of 450 milliseconds or greater (Frierdericia corrected).

Mean \pm SD baseline cholesterol levels were high across all groups (207 \pm 47 mg/dL [5.35 \pm 1.21 mmol/L] for placebo, 206 \pm 46 mg/dL [5.34 \pm 1.18 mmol/L] for olanzapine, and 207 \pm 68 mg/dL [5.36 \pm 1.75 mmol/L] for olanzapine-fluoxetine) but increased significantly at the end point for the olanzapine (6 \pm 31 mg/dL [0.16 \pm 0.80 mmol/L]; $F_{1,667}=16.66$; $P<.001$) and olanzapine-fluoxetine (10 \pm 67 mg/dL [0.27 \pm 1.74 mmol/L]; $F_{1,667}=11.54$; $P<.001$) groups compared with the placebo group (-6 \pm 30 mg/dL [-0.15 \pm 0.78 mmol/L]), with no significant difference between the olanzapine and olanzapine-fluoxetine groups ($F_{1,667}=0.82$; $P=.37$). Mean \pm SD changes in nonfasting glucose levels were significantly higher for the olanzapine (4 \pm 30 mg/dL [0.2 \pm 1.7 mmol/L]; $F_{1,658}=5.41$; $P=.02$) and olanzapine-fluoxetine (6 \pm 40 mg/dL [0.3 \pm 2.2 mmol/L]; $F_{1,658}=9.99$; $P=.002$) groups compared with the placebo group (-4 \pm 26 mg/dL [-0.2 \pm 1.5 mmol/L]), with no significant difference between the olanzapine and olanzapine-fluoxetine groups ($F_{1,658}=0.16$; $P=.69$). The incidence of treatment-emergent glucose elevation of 200 mg/dL or greater (≥ 11.1 mmol/L) was 0.3% (1/298) for the placebo group, 1.4% (4/289) for the olanzapine group, and 1.5% (1/65) for the olanzapine-fluoxetine group. These percentages were not significantly different (overall $P=.30$).

COMMENT

To our knowledge, this is the first placebo-controlled trial comparing the use of an antipsychotic or mood-stabilizing agent alone and in combination with an antidepressant agent. Results indicate that olanzapine therapy significantly improved depressive symptoms in patients with bipolar depression and that the olanzapine-fluoxetine combination had an even more robust antidepressant effect without a greater risk of switch into mania. The reduction in depressive symptoms by both therapies was evident by week 1 of acute therapy and was maintained throughout the 8-week trial. The olanzapine-fluoxetine combination was statistically significantly superior in all efficacy measures of depression compared with olanzapine monotherapy, including higher completion rates, lower discontinuation rates due to adverse events, higher rates of response and remission, and quicker times to response and remission. Analysis of the individual items on the MADRS indicated that the olanzapine-

fluoxetine combination, but not olanzapine, was effective at reducing core mood symptoms of depression.

Despite some methodological and sample differences, the present findings may be compared with those of a recent double-blind, placebo-controlled, 7-week study of lamotrigine therapy for bipolar I depression.¹¹ In that study, patients receiving lamotrigine had MADRS response rates of 48% to 54%, depending on dose, with a placebo response rate of 29%. The present study had response rates of 39% for olanzapine and 56% for olanzapine-fluoxetine, with a placebo response rate of 30%. Note, however, that the present study required at least 4 weeks of treatment to be eligible for response. Also, comparison of baseline illness characteristics indicates that the lamotrigine sample may have been less symptomatic, as indicated by fewer melancholic patients, no inpatients, and no patients with a rapid cycling course.

Divalproex sodium, another anticonvulsant agent known to be effective in treating bipolar mania,^{32,33} has also been studied in bipolar depression. In an 8-week, double-blind pilot study of bipolar I and II patients with major depression, Sachs and collaborators³⁴ found that patients treated with divalproex had a recovery rate of 43% compared with the placebo rate of 27%, with recovery defined as a 50% improvement on the Hamilton Depression Rating Scale and a YMRS score less than 10. However, this difference was not statistically significant.

Regarding the possibility of treatment-emergent mania, the present findings indicate no additional risk when fluoxetine was added to olanzapine therapy. Mean ratings of manic symptoms, which were low at baseline, showed small (not clinically meaningful) but statistically significant improvement in patients treated with olanzapine and olanzapine-fluoxetine compared with placebo. Moreover, there were no significant differences in the incidences of treatment-emergent mania among the 3 groups. Lastly, the rates of treatment-emergent mania reported in this study approximate those reported previously for placebo^{11,35} and are lower than rates reported with tricyclic antidepressant use.³⁵

In terms of safety, the olanzapine adverse event profile was consistent with previously reported findings,^{36,37} whereas the olanzapine-fluoxetine profile was similar to that of olanzapine, except for higher rates of nausea and diarrhea. Mean weight increases of 2.6 and 2.8 kg were noted in patients treated with olanzapine and olanzapine-fluoxetine, respectively, and small but statistically significant mean increases in glucose and cholesterol levels were also seen.

One question raised by the present findings is whether similar results could be achieved by using other atypical antipsychotic agents, such as risperidone or quetiapine, in combination with a selective serotonin reuptake inhibitor or other antidepressants. Controlled clinical trials are needed to determine the therapeutic efficacy of different combinations. The safety of such combinations must be considered as well.

Limitations of the present study should be noted when interpreting the results. One limitation was the high overall dropout rate. Although the present rates were in line with those of a previous 6-week study³⁸ of bipolar depression, which reported a placebo group completion

rate of 34% (compared with 38.5% in the present 8-week study), this is in direct contrast to the placebo group completion rate of 71% in the 7-week lamotrigine study,¹¹ which may have had a less severe and more stable population given that rapid cyclers were excluded. Nevertheless, examination of the current between-group differences in dropout due to lack of efficacy is informative. The higher rate of dropout due to lack of antidepressant efficacy with olanzapine monotherapy suggests that although this treatment may be effective for some patients, the addition of an appropriately tested antidepressant drug may be warranted for others. Another limitation was the lack of a fluoxetine monotherapy comparison arm because of concerns regarding possible induction of mania. Future studies might also more thoroughly address the issue of patients' baseline proneness to mania. For example, the present finding that the addition of fluoxetine did not increase the risk of mania would be further strengthened by similar findings in a bipolar I depressed population specifically selected for recent manic episodes. Studies with longer durations are necessary to evaluate maintenance of response and to determine the safety and efficacy of olanzapine monotherapy after treatment with olanzapine-fluoxetine combination therapy. Also, head-to-head controlled trials would be useful to establish how the efficacy of this combination compares with that of lamotrigine or other putative combination treatments for bipolar depression.

In summary, the results of this study suggest that although olanzapine may be effective in the treatment of bipolar depression, these effects are significantly enhanced with the coadministration of fluoxetine. In addition, patients receiving such combination therapy did not demonstrate any higher likelihood of treatment-emergent mania. The roles of olanzapine and olanzapine-fluoxetine, as well as other combinations of antidepressants with lithium, anticonvulsants, or atypical antipsychotics, in the longer-term treatment of patients with bipolar disorder should be further evaluated in controlled studies.

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Correction

Error in Figure. In the original article titled "Efficacy of Olanzapine and Olanzapine-Fluoxetine Combination in the Treatment of Bipolar I Depression," published in the November issue of the ARCHIVES (2003;60:1079-1088), the key in **Figure 3** was incorrect. In the corrected key, the top line is for the olanzapine-fluoxetine combination group, and the middle line is for the olanzapine monotherapy group. Figure 3 is reprinted correctly here.

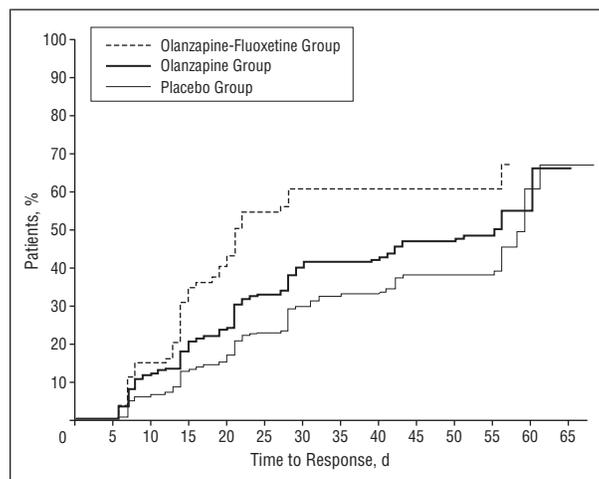


Figure 3. Kaplan-Meier estimates of time to response. Response is defined as a decrease in Montgomery-Åsberg Depression Rating Scale total score of 50% or more after at least 4 weeks of treatment. Median time to response for the olanzapine group (55 days) was significantly earlier compared with the placebo group (59 days). Median time to response for the olanzapine-fluoxetine combination group (21 days) was significantly earlier than for the olanzapine and placebo groups.