Olanzapine/Fluoxetine Combination for the Treatment of Mixed Depression in Bipolar I Disorder: A Post Hoc Analysis

Franco Benazzi, MD, PhD, DTMH†; Michael Berk, MD; Mark A. Frye, MD; Wei Wang, MPH; Alessandra Barraco, MD; and Mauricio Tohen, MD, DrPH, MBA

Objective: Mixed depression (ie, co-occurrence of syndromal depression and subsyndromal mania/hypomania) is a common variant of bipolar depression. However, its treatment is much understudied. The aim of the study was to assess the efficacy of the antipsychotic and mood-stabilizing agent olanzapine and the efficacy of the combination of an antidepressant (fluoxetine) and olanzapine (olanzapine/fluoxetine combination; OFC) for the treatment of bipolar I mixed depression.

Method: We carried out a post hoc analysis of an 8-week, double-blind trial of adult bipolar I depression treated with placebo (n = 355), olanzapine (5–20 mg/d; n = 351), or OFC (olanzapine/fluoxetine doses: 6/25, 6/50, 12/50 mg/d; n = 82). Studying mixed depression was not a previous goal of the double-blind trial. Subjects in the trial were diagnosed according to *DSM-IV* and were randomly assigned to treatment during the period June 2000 to December 2001. Mixed depression was defined as the co-occurrence of a major depressive episode and ≥ 2 manic/hypomanic symptoms (ie, ≥ 2 Young Mania Rating Scale [YMRS] items scoring ≥ 2). Response was defined as a ≥ 50% reduction in Montgomery-Asberg Depression Rating Scale score and < 2 concurrent manic/hypomanic symptoms. Switching to mania/hypomania was defined as a YMRS score ≥ 15.

Results: Frequency of mixed depression was 45.1% in the OFC arm, 49.3% in the olanzapine arm, and 46.8% in the placebo arm ($P = .705$). The most frequent manic/hypomanic symptoms of mixed depression were irritability, reduced need for sleep, talkativeness, and racing thoughts. Response rates in patients with nonmixed depression versus patients with mixed depression were the following: in the OFC arm, 48.9% versus 43.2% (OR = 1.24; 95% CI, 0.51–2.98); in the olanzapine arm, 39.9% versus 26.6% (OR = 1.84; 95% CI, 1.17–2.90); in the placebo arm, 27.5% versus 16.3% (OR = 1.94; 95% CI, 1.15–3.28). Response rates in the samples of patients with mixed depression were the following: OFC versus olanzapine, OR = 2.00 (95% CI, 0.96–4.19); OFC versus placebo, OR = 3.91 (95% CI, 1.80–8.49); olanzapine versus placebo, OR = 1.95 (95% CI, 1.14–3.34). It was found that no baseline manic/hypomanic symptom of mixed depression predicted treatment response. A higher number of baseline concurrent manic/hypomanic symptoms predicted a lower response rate in the olanzapine and placebo arms, but not in the OFC arm. The rates of switching were the following: in the OFC arm, 8.5%; in the olanzapine arm, 6.8%; and in the placebo arm, 7.9% ($P = .808$). The rates of dropouts in patients with mixed depression versus patients with nonmixed depression were not significantly different within any of the treatment arms. The rates of dropouts in the samples of patients with mixed depression were the following: in the OFC arm, 29.7%; in the olanzapine arm, 53.8%; and in the placebo arm, 59.6% (olanzapine vs OFC: OR = 2.66; 95% CI, 1.23–5.75; placebo vs OFC: OR = 3.48; 95% CI, 1.61–7.54; placebo vs olanzapine: OR = 1.30; 95% CI, 0.84–2.01).

Conclusion: Olanzapine/fluoxetine combination may be an effective treatment for bipolar I mixed depression. Statistically, the efficacy of OFC was not significantly different from that of olanzapine, but inspection of the 95% CI showed a trend in favor of a possible superiority of OFC. Supporting the study findings are the similar efficacy of OFC in bipolar mixed depression independent of the number of concurrent manic/hypomanic symptoms, a lower dropout rate, and a similarly low switching rate compared to olanzapine. Contrary to other current limited evidence, an antidepressant (fluoxetine) showed efficacy and did not worsen bipolar mixed depression if combined with a mood-stabilizing agent (olanzapine).

J Clin Psychiatry 2009;70(10):1424–1431

Submitted: *October 3, 2008; accepted January 2, 2009 (doi:10.4088/JCP.08m04772gre).*
†Deceased.
Corresponding author: *Franco Benazzi, MD, Via Pozzetto 17, 48015 Castiglione Cervia RA, Italy (FrancoBenazzi@FBenazzi.it).*

Reports of the co-occurrence of depression and subsyndromal manic/hypomanic symptoms, labeled "mixed depression" (or "depressive mixed states"), date back to antiquity.[1,2] Kraepelin's[3] manic and depressive mixed states were defined by the combinations of the symptoms of opposite polarity domains (ie, mood, thinking, and activity) of "manic-depressive insanity" (which would include most *DSM-IV-TR* bipolar and depressive disorders[4]). Differently from the current diagnostic classifications, ie, *DSM-IV-TR* and the *International Classification of Diseases, Tenth Revision (ICD-10)*,[5] Kraepelin's criteria for diagnosing mixed states required the co-occurrence of the syndrome of 1 polarity and at least 1 symptom of the domains of the opposite polarity syndrome (eg, "excited depression").

Instead, *DSM-IV-TR* and *ICD-10* follow narrow definitions of mixed states, by requiring concurrent syndromal

(ie, full criteria) mania (but not hypomania) and syndromal depression for at least 1 week (in *DSM-IV-TR*) or by requiring the co-occurrence of "prominent" (ie, syndromal or near-syndromal) mania/hypomania and depression symptoms for at least 2 weeks (in *ICD-10*). These criteria would include narrowly defined mixed mania, mixed hypomania, and mixed depression.

Using broad definitions of mixed states (ie, co-occurrence of syndromal depression and subsyndromal mania/hypomania),[1,6–12] in bipolar disorders, mixed depression was found to be present in up to 70% of mixed episodes in patients with bipolar depression,[9,10] a finding recently replicated by post hoc analyses of the large databases of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[13] and the Stanley Foundation Bipolar Network (SFBN).[14]

Several definitions of mixed depression have been suggested.[9,10,15] The most supported definition requires at least 2 to 3 manic/hypomanic symptoms concurrent with a syndromal depression for at least 1 week. The diagnostic validity of this definition has been partly supported by independent groups using, as main validators, bipolar family history, age at onset, and multivariate analyses.[16–24]

The most common *DSM-IV-TR* manic/hypomanic symptoms of mixed depression in these studies[16–24] were irritability, racing thoughts, psychomotor agitation, and talkativeness. These same symptoms represented, according to Kraepelin,[3] the "manic foundation" of "depressive mixed states." Because the broad definitions of mixed states (manic and depressive) are not fully validated (as the *DSM-IV-TR/ICD-10* definitions are)[1,8,10] and are not included in the current diagnostic systems, misdiagnosis and mistreatment of mixed states (especially the much less studied mixed depression) are likely.[25] Of note, features of mixed depression are listed by the US Food and Drug Administration[26] as possible precursors to suicidality related to antidepressants (eg, irritability, psychomotor agitation, bipolarity).

The pharmacologic treatment of mixed depression is largely neglected and is mainly based on clinical observations[15,27] and on a small number of naturalistic studies of patients with bipolar depression (studies likely to be confounded by many factors).[17,18,28,29] To date, a controlled study of mixed depression was investigated in only 1 post hoc analysis of a large controlled study of antidepressants in bipolar depression.[14] Nevertheless, these studies have found that in mixed depression (in contrast with nonmixed depression) antidepressants (even if added to mood-stabilizing agents) were more likely to have lower efficacy, to increase the severity of the concurrent manic/hypomanic symptoms, and to increase the rate of switching to mania/hypomania.

To learn more about treatment response in mixed depression, we conducted a post hoc analysis of a study that evaluated the treatment of bipolar I depression with the atypical antipsychotic and mood-stabilizing agent olanzapine as monotherapy and in combination with the antidepressant fluoxetine (OFC).[30] Our main objectives were (1) to assess differences in treatment outcome between mixed and nonmixed depression treated by olanzapine, OFC, and placebo and (2) to assess the effects of OFC in treating mixed depression compared with olanzapine and placebo.

METHOD

This study is a post hoc analysis of a previously published double-blind treatment trial in bipolar I depression (see Tohen et al[30] for full details of study methods) with the goal of exploring treatment outcome in patients with bipolar mixed depression versus bipolar nonmixed depression (a goal not planned in the original study whose database was used for the present study). Briefly, 833 adult patients with *DSM-IV*[31] bipolar I disorder in a current major depressive episode (requiring an initial Montgomery-Asberg Depression Rating Scale [MADRS][32] score ≥ 20) were randomly assigned to an 8-week trial of treatment with placebo (n = 377), olanzapine (5–20 mg/d; n = 370), or OFC (6/25, 6/50, or 12/50 mg/d; n = 86), over the period of June 2000 to December 2001, from the inpatient and outpatient services of 84 study sites in 13 countries.* Patients were diagnosed by the investigators using the Structured Clinical Interview for *DSM-IV* (SCID)[33] after the investigators, who were the treating clinical psychiatrists, received training on the study methods. Investigators were regularly supervised and monitored. Exclusion criteria were the following: substance-related disorders, suicidality, and unstable/untreated medical disorders. For our analyses, we included only those patients (OFC n = 82, olanzapine n = 351, placebo n = 355, total = 788) who had scores for both the Young Mania Rating Scale (YMRS)[34] and the MADRS at baseline before randomization and postrandomization (postbaseline last visit). All patients provided informed consent after the procedure and possible side effects were fully explained, and the study was approved by the institutional review board at each site.

For our analyses, we used a definition of mixed depression requiring ≥ 2 manic/hypomanic symptoms concurrent with on depression (ie, ≥ 2 YMRS items scoring ≥ 2) at study entry, as this was the definition most supported by previous studies.[9,10,13,17–19,35] The criterion of an individual YMRS item scoring ≥ 2 was chosen in order to include only clinically significant manic/hypomanic symptoms. The YMRS covers most of *DSM-IV-TR* manic/hypomanic symptoms and all of the most common symptoms of mixed depression.

The baseline features of patients with bipolar mixed depression versus patients with bipolar nonmixed depression are presented for each treatment arm. Outcomes of

*More than 50% of the study sites (inpatient and outpatient academic and public services) were in the United States. The participating countries were Australia, Bulgaria, Colombia, Croatia, Greece, Lebanon, Mexico, Portugal, Romania, Russia, Spain, Turkey, and the United States.

Table 1. Baseline Sample Features of Patients With Bipolar I Mixed Depression Versus Nonmixed Depression: Demographics and Course of Illness

	OFC		Olanzapine		Placebo	
Characteristic	Nonmixed	Mixed	Nonmixed	Mixed	Nonmixed	Mixed
Age, y						
n	45	37	178	173	189	166
Mean (SD)	43.4 (12.8)	36.4 (12.6)*	43.7 (12.8)	41.0 (12.4)*	42.8 (12.6)	40.3 (12.0)
Median	45	34	45	40	44	39
Gender						
n	45	37	178	173	189	166
Female, n (%)	29 (64.4)	27 (73.0)	111 (62.4)	106 (61.3)	122 (64.6)	103 (62.1)
Age at onset of bipolar disorder, y						
n	45	37	178	173	189	166
Mean (SD)	25.2 (12.0)	20.4(11.4)	26.3 (11.8)	21.6 (11.2)*	26.2 (10.9)	22.5 (11.4)*
Median	20	17	25	18	25	19
Lifetime no. of depression episodes						
n	34	16	133	93	154	93
Mean (SD)	25.9 (101.9)	26.7 (39.1)	11.0 (24.5)	28.1 (65.9)*	11.1 (26.8)	15.6 (23.8)*
Median	4	13	5	8	4	8
Lifetime no. of mania episodes						
n	34	20	148	106	164	113
Mean (SD)	10.7 (34.2)	15.2 (22.1)*	7.8 (21.3)	21.1 (57.3)*	7.8 (13.2)	13.6 (21.1)*
Median	2	5	3	6	3	7
Lifetime no. of mixed episodes						
n	36	23	156	129	169	130
Mean (SD)	1.0 (2.7)	8.0 (19.5)	1.8 (7.2)	11.9 (64.0)*	1.0 (4.0)	5.9 (14.3)*
Median	0	0	0	0	0	0
Rapid cycling						
n	45	37	175	173	186	166
Patients with rapid cycling, n (%)	13 (28.9)	21 (56.8)*	44 (25.1)	88 (50.9)*	44 (23.7)	83 (50.0)*

*Statistically significant differences between mixed versus nonmixed patients at .05 α level. Age and age at onset were tested using the Student *t* test, median numbers of past episodes were tested using the Mann-Whitney test, and frequencies were tested using the Pearson χ^2 test.
Abbreviation: OFC = olanzapine/fluoxetine combination.

interest, including changes in the MADRS total score and in the Clinical Global Impressions-Severity of Illness scale (CGI-S)[36] score for depression, as well as percentages of responders, were compared between patients with mixed depression and patients with nonmixed depression in each treatment arm.

Response was defined as a ≥ 50% reduction in the MADRS total score and < 2 concurrent manic/hypomanic symptoms (measured by the YMRS) at the end of the study. Switch rates to mania/hypomania, as well as dropout rates, were compared between patients with mixed depression and patients with nonmixed depression. The switch to mania/hypomania was defined as a YMRS total score ≥ 15 at any time during the 8-week study period.

Logistic regression was used in the analyses of response rates, switch rates, and dropout rates, comparing patients with mixed depression versus patients with nonmixed depression within each treatment arm. Unless otherwise specified, logistic regression included terms of baseline MADRS total score, mixed status, therapy, and therapy-by–mixed status interaction. Odds ratios (ORs) and *P* values are from logistic regression. *P* values were 2-tailed, and α level was set at .05 (given the exploratory nature of the study) for all statistical analyses. Inspection of the 95% confidence intervals was also carried out. The statistical software used was SAS (version 8.2; SAS Institute; Cary, North Carolina).

RESULTS

Baseline Sample Features

Frequency of mixed depression was 47.7% in the entire bipolar I sample (376/788); it was 45.1% (37/82) in the OFC arm, 49.3% (173/351) in the olanzapine arm, and 46.8% (166/355) in the placebo arm ($\chi^2_2 = 0.699$, $P = .705$).

The baseline sample features (patients with bipolar mixed depression vs patients with nonmixed depression) are presented in Tables 1 and 2. Patients with mixed depression, compared to patients with nonmixed depression, had a more severe course of illness, as suggested by more past episodes and more rapid cycling. There was no statistically significant difference in the severity of baseline depression as assessed by the MADRS and the CGI-S between patients with mixed depression and patients with nonmixed depression in any of the 3 treatment arms. However, it should be noted that the MADRS does not assess any manic/hypomanic symptoms. In the samples with mixed depression versus the samples with nonmixed depression, the YMRS scores were higher by definition. The baseline mean YMRS scores were not significantly different in the 3 treatment arms. In all treatment arms of patients with mixed depression, the most frequent baseline manic/hypomanic symptoms, as measured by the YMRS, were irritability (94%–95%), reduced need for sleep (62%–65%), talkativeness (35%–43%), and racing thoughts (26%–35%).

Table 2. Baseline Sample Features of Bipolar I Mixed Depression Versus Nonmixed Depression: Episode Severity at Study Entry

	OFC		Olanzapine		Placebo	
Characteristic	Nonmixed	Mixed	Nonmixed	Mixed	Nonmixed	Mixed
Baseline CGI-S score						
n	45	37	178	173	189	166
Mean (SD)	4.9 (0.8)	4.8 (0.8)	4.9 (0.8)	4.9 (0.9)	4.8 (0.8)	4.8 (0.8)
Median	5	5	5	5	5	5
Baseline YMRS total score						
n	45	37	178	173	189	166
Mean (SD)	1.9 (1.5)	8.7 (4.9)*	1.9 (1.5)	8.1 (4.7)*	2.0 (1.5)	8.1 (4.7)*
Median	2	8	2	6	2	6
Baseline MADRS total score						
n	45	37	178	173	189	166
Mean (SD)	30.6 (5.7)	31.1 (6.6)	32.5 (6.0)	32.6 (6.0)	31.2 (6.4)	31.5 (5.8)
Median	31	30	32	32	31	32
No. of manic symptoms (number of YMRS items scoring ≥ 2)						
n	45	37	178	173	189	166
Mean (SD)	0.6 (0.5)	3.2 (1.5)*	0.6 (0.5)	2.9 (1.4)*	0.6 (0.5)	1.9 (1.3)*
Median	1	3	1	2	1	2

*Statistically significant differences between mixed vs nonmixed patients at .05 α level. Differences between mixed and nonmixed patients in each treatment arm were tested using Student *t* test.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination, YMRS = Young Mania Rating Scale.

Response to Treatment

In the patients treated with OFC, there was no statistically significant difference in the percentages of responders, with 43.2% (16/37) responders in the group of patients with mixed depression and 48.9% (22/45) in the group of patients with nonmixed depression (OR = 1.24; 95% CI, 0.51–2.98).

In contrast, in both the olanzapine and the placebo groups, patients with mixed depression had a statistically significantly lower percentage of responders compared to the patients with nonmixed depression. In the olanzapine arm, 26.6% (46/173) of the patients with mixed depression responded and 39.9% (71/178) of the patients with nonmixed depression responded (nonmixed depression vs mixed depression patients: OR = 1.84; 95% CI, 1.17–2.90; *P* = .009). In the placebo arm, 16.3% (27/166) of the patients with mixed depression responded, and 27.5% (52/189) of the patients with nonmixed depression responded (nonmixed vs mixed depression patients: OR = 1.94; 95% CI, 1.15–3.28; *P* = .013). Of the patients with mixed depression, no statistically significant difference was observed between OFC and olanzapine in the rate of responders (OR = 2.00; 95% CI, 0.96–4.19; *P* = .065). However, inspection of the 95% CI showed a trend in favor of a possibly higher response rate with OFC. Patients treated with OFC showed a significantly higher response rate versus patients treated with placebo (OR = 3.91; 95% CI, 1.80–8.49; *P* = .0006). Patients treated with olanzapine showed a significantly higher response rate versus patients treated with placebo (OR = 1.95; 95% CI, 1.14–3.34; *P* = .014). Inspection of the 95% CIs showed a trend in favor of superior efficacy for OFC compared to olanzapine versus placebo.

The relationship between each baseline manic/hypomanic symptom of mixed depression (measured by a YMRS item score of 2+) and response at the end of the study, for each treatment arm, was tested by logistic regression. It was shown that no baseline manic/hypomanic symptom of mixed depression was significantly associated with response to treatment, in any of the treatment arms.

Table 3. Relationship Between Percentage of Responders and Number of Concurrent Manic/Hypomanic Symptoms at Baseline in Bipolar I Depression

No. of Manic/ Hypomanic Symptoms	Logistic Model[a] Predicting Percentage of Responders at End of Study Period		
	Placebo	Olanzapine	OFC
0	30.4	44.8	48.0
1	24.8	37.6	47.1
2	20.0	30.9	46.1
3	15.8	24.8	45.2
4	12.5	19.7	44.3
5	9.7	15.3	43.4
6	7.5	11.8	…
7	5.8	9.0	41.5
8	…	6.9	41.5
9	3.4	…	…
Odds ratio (95% CI)	0.755 (0.617–0.925)*	0.741 (0.623–0.881)*	0.963 (0.742–1.251)

[a]Logistic regression model: response versus number of symptoms tested by the Wald χ^2 test from a logistic model including adjustment for baseline Montgomery-Asberg Depression Rating Scale score.
*Statistically significant difference in response rate by 1 unit of difference in manic symptoms.
Abbreviation: OFC = olanzapine/fluoxetine combination. Symbol: … = no patients in the group had the indicated number of symptoms.

The relationship between response rates and the number of baseline manic/hypomanic symptoms of mixed depression was tested by logistic regression (Table 3). A statistically significant negative association was found between the number of baseline manic/hypomanic symptoms and response rates (ie, the higher the number of baseline manic/hypomanic symptoms, the lower the response rate) in the

Table 4. Study Discontinuations (dropouts) in Patients With Bipolar I Mixed Depression Versus Nonmixed Depression

	OFC		Olanzapine		Placebo	
	Nonmixed (n = 45)	Mixed (n = 37)	Nonmixed (n = 178)	Mixed (n = 173)	Nonmixed (n = 189)	Mixed (n = 166)
Completed study period, n	29	26	99	80	78	67
Dropped out, n (%)	16 (35.6)	11 (29.7)	79 (44.4)	93 (53.8)	111 (58.7)	99(59.6)
Reasons for dropout, n						
Adverse event	1	1	16	16	6	6
Death	0	0	0	0	1	1
Induction of mania	3	1	5	10	12	11
Lack of efficacy, patient and physician perception	4	3	34	22	44	54
Lack of efficacy, patient perception	1	0	4	5	6	9
Lack of efficacy, physician perception	0	0	2	5	6	2
Patient moved	0	0	2	1	2	0
Personal conflict or other patient decision	0	0	6	9	7	2
Physician decision	0	1	3	1	2	4
Protocol violation	1	2	0	8	5	3
Protocol entry criteria not met	0	0	1	0	2	0
Relapse of depression	1	0	3	2	6	2
Satisfactory response, patient perception	0	0	0	1	0	0
Sponsor's decision	1	0	0	1	1	0
Unable to contact patient (lost to follow-up)	4	3	3	12	11	5

Abbreviation: OFC = olanzapine/fluoxetine combination.

olanzapine and the placebo arms, but not in the OFC arm (which showed similar response rates independently of the number of baseline manic/hypomanic symptoms).

The switch rate was very low in all 3 arms: 8.5% (7/82) in the OFC arm, 6.8% (24/351) in the olanzapine arm, and 7.9% (28/355) in the placebo arm ($\chi^2 = 0.426$, $df = 2$, $P = .808$).

Table 4 shows the dropout rates according to mixed status and treatment. The comparison between patients with mixed depression and patients with nonmixed depression showed no statistically significant differences in dropout rates within any of the treatment arms (OFC arm: OR = 0.76; 95% CI, 0.30–1.93; $P = .558$; olanzapine arm: OR = 1.46; 95% CI, 0.96–2.22; $P = .080$; placebo arm: OR = 1.03; 95% CI, 0.67–1.58; $P = .884$). In the samples with mixed depression, the percentage of dropouts was significantly lower in the OFC arm than in the olanzapine and the placebo arms: 29.7% (11/37) in the OFC arm, 53.8% (93/173) in the olanzapine arm, and 59.6% (99/166) in the placebo arm (olanzapine vs OFC: OR = 2.67; 95% CI, 1.23–5.75; $P = .012$; placebo vs OFC: OR = 3.48; 95% CI, 1.61–7.54; $P = .002$). The dropout rates were not significantly different in the olanzapine arm and in the placebo arm (placebo vs olanzapine: OR = 1.30; 95% CI, 0.84–2.01; $P = .227$).

DISCUSSION

Our main objectives were (1) to assess differences in treatment outcome between mixed and nonmixed depression treated by olanzapine, OFC, and placebo and (2) to assess the effects of OFC in treating mixed depression compared with olanzapine and placebo.

We found that the efficacy of OFC was similar in patients with bipolar I mixed depression and patients with nonmixed depression, with response rates similar to those found in unipolar depression studies.[37,38] The OFC response rate resulted independent of the number of baseline concurrent manic/hypomanic symptoms of mixed depression; that is, response was similar even when the number of manic/hypomanic symptoms increased. This finding was different from that seen with olanzapine, which showed progressively lower response rates as the number of manic/hypomanic symptoms increased. This olanzapine trend of response according to the number of baseline manic/hypomanic symptoms might be related to the use of higher doses as the number of manic/hypomanic symptoms increased, which, in turn, might have worsened depressive symptoms by an antidopaminergic effect, among its various pharmacodynamic effects. The efficacy of OFC and olanzapine in patients with bipolar I mixed depression was not significantly different, but inspection of the 95% CI of the difference showed a trend for higher efficacy with OFC (OR = 2.00; 95% CI, 0.96–4.19; $P = .065$), a finding needing replication in larger, more statistically powerful OFC samples. Compared to placebo, OFC had significantly higher efficacy than olanzapine in patients with mixed depression (OR = 3.91 for OFC vs placebo, OR = 1.95 for olanzapine vs placebo). The lower response rate seen with olanzapine (and placebo) in patients with mixed depression versus patients with nonmixed depression might have been related to the more severe course of mixed depression, which might have made it less responsive to treatment. However, a similar response rate was seen with OFC in patients with mixed depression versus patients with nonmixed depression.

Other important findings of the present study were the following: (1) a high frequency of bipolar I mixed depression was found (defined as co-occurrence of a major depressive

episode and at least 2 manic/hypomanic symptoms); (2) a more severe course of illness was seen with bipolar I mixed depression than with bipolar I nonmixed depression, but cross-sectional measures of depression severity (assessed by the MADRS and the CGI-S) were not significantly different compared to nonmixed depression; and (3) the current depression rating scales (eg, the MADRS) miss the diagnosis of mixed depression, which requires the concurrent assessment of both depression and manic/hypomanic symptoms using also mania/hypomania rating scales or scales that concurrently assess symptoms of both polarity.[39,40]

We also explored a definition of mixed depression defined not by a cutoff number of concurrent manic/hypomanic symptoms (the present study definition), but by a cutoff YMRS total score (>6). Findings were consistent using both definitions, suggesting that this alternative definition of mixed depression could have a similar diagnostic utility compared to that used in this study (which was more in line with previous studies[9,10,13,17–19,35]). The use of YMRS score as a cutoff to define mixed depression and mixed hypomania has already been reported.[12,14] Some previous studies,[23,41] using a definition of bipolar II mixed depression based on both a cutoff number of concurrent hypomanic symptoms and a cutoff score of a hypomania rating scale, found similar clinical findings compared to a definition based on a cutoff number of concurrent hypomanic symptoms (as in the present study). These studies, including our own, seem to suggest that a definition of bipolar mixed depression could be based on both cutoffs of the number of concurrent manic/hypomanic symptoms and cutoffs of scores on mania/hypomania rating scales, such as the YMRS.

In the entire sample, the frequency of bipolar I mixed depression was 48%, a figure in line with previous reports.[1,9,10,13] Patients with mixed depression, versus patients with nonmixed depression, showed a more severe course of illness, as described by Kraepelin and in more recent studies.[3,9,10,15,17] The severity of depression at baseline, as assessed by the MADRS and the CGI-S, was not significantly higher in patients with mixed depression versus patients with nonmixed depression, but the MADRS, like all of the other current rating scales for depression, does not assess the concurrent manic/hypomanic symptoms of mixed depression.

The most frequent manic/hypomanic symptoms in all patients in the bipolar I mixed depression arms were irritability (94%–95%), reduced need for sleep (62%–65%), talkativeness (35%–43%), and racing thoughts (26%–35%). Apart from irritability and talkativeness, which are in line with the frequencies reported in previous studies,[10] reduced need for sleep was more common and racing thoughts were less common than previously reported. This finding may be related, among other factors, to the instrument (ie, YMRS) used in this study to assess the manic/hypomanic symptoms of mixed depression, as the YMRS was designed mainly for inpatient mania and may not detect correctly symptoms of lower severity such as the hypomanic symptoms.[23,41]

Interestingly, the efficacy of OFC in patients with mixed depression was independent of the number of baseline manic/hypomanic symptoms; that is, it was similar despite the number of manic/hypomanic symptoms (Table 3). In contrast, patients treated with olanzapine (and placebo) showed a significantly progressive decrease in efficacy (response rate) as the number of baseline manic/hypomanic symptoms increased. This finding could suggest a higher efficacy of OFC versus olanzapine for bipolar I mixed depression.

We found that no baseline manic/hypomanic symptom predicted response rates in any treatment arm. The Frye et al[14] SFBN study found instead that bipolar mixed depression (defined by few manic symptoms) versus nonmixed depression was more likely to switch and to show a lower response rate during antidepressant treatment. In that study, response to antidepressants was defined by a drop in a depression rating scale score (not the MADRS, used in the present study) to below a cutoff. This definition of response was different from our definition of response, which required a drop below a cutoff in both MADRS score and the number of concurrent manic/hypomanic symptoms. The findings of that controlled trial (a post hoc analysis)[14] are different from those of the present study. Factors related to these differences may be several: different settings, different sample features (eg, gender, severity of illness course), different rating scales, inclusion of patients with bipolar II disorder, different definitions of response and of mania/hypomania (using a different rating scale with a much smaller range of scores as compared to the YMRS and the MADRS), use of mainly lithium and anticonvulsants as mood-stabilizing agents, and use of different antidepressants (ie, sertraline, bupropion, venlafaxine). The marked difference in switching rates between the Frye et al[14] study (24%) and our study (7%–8%) may suggest more antimanic protection by olanzapine and/or less switch-inducing effect by fluoxetine (the drugs used in the present study) compared to the drugs used in the above study. Our study findings, pending replications, might be more specific to the drugs used (ie, fluoxetine and olanzapine): there are pharmacodynamic differences among the antidepressants fluoxetine (the one used in the present study), sertraline, bupropion, and venlafaxine (those used in the study by Frye et al[14]), and there are also strong pharmacodynamic differences among the mood-stabilizing agents olanzapine (the one used in the present study), lithium, and anticonvulsants (used in the study by Frye et al[14]). In the STEP-BD naturalistic study by Goldberg et al,[29] antidepressants added to mood-stabilizing agents for bipolar (type I and type II) mixed depression (defined by ≥2 concurrent manic/hypomanic symptoms, as in the present study) did not hasten time to recovery (defined by a drop of a depression rating scale) and induced greater manic symptom severity. In that study, as in the Frye et al[14] study, most patients received lithium and anticonvulsants as mood-stabilizing agents, and fluoxetine was given to a minority (11.7%).

In our study, the expected finding (on the basis of the above and of other studies reported in the Introduction) was a worsening of the manic/hypomanic symptoms of mixed depression and more switching with the addition of an antidepressant to a mood-stabilizing agent for the treatment of bipolar mixed depression. Instead, we found the opposite, ie, for the treatment of bipolar I mixed depression, the combination of the antidepressant fluoxetine with the mood-stabilizing agent olanzapine was effective and did not cause more switching or more dropouts. The possibility that our findings might be related to the drug combination we used needs exploration and replication.

The use of antidepressants in bipolar depression (the most studied is type I) is a hot topic, with attention centering on the efficacy and the possible negative impacts of antidepressants (eg, more switching, more rapid cycling). With regard to bipolar (mainly including type I) depression, different reviews have reached opposite conclusions, few controlled studies did not support the efficacy of antidepressants, and some large naturalistic studies did instead support the acute, and partly the long-term, efficacy of antidepressants.[1,42–46] On the other side, the current mood-stabilizing agents have shown weak or no acute, and long-term, efficacy for bipolar depression.[43] It has been emphasized[42] that the inconsistent findings in the studies on antidepressants for bipolar depression might be related to not having stratified the analyses according to the mixed status, as suggested some years ago.[47]

The results of the present study add evidence supporting the diagnostic utility of the concept of mixed depression in bipolar I disorder and suggest that the combination of an antidepressant (fluoxetine) and of an atypical antipsychotic and mood-stabilizing agent such as olanzapine may be an effective treatment option for mixed depression. This finding runs contrary to previous reports, mainly based on clinical observations and naturalistic studies, that have reported negative effects of antidepressants in bipolar mixed depression.[13–18,27,28]

Limitations

The post hoc analysis method may inflate the chance of false-positive findings.[48] However, post hoc analysis avoids possible interviewer biases (mixed depression had not been planned as an outcome of interest in the present study database), which may overcome that limitation. Use of large samples reduced the risk of Type II error except, perhaps, in the smaller OFC arm. Given the exploratory nature of the study, the α level was set at .05, and the 95% CIs were inspected. The inspection of the 95% CIs, differently from *P* values, has the advantage of being an estimate (and not a probability) of both the strength of an association and its precision.[49,50] Estimation is more strongly supported than reliance on *P* values only: as Rothman[50] states, "In nearly all instances, there is no need for any test of statistical significance to be calculated, reported, or relied upon, and we are much better off without them."

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author affiliations: Hecker Psychiatry Research Center, Forli, Italy, a University of California at San Diego Collaborating Center; the Department of Psychiatry, University of Szeged, Szeged, Hungary; and the Department of Psychiatry, National Health Service, Forli, Italy (Dr Benazzi); the Department of Clinical and Biomedical Sciences, University of Melbourne, Parkville, Australia; ORYGEN Research Centre, Melbourne, Australia; Barwon Health and the Geelong Clinic, Swanston Centre, Geelong, Victoria, Australia; and the Mental Health Research Institute, Parkville, Australia (Dr Berk); the Mayo Clinic College of Medicine, the Mayo Mood Clinic and Research Program, Rochester, Minnesota (Dr Frye); Eli Lilly Canada, Toronto, Ontario (Mr Wang); Eli Lilly Italy, Florence (Dr Barraco); and the Department of Psychiatry, University of Texas, San Antonio (Dr Tohen).

Financial disclosure: **Dr Berk** is a consultant for Astra, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Servier, and Janssen; has received grant/research support from Stanley Foundation, National Health and Medical Research Council, Bristol-Myers Squibb, Eli Lilly, Organon, and Astra; has received honoraria from Astra, Servier, Eli Lilly, and Lundbeck; and has served on speakers/advisory boards for Astra, Eli Lilly, Janssen, Lundbeck, and Wyeth. **Dr Frye** is a consultant for Bristol-Myers Squibb, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, and Ortho McNeil; has received grant/research support from Pfizer; and has participated in CME-supported activity for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Otsuka, Pfizer, and Schering-Plough. **Mr Wang** is an employee of Eli Lilly Canada and a stock shareholder in Eli Lilly. **Dr Barraco** is an employee of Eli Lilly and Company, Italy. **Dr Tohen** is a consultant for Eli Lilly, Johnson & Johnson, and Bristol-Myers Squibb; has received grant/research support from the Atlas Foundation; has received honoraria from AstraZeneca and Wyeth; and has served on speakers/advisory boards for and is a stock shareholder in Eli Lilly. Dr Tohen's spouse is an employee of and stock shareholder in Eli Lilly, and Dr Tohen was an employee of Eli Lilly at the time this report was produced. **Dr Benazzi** reports no conflict of interest.

Funding/support: The original trial that provided the data for this analysis was funded by Lilly Research Laboratories.

REFERENCES

1. Goodwin FK, Jamison KR. *Manic-Depressive Illness*. 2nd ed. Oxford, England: Oxford University Press; 2007.
2. Marneros A. Origin and development of concepts of bipolar mixed states. *J Affect Disord.* 2001;67(1–3):229–240.
3. Kraepelin E. *Manic-Depressive Insanity and Paranoia*. Edinburgh, Scotland: Livingstone E & S; 1921.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
5. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders*. Geneva, Switzerland: World Health Organization; 1992.
6. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry.* 1990;47(12):1106–1111.
7. McElroy SL, Keck PE Jr, Pope HG Jr, et al. Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. *Am J Psychiatry.* 1992;149(12):1633–1644.
8. Cassidy F, Yathan LN, Berk M, et al. Pure and mixed manic subtypes: a review of diagnostic classification and validation. *Bipolar Disord.* 2008;10(1, pt 2):131–143.
9. Benazzi F. Bipolar disorder–focus on bipolar II disorder and mixed depression. *Lancet.* 2007;369(9565):935–945.
10. Benazzi F. Reviewing the diagnostic validity and utility of mixed depression (depressive mixed states). *Eur Psychiatry.* 2008;23(1):40–48.
11. Bauer MS, Simon GE, Ludman E, et al. "Bipolarity" in bipolar disorder: distribution of manic and depressive symptoms in a treated population. *Br J Psychiatry.* 2005;187:87–88.
12. Suppes T, McElroy SL, Altshuler LL, et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the

Stanley Bipolar Treatment Network: a gender-specific phenomenon. *Arch Gen Psychiatry.* 2005;62(10):1089–1096.
13. Goldberg JF, Perlis RH, Bowden CL, et al. Mania symptoms during depressive episodes in 1380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry.* 2009;166(2):173–181.
14. Frye MA, Helleman G, McElroy SL, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry.* 2009;166(2):164–172.
15. Koukopoulos A, Albert MJ, Sani G, et al. Mixed depressive states: nosologic and therapeutic issues. *Int Rev Psychiatry.* 2005;17(1):21–37.
16. Sato T, Bottlender R, Kleindienst N, et al. Irritable psychomotor elation in depressed inpatients: a factor validation of mixed depression. *J Affect Disord.* 2005;84(2-3):187–196.
17. Maj M, Pirozzi R, Magliano L, et al. Agitated depression in bipolar I disorder: prevalence, phenomenology, and outcome. *Am J Psychiatry.* 2003;160(12):2134–2140.
18. Maj M, Pirozzi R, Magliano L, et al. Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. *J Clin Psychiatry.* 2006;67(5):712–719.
19. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. *J Affect Disord.* 2003;73(1–2):113–122.
20. Akiskal HS, Benazzi F, Perugi G, et al. Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. *J Affect Disord.* 2005;85(3):245–258.
21. Swann AC, Gerard Moeller F, Steinberg JL, et al. Manic symptoms and impulsivity during bipolar depressive episodes. *Bipolar Disord.* 2007;9(3):206–212.
22. Biondi M, Picardi A, Pasquini M, et al. Dimensional psychopathology of depression: detection of an "activation" dimension in unipolar depressed outpatients. *J Affect Disord.* 2005;84(2–3):133–139.
23. Benazzi F. Defining mixed depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(4):932–939.
24. Benazzi F. A tetrachoric factor analysis validation of mixed depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(1):186–192.
25. Berk M, Malhi GS, Cahill AC, et al. The Bipolar Depression Rating Scale (BDRS): its development, validation and utility. *Bipolar Disord.* 2007;9(6):571–579.
26. US Food and Drug Administration. Revisions to Product Labeling. http://www.fda.gov/cder/drug/antidepressants/antidepressants_label_change_2007. Accessed March 3, 2008.
27. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. *J Clin Psychopharmacol.* 1996;16(2):4S–14S.
28. Bottlender R, Sato T, Kleindienst N, et al. Mixed depressive features predict maniform switch during treatment of depression in bipolar I disorder. *J Affect Disord.* 2004;78(2):149–152.
29. Goldberg JF, Perlis RH, Ghaemi SN, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry.* 2007;164(9):1348–1355.
30. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry.* 2003;60(11):1079–1088.
31. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
32. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382–389.
33. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Version (SCID)*. Washington, DC: American Psychiatric Press; 1997.
34. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry.* 1978;133:429–435.
35. Sato T, Bottlender R, Schroter A, et al. Frequency of manic symptoms during a depressive episode and unipolar "depressive mixed state" as bipolar spectrum. *Acta Psychiatr Scand.* 2003;107(4):268–274.
36. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.
37. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905–1917.
38. Rihmer Z, Gonda X. Is drug-placebo difference in short-term antidepressant drug trials on unipolar major depression much greater than previously believed? *J Affect Disord.* 2008;108(3):195–198.
39. Berk M, Dodds S, Malhi GS. "Bipolar missed states": the diagnosis and clinical salience of bipolar mixed states. *Aust N Z J Psychiatry.* 2005;39(4):215–221.
40. Bowden CL, Singh V, Thompson P, et al. Development of the Bipolar Inventory of Symptoms Scale. *Acta Psychiatr Scand.* 2007;116(3):189–194.
41. Benazzi F. Depressive mixed state: dimensional versus categorical definitions. *Prog Neuropsychopharmacol Biol Psychiatry.* 2003;27(1):129–134.
42. Ghaemi SN. Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression. *Bipolar Disord.* 2008;10(8):957–968.
43. Goldberg JF. The modern pharmacopeia: a return to depressive realism? *Bipolar Disord.* 2008;10(8):969–972.
44. Cassidy F. Antidepressants treatment practice in the face of STAR*D and STEP-BD. *Bipolar Disord.* 2008;10(8):973–974.
45. Benazzi F. Bipolar II disorder: epidemiology, diagnosis and management. *CNS Drugs.* 2007;21(9):727–740.
46. Malhi GS. Upping the ante on antidepressants. *Bipolar Disord.* 2008;10(8)975–978.
47. Benazzi F. The problem of the treatment of bipolar-II depression. *Bipolar Disord.* 2004;6(5):440–441.
48. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. *Ann Intern Med.* 1992;116(1):78–84.
49. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*, 3rd edition. Philadelphia, PA: Wolters Kluwer / Lippincott Williams & Wilkins; 2008
50. Rothman KJ. *Epidemiology. An Introduction*. Oxford, England: Oxford University Press; 2002:126.

