A 7-Week, Randomized, Double-Blind Trial of Olanzapine/Fluoxetine Combination Versus Lamotrigine in the Treatment of Bipolar I Depression

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Objective: Determine the efficacy and tolerability of olanzapine/fluoxetine combination (OFC) for treatment of acute bipolar I depression compared with lamotrigine.

Method: The 7-week, acute phase of a randomized, double-blind study compared OFC (6/25, 6/50, 12/25, or 12/50 mg/day; N = 205) with lamotrigine ([LMG] titrated to 200 mg/day; N = 205) in patients with DSM-IV–diagnosed bipolar I disorder, depressed. The study was conducted from November 2003 to August 2004.

Results: Completion rates were similar between treatments (OFC, 66.8% vs. LMG, 65.4%; p = .835). OFC-treated patients had significantly greater improvement than lamotrigine-treated patients in change from baseline across the 7-week treatment period on the Clinical Global Impressions-Severity of Illness scale (primary outcome) (p = .002, effect size = 0.26), Montgomery-Asberg Depression Rating Scale (MADRS) (p = .002, effect size = 0.24), and Young Mania Rating Scale total scores (p = .001, effect size = 0.24). Response rates did not significantly differ between groups when defined as ≥ 50% reduction in MADRS score (OFC, 68.8% vs. LMG, 59.7%; p = .073). Time to response was significantly shorter for OFC-treated patients (median days [95% CI] = OFC, 17 [14 to 22] vs. LMG, 23 [21 to 34]; p = .010). There was a significant difference in incidence of "suicidal and self-injurious behavior" adverse events (OFC, 0.5% vs. LMG, 3.4%; p = .037). Somnolence, increased appetite, dry mouth, sedation, weight gain, and tremor occurred more frequently (p < .05) in OFC-treated patients than lamotrigine-treated patients. Weight, total cholesterol, and triglyceride levels were significantly elevated in OFC-treated patients compared with lamotrigine-treated patients (all p ≤ .001).

Conclusions: Patients with acute bipolar I depression had statistically significantly greater improvement in depressive and manic symptoms, more treatment-emergent adverse events, greater weight gain, and some elevated metabolic factors with OFC than lamotrigine. Treatment differences were of modest size.

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Bipolar depression is a difficult-to-treat form of depression that is associated with significant suffering, disability, and mortality. Depressive episodes of bipolar disorder tend to occur more often and last longer than manic episodes.[1–3] In addition, bipolar depression is associated with greater disruption of occupational, family, and social functioning; increased long-term disability; and greater rates of mortality compared with bipolar mania.[1,2,4] The risk of attempted and completed suicide is greater in patients with bipolar depression compared with patients with mania.[5–7] However, the identification and demonstration of effective treatments for bipolar depression has lagged behind that for bipolar mania, and bipolar depression remains a treatment challenge.[8]

Lithium has demonstrated some efficacy for bipolar depression in placebo-controlled trials, but response was suboptimal for many patients.[9] The risk-to-benefit ratio of standard antidepressants for bipolar depression remains controversial. In a recent review and meta-analysis of randomized controlled trials, Gijsman et al.[10] concluded that antidepressants demonstrated efficacy in the short-term treatment of bipolar depression, with a lower incidence of mania with selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors than tricyclic antidepressants. In this meta-analysis, the majority of patients received concomitant mood stabilizers.

The current (2002) American Psychiatric Association practice guidelines recommend either lithium or lamotri-

gine as first-line treatment for bipolar depression.[11] Lamotrigine is also a stage 1 treatment recommendation for bipolar depression according to the revised Texas medication algorithm,[12] the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines,[13] and The Expert Consensus Guideline Series: Treatment of Bipolar Disorder 2004.[14] Lamotrigine, an approved treatment of seizure disorders, has subsequently been approved for maintenance treatment of bipolar I disorder.[15] Although not U.S. Food and Drug Administration (FDA) approved for acute bipolar depression, at least 2 studies[16,17] suggest that lamotrigine may be effective for this phase of the disorder. In a 7-week, double-blind, placebo-controlled trial in patients with bipolar I depression, lamotrigine had greater efficacy than placebo at 50 and 200 mg/day.[16] In a small, acute-treatment, crossover trial of patients with refractory mood disorders, patients treated with lamotrigine had significant reductions in depressive symptoms compared with patients receiving placebo.[17] Lamotrigine is associated with a small but significant risk of developing serious rash.[18] A slow titration from an initial dosage of 25 mg/day up to the optimal maintenance dosage of 200 mg/day over several weeks is recommended to reduce this risk.[18]

The combination of the psychotropic agent olanzapine with the SSRI fluoxetine has been demonstrated to be effective in the treatment of acute bipolar I depression. In preclinical studies, the combination of olanzapine and fluoxetine produced synergistic increases in dopamine and norepinephrine,[19] increases in serotonin similar to fluoxetine alone,[19] and synergistic effects in the modulation of a neurotrophic factor[20] in the rat prefrontal cortex, suggesting potential as an antidepressant. Olanzapine/fluoxetine combination (OFC) is currently the only FDA-approved treatment for bipolar depression.[21] In a large, double-blind, 8-week, placebo-controlled study in patients with bipolar I depression, patients treated with OFC showed statistically significant improvement in depressive symptoms compared with the placebo group, starting at week 1.[22] In addition, the OFC group displayed significantly greater improvement than the olanzapine group at weeks 4 to 8.[22] The safety profile of OFC appears similar to that of a combination of olanzapine and fluoxetine monotherapies, with no newly arising adverse events or increased rate of the incidence of adverse events.[22,23]

Given the existing clinical data on OFC and lamotrigine, this study aimed to assess their comparative efficacy, safety, and tolerability in the acute treatment of bipolar I depression.

METHOD

Patient Population

This study was conducted in 18- to 60-year-old subjects who were outpatients or hospital inpatients. The study protocol was approved by the sites' institutional review boards, and written informed consent was obtained from all participants prior to study entry. Patients met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[24] diagnostic criteria for bipolar I disorder, depressed, based on the Structured Clinical Interview for DSM-IV (SCID).[25] Patients who met DSM-IV criteria for a mixed state were excluded. Inclusion criteria required a total score ≥ 20 on the Montgomery-Asberg Depression Rating Scale (MADRS)[26] as well as a rating of 4 (moderately ill) or higher on the Clinical Global Impressions-Severity of Illness scale (CGI-S)[27] at both the screening visit and the visit prior to randomization. Patients must have also experienced at least 1 previous manic or mixed episode of sufficient severity to require treatment with a mood stabilizer or antipsychotic. Exclusion criteria included serious suicidal risk, DSM-IV substance dependence within the previous 30 days (except for nicotine and caffeine), a Young Mania Rating Scale (YMRS)[28] total score ≥ 15 at randomization, and patients who were currently taking or had previously failed or responded poorly to an adequate trial of olanzapine, olanzapine plus an antidepressant, or lamotrigine. The study was conducted from November 2003 to August 2004 at 38 sites (mean number of patients per site was 11) in the United States.

Study Design

This was a randomized, double-blind, parallel-group study. Patients entered the screening period for at least 2 days, and all psychotropic agents were tapered off gradually and discontinued by 24 hours prior to randomization. For patients tapering off lithium or fluoxetine, a taper period of up to 5 weeks was allowed. Patients were randomly assigned in a 1:1 fashion to receive OFC or lamotrigine for 7 weeks of acute therapy. Patients continued on their original randomly assigned treatment in a continuation phase of the study for another 18 weeks. This article reports the results of the acute phase only.

Patients randomly assigned to lamotrigine received 25 mg on the day of randomization and were titrated up to 200 mg over 5 weeks according to package insert recommendation.[15] In the Calabrese et al.[16] study, the 200-mg group was titrated up from 25 mg to 200 mg over 4 weeks. After the titration period in the current study, the lamotrigine dose could be decreased to 150 mg/day if patients could not tolerate the target dose of 200 mg/day. Patients in the OFC treatment group received 6 mg of olanzapine and 25 mg of fluoxetine (6/25) and, after 1 week, were increased to 12 mg of olanzapine and 25 mg of fluoxetine (12/25). After 1 day of the 12/25, dosage could be adjusted to any of 4 possible doses, 6/25, 12/25, 6/50, or 12/50, via an automated telephone interactive voice response system (Eli Lilly and Company, Indianapolis, Ind.). In a previous flexible-dose trial evaluating OFC for bipolar I depression, it was found that the

mean modal dose of fluoxetine was 39.3 mg,[22] which motivated the decision in the current study to offer up to 50 mg of fluoxetine.

To preserve the blind aspect of the study, the number of capsules and the frequency for taking the drug were identical for each of the 2 treatment groups. Patients were evaluated 3 days after randomization, then 4 days later, and, subsequently, weekly. Anticholinergic medication was permitted for extrapyramidal symptoms (benztropine mesylate, 6 mg/day maximum; but not for prophylaxis), and benzodiazepines or other hypnotics were permitted, if needed (up to 2 mg/day of lorazepam equivalents).

Outcome Measures

The primary outcome measure, as defined a priori in the protocol, was the change in overall bipolar status as measured by CGI-S from baseline. Improvement in depressive symptoms was measured by the MADRS. Other secondary outcome measures were the YMRS, the Brief Psychiatric Rating Scale (BPRS),[29] the Clinical Global Impressions-Improvement scale (CGI-I),[27] the Patient Global Impression of Improvement scale (PGI),[27] the Global Assessment of Functioning scale (GAF),[24] the Medical Outcomes Study Short Form (MOS),[30] and the Brief Symptom Inventory (BSI).[31] The BSI is a patient self-rated scale that is made up of 53 items and includes a global severity score along with 9 different scored dimensions.[31] The CGI-S, MADRS, YMRS, and GAF results were obtained at every visit, whereas the CGI-I and the PGI were obtained at the first week postrandomization and thereafter. The BPRS, MOS, and BSI were obtained at baseline, week 4, and week 7.

Safety was assessed by the evaluation of treatment-emergent adverse events, discontinuation due to adverse events, vital sign measurements, and clinical laboratory tests. Clinical laboratory tests were performed by a central laboratory, Covance (Indianapolis, Ind.), and Covance reference ranges were used to determine abnormal lab values. Adverse events were elicited by nonprobing inquiry, were recorded regardless of perceived causality, and were coded and mapped to standard coding using the *Medical Dictionary for Regulatory Activities* (MedDRA). An event was considered treatment emergent if it occurred for the first time or worsened during the double-blind treatment period. Tardive dyskinesia was assessed by the Abnormal Involuntary Movement Scale (AIMS),[32] which was obtained at baseline and week 7.

Statistical Methods

The primary, protocol-defined, efficacy analysis evaluated the difference between treatment groups in mean change from baseline in CGI-S score across the entire 7-week period. A mixed-effects model repeated-measures (MMRM) approach was used, with visit, treatment, investigator, visit-by-treatment interaction, and baseline score in the model. An unstructured covariance matrix was fit to the within-patient repeated measures. To assess the differential treatment effects across the entire double-blind acute period, the main effect of treatment from the MMRM model was defined as the primary outcome. In addition, change from baseline to each visit was tested between treatment groups within the repeated-measures model. The same methodology was used for the secondary efficacy outcome measures. As a robustness check of the primary methodology, an analysis of variance (ANOVA) was performed for the key efficacy variables on the change from baseline to endpoint, last observation carried forward (LOCF). The model included treatment, investigator, and baseline score. Effect sizes were calculated for the MMRM and the LOCF models as the difference between treatment groups in the least-squares means divided by the standard deviation as estimated from the model.

The study was designed to detect a difference between treatment groups in the change from baseline in CGI-S score (overall treatment effect from MMRM model) of 0.29 with 90% power.

Response and remission rates were also used to compare efficacy between treatment groups. Response was defined in 2 different ways: $\geq 50\%$ reduction in the MADRS total score and, alternatively, a CGI-S score ≤ 3. Remission was defined as an endpoint (last observation available) MADRS total score ≤ 12 and, more conservatively, as ≤ 7. Rate of response was compared between groups with Fisher exact test; Kaplan-Meier estimators of time to event (response or remission) were calculated, and the treatment groups were compared with the log-rank test.

Treatment-emergent adverse events and rates of discontinuation were compared between treatment groups with Fisher exact test. Time to discontinuation was estimated using Kaplan-Meier methodology and compared between groups using the log-rank test. Change from baseline to endpoint (LOCF) in laboratory values and vital signs was compared between treatment groups with ANOVA, with treatment, investigator, and baseline value in the model. Treatment-emergent abnormal laboratory values were compared between treatment groups using Fisher exact test. The average rate of compliance was calculated (number of days compliant divided by number of days in study) for each patient and compared between treatment groups with ANOVA, with treatment and investigator in the model.

All analyses were based on the intent-to-treat principle and were performed using Statistical Application Software (SAS Institute Inc., Cary, N.C.). All tests of treatment effects were conducted at a 2-sided α level of 0.05. Data from investigators with fewer than 2 randomly assigned patients per treatment group were pooled for the purpose of statistical analysis.

Table 1. Patient Characteristics and Illness Severity at Baseline

Variable	OFC (N = 205)	Lamotrigine (N = 205)	Total (N = 410)
Female, %	57.6	62.4	60.0
White, %	80.5	82.9	81.7
Age, mean (SD), y	36.8 (11.5)	37.2 (10.7)	37.0 (11.1)
Psychotic features, % yes	4.4	7.3	5.9
Age at onset, mean (SD), y	18.7 (8.0)	19.3 (8.1)	19.0 (8.0)
Rapid cycling, % yes	33.2	34.6	33.9
Outpatients, %	99.0	99.5	99.3
Prior treatment history (within 2 y), N (%)			
Antidepressants	125 (61.0)	115 (56.1)	240 (58.5)
Anticonvulsants	75 (36.6)	67 (32.7)	142 (34.6)
Antipsychotics	50 (24.4)	40 (19.5)	90 (22.0)
Lithium	21 (10.2)	27 (13.2)	48 (11.7)
Sedatives	48 (23.4)	32 (15.6)	80 (19.5)
CGI-S score, mean (SD)[a]	4.6 (0.7)	4.6 (0.6)	4.6 (0.6)
MADRS total score, mean (SD)[a]	30.9 (5.4)	31.4 (5.2)	31.2 (5.3)
YMRS total score, mean (SD)[a]	5.21 (3.5)	4.64 (3.3)	4.9 (3.4)
GAF score, mean (SD)[a]	52.2 (6.3)	52.8 (6.1)	52.5 (6.2)
BSI-Global Severity Index score, mean (SD)[a]	1.7 (0.7)	1.7 (0.7)	1.68 (0.7)
BPRS total score, mean (SD)[a]	21.8 (9.7)	22.2 (9.7)	22.0 (9.7)

[a]Obtained for those patients with a baseline measurement and at least 1 postbaseline measurement: OFC, N = 202; lamotrigine, N = 191.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, BSI = Brief Symptom Inventory, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning scale, MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination, YMRS = Young Mania Rating Scale.

RESULTS

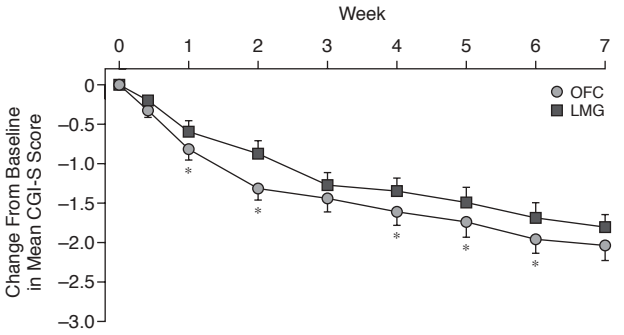
Patient and Illness Characteristics

The study included 410 randomly assigned patients (OFC, N = 205; lamotrigine [LMG], N = 205). At baseline, patient characteristics and illness severity in the treatment groups were comparable (Table 1). Participants were mostly outpatients and predominately white. In general, patients were severely depressed with minimal manic symptoms.

Treatment Disposition and Completer Status

There were no significant treatment differences in the proportion of patients completing the acute phase of the study (OFC, 66.8% vs. LMG, 65.4%; p = .835) or time to discontinuation (median time in days [95% CI] = OFC, 31.0 [23 to 35] vs. LMG, 23.5 [19 to 30]; p = .683). The most common reasons for treatment discontinuation were "lost to follow-up" (OFC, 9.3% vs. LMG, 13.7%), patient decision (OFC, 9.8% vs. LMG, 7.3%), and adverse events (OFC, 8.3% vs. LMG, 7.3%). Rash (OFC, 1.5% vs. LMG, 2.5%) and sedation (OFC, 2.0% vs. LMG, 0.0%) were the most common adverse events leading to discontinuation. Lack of efficacy was a less common reason for treatment discontinuation (OFC, 1.0% vs. LMG, 2.0%).

Figure 1. Change From Baseline to Each Treatment Visit in Mean CGI-S Total Score (with 95% confidence interval bars)[a]



[a]The OFC group had significantly greater least-squares mean (SE) improvement across the 7 weeks compared with the lamotrigine group (OFC = –1.43 [0.06] vs. lamotrigine = –1.18 [0.06]; p = .002, overall mixed-effects model repeated-measures analysis).
*The OFC group had significantly greater improvement than the lamotrigine group at weeks 1, 2, 4, 5, and 6 (p < .05).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, LMG = lamotrigine, OFC = olanzapine/fluoxetine combination.

Study Drug Dose

The percentages of OFC patients in each daily dose group at endpoint were as follows: 53.6% patients at 12/50, 23.6% at 12/25, 13.7% at 6/25, and 8.8% at 6/50 mg; 73.3% of the lamotrigine patients reached the optimal dose of 200 mg/day by the end of week 5, whereas the rest of the patients dropped out prior to obtaining 200 mg/day. One patient's dose was reduced to 150 mg/day. The mean modal daily dose for OFC was 38.3 mg (SD = 12.5) for fluoxetine and 10.7 mg (SD = 2.4) for olanzapine. The mean modal daily dose was 106.4 mg (SD = 81.9) for lamotrigine. There was no significant difference in overall treatment compliance (p = .650).

Efficacy

CGI-S. The OFC group had significantly greater least-squares mean improvement across the 7 weeks on the CGI-S compared with the lamotrigine group (p = .002, overall MMRM; Figure 1, Table 2). Analyzing the change from baseline to each week, the OFC group had significantly greater improvement than the lamotrigine group at weeks 1, 2, 4, 5, and 6 (all p < .05). In addition, the LOCF analysis showed a significant improvement for the OFC group compared with the lamotrigine group (p = .042; Table 3).

MADRS. Using MADRS total score, greater improvements in depressive symptoms were observed in the OFC group compared with the lamotrigine group across the 7-week acute period (p = .002, overall MMRM; Figure 2). The OFC-treated patients had significantly greater improvement in MADRS total score at weeks 1, 2, 4, 5, 6, and 7 (all p < .05). The LOCF analysis showed a similar resultant endpoint (p = .026; Table 3). Analysis of individual MADRS items detected significantly greater

Table 2. Efficacy of OFC Versus Lamotrigine for Bipolar I Depression During a 7-Week Trial (mixed-effects model repeated measures)

Efficacy Measure	Change From Baseline in Mean Score For Each Postbaseline Visit, Least-Squares Mean (SE)		p Value	Effect Size
	OFC	Lamotrigine		
CGI-S score	–1.43 (0.06)	–1.18 (0.06)	.002	0.26
MADRS total score	–14.91 (0.49)	–12.92 (0.50)	.002	0.24
YMRS total score	–1.68 (0.18)	–0.94 (0.18)	.001	0.24
GAF score	11.00 (0.52)	9.22 (0.52)	.010	0.21
BSI-Global Severity Index score	–0.80 (0.05)	–0.67 (0.05)	.028	0.23
CGI-I score[a]	2.41 (0.06)	2.63 (0.06)	.003	0.23
PGI score[a]	2.59 (0.06)	2.84 (0.06)	.002	0.25
BPRS total score	–11.62 (0.55)	–10.80 (0.57)	.253	0.11

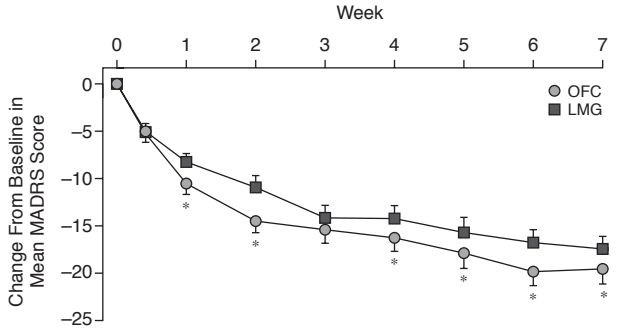
[a]The scales are not collected at baseline since the score itself is a measure of improvement and ranges from 1 = very much improved to 7 = very much worse.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, BSI = Brief Symptom Inventory, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning scale, MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination, PGI = Patient Global Impression of Improvement scale, YMRS = Young Mania Rating Scale.

Table 3. Efficacy of OFC Versus Lamotrigine for Bipolar I Depression During a 7-Week Trial (last observation carried forward)

Efficacy Measure	Change From Baseline to Endpoint, Mean (SD)		p Value	Effect Size
	OFC	Lamotrigine		
CGI-S score	–1.85 (1.33)	–1.62 (1.30)	.042	0.21
MADRS total score	–18.49 (9.73)	–16.41 (10.70)	.026	0.23
YMRS total score	–1.84 (4.44)	–1.26 (4.66)	.013	0.26

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.

Figure 2. Change From Baseline to Each Treatment Visit in Mean MADRS Total Score (with 95% confidence interval bars)[a]



[a]The OFC group had significantly greater least-squares mean (SE) improvement across the 7 weeks compared with the lamotrigine group (OFC, –14.91 [0.49] vs. lamotrigine, –12.92 [0.50]; p = .002, overall mixed-effects model repeated-measures analysis).
*The OFC group had significantly greater improvement at weeks 1, 2, 4, 5, 6, and 7 (p < .05).
Abbreviations: LMG = lamotrigine, MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination.

improvement (p < .05) for the OFC group compared with the lamotrigine group for MADRS item 2 (reported sadness), item 3 (inner tension), item 4 (reduced sleep), item 5 (reduced appetite), item 9 (pessimistic thoughts), and item 10 (suicidal thoughts).

YMRS. Baseline manic symptoms were low for both treatment groups as measured by YMRS total score (OFC, 5.21 vs. LMG, 4.64; Table 1). However, greater mean improvements in manic symptoms were observed over the 7 weeks in the OFC group compared with the lamotrigine group (p = .001, overall MMRM; Table 2). The OFC-treated patients had significantly greater improvement than the lamotrigine group in YMRS total score at day 3 and weeks 1, 2, 4, 5, and 7 (all p < .05). At endpoint, the LOCF analysis also detected a significant benefit for OFC-treated patients compared with the lamotrigine group (p = .013; Table 3).

Response and Remission

The response rates did not significantly differ by treatment group when response was defined as a ≥ 50% reduction in MADRS total score (OFC, 68.8% vs. LMG, 59.7%; p = .073; Table 4) or when response was defined as a CGI-S score ≤ 3 (OFC, 71.8% vs. LMG, 64.4%; p = .130). The time to 50% reduction in MADRS total score was significantly shorter for the OFC group compared with the lamotrigine group (median days [95% CI] = OFC, 17 [14 to 22] vs. LMG, 23 [21 to 34]; p = .010). The rate of remission (OFC, 56.4% vs. LMG, 49.2%; p = .158) and the time to remission (p = .072) did not significantly differ between treatment groups when remission was defined as a MADRS score ≤ 12. The rate of remission (OFC, 37.1% vs. LMG, 30.9%; p = .203) and the time to remission (p = .181) also did not significantly differ between the treatment groups when remission was defined as a MADRS score ≤ 7.

Table 4. Completer Status, Response and Remission Rates, and Treatment-Emergent Mania and Self-Injurious Behavior in Patients Taking OFC Versus Lamotrigine for Bipolar Disorder

Measure	OFC	Lamotrigine	p Value
Patients completing 7-week acute phase, %	66.8	65.4	.835
Median time to discontinuation, d (95% CI)	31.0 (23 to 35)	23.5 (19 to 30)	.683
Responders (≥ 50% reduction in MADRS score), %	68.8	59.7	.073
Median time to response, d (95% CI)	17 (14 to 22)	23 (21 to 34)	.010
Remission (MADRS score ≤ 12), %	56.4	49.2	.158
Median time to remission, d (95% CI)	32 (21 to 42)	41 (35)[a]	.072
Remission (MADRS ≤ 7), %	37.1	30.9	.203
Median time to remission, d (95% CI)	55 (49)[a]	58 (52)[a]	.181
Rate of emerging mania (YMRS score > 15), %	4.0	5.2	.633
Suicidal and self-injurious behavior, %[b]	0.5	3.4	.037

[a]Lower limit of confidence interval is shown. Upper limit was not calculable.
[b]Medical Dictionary for Regulatory Activities (MedDRA) term collapsing suicide acts, suicide attempts, and self-harm events.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination, YMRS = Young Mania Rating Scale.

Other Secondary Efficacy Measures

The OFC-treated patients had significantly greater mean improvements over the 7-week period than lamotrigine-treated patients as measured by the BSI-Global Severity Index (Table 2). Of the 9 dimensions measured by this scale (anxiety, depression, hostility, interpersonal sensitivity, obsessive compulsive, paranoid, phobic, psychoticism, and somatization), OFC-treated patients showed significantly greater improvement on the depression ($p = .035$), psychoticism ($p = .046$), and hostility ($p < .001$) dimensions than lamotrigine-treated patients. Significant differences were not detected on the other 6 dimensions (data not shown). The OFC-treated patients also showed greater improvement over the 7-week period in GAF, CGI-I, and PGI scores compared with lamotrigine-treated patients, but there were no differences detected between groups on the BPRS (Table 2).

Table 5. Treatment-Emergent Adverse Events With an Incidence > 5% in Either Group

Adverse Event	OFC (N = 205) %	Lamotrigine (N = 204) %	p Value
Somnolence	18.5	8.3	.003
Increased appetite	17.6	8.3	.008
Dry mouth	15.6	5.9	.002
Increased weight	14.1	2.0	< .001
Dizziness	13.7	7.8	.078
Sedation	13.7	2.5	< .001
Headache	11.7	9.3	.52
Tremor	10.7	1.5	< .001
Fatigue	8.3	5.4	.328
Nausea	7.8	7.8	.99
Insomnia	4.4	8.8	.076
Rash	2.9	6.9	.071

Abbreviation: OFC = olanzapine/fluoxetine combination.

Treatment-Emergent Mania

Treatment-emergent mania was defined as a YMRS total score ≥ 15 at any time after baseline (patients were required to have a YMRS total score < 15 to enter the study). The incidence of treatment-emergent mania was low and not statistically significantly different between the treatment groups ($p = .633$; Table 4). Rates of treatment-emergent mania were 4.0% (8/202) for the OFC group and 5.2% (10/191) for the lamotrigine group.

Safety and Tolerability

Treatment-emergent adverse events with an incidence greater than 5% for either treatment group are reported in Table 5. None of these adverse events, including rash, were significantly more common with lamotrigine. Significantly more patients treated with OFC than lamotrigine reported somnolence, increased appetite, dry mouth, sedation, weight gain, and tremor.

There was a significant difference in the incidence of "suicidal and self-injurious behavior" (the MedDRA term that includes all suicidal and self-harm events) as captured as treatment-emergent adverse events in favor of the OFC treatment group (OFC, 0.5% vs. LMG, 3.4%; $p = .037$). Two suicide attempts led to discontinuation in lamotrigine-treated patients, and 1 suicide attempt led to discontinuation in an OFC-treated patient. As specified a priori, the suicide item of the MADRS (item 10) was also analyzed. Across the 7 weeks, OFC patients had significantly greater mean improvement than lamotrigine patients (OFC, –0.91 vs. LMG, –0.74; $p = .004$); significant differences between groups were detected at weeks 1, 2, 4, and 5.

Clinically relevant laboratory values are reported in Table 6. Laboratory samples were collected in a fasting state. There were significant treatment differences in the mean change from baseline to endpoint for weight, hemoglobin A1c, prolactin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels in favor of lamotrigine. There were also significant treatment differences for the

Table 6. Change From Baseline to Endpoint in Laboratory Values During a 7-Week Trial of OFC vs. Lamotrigine for Bipolar I Depression (last observation carried forward)

Item	Treatment	N	Baseline Mean (SD)	Mean Change to Endpoint (SD)	p Value
Weight, kg	OFC	201	83.4 (25.0)	3.1 (3.4)	< .001
	LMG	190	84.7 (22.1)	–0.3 (2.4)	
Fasting glucose, mg/dL	OFC	134	91.1 (16.3)	1.4 (14.0)	.538
	LMG	128	91.8 (12.1)	0.1 (14.0)	
Hemoglobin A1c, %	OFC	167	5.3 (0.5)	0.0 (0.2)	< .001
	LMG	156	5.3 (0.4)	–0.1 (0.2)	
Prolactin, ng/mL	OFC	167	12.5 (13.5)	9.3 (20.0)	< .001
	LMG	156	12.2 (10.7)	0.0 (10.7)	
Total cholesterol, mg/dL	OFC	165	197.3 (45.6)	15.3 (31.9)	< .001
	LMG	151	197.4 (40.9)	–8.0 (27.1)	
HDL cholesterol dextran precipitation, mg/dL	OFC	165	48.4 (13.8)	1.8 (10.4)	.032
	LMG	150	47.1 (13.5)	–0.6 (8.0)	
LDL cholesterol, mg/dL	OFC	157	120.2 (39.4)	9.1 (26.6)	< .001
	LMG	137	120.8 (35.7)	–6.8 (25.3)	
Triglycerides, mg/dL	OFC	165	137.9 (76.1)	27.0 (91.3)	.001
	LMG	151	155.6 (121.7)	–13.5 (110.3)	

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, LMG = lamotrigine, OFC = olanzapine/fluoxetine combination.

incidence of treatment-emergent abnormally high laboratory values for total cholesterol (OFC, 13.6% vs. LMG, 3.7%; p = .003), low-density lipoprotein cholesterol (OFC, 7.7% vs. LMG, 1.5%; p = .021), and prolactin (OFC, 25.7% vs. LMG, 5.7%; p < .001) based on Covance, Inc. (Indianapolis, Ind.) reference ranges. In addition, there was a numerical difference in the incidence of treatment-emergent abnormally high fasting glucose (Covance, Inc. [Indianapolis, Ind.] reference range) that was not statistically significant (OFC, 7.1% vs. LMG, 1.6%; p = .060). There were no significant differences in the incidence of treatment-emergent abnormally high laboratory values for triglycerides (OFC, 16.8% vs. LMG, 10.5%; p = .157). There was a significantly greater incidence of potentially clinically relevant weight gain as defined by an increase ≥ 7% in weight in OFC-treated patients (OFC, 23.4% vs. LMG, 0%; p < .001). There was no difference in the severity of tardive dyskinesia symptoms, as measured by the AIMS (OFC, –0.23 vs. LMG, –0.01; p = .733). As allowed by the protocol, 22% of patients took benzodiazepines during the study, whereas only 1% of patients took any anticholinergics. There were no differences between treatment groups in those taking benzodiazepines (p = .721) or anticholinergics (p = .215).

DISCUSSION

This is the first randomized, double-blind, direct comparison of OFC with lamotrigine for the acute treatment of bipolar I depression. The OFC-treated patients had statistically significantly greater improvement in overall symptom severity and in depressive and manic symptoms compared with lamotrigine-treated patients. More adverse events, including weight gain and metabolic abnormalities, were documented in the OFC-treated patients than the lamotrigine-treated patients; lamotrigine-treated patients had more adverse events related to suicidal and self-injurious behavior than the OFC-treated patients.

Response rates for both OFC (68.8%) and lamotrigine (59.7%) as defined by a MADRS score reduction ≥ 50% were higher in this study than what has previously been reported for placebo groups in the acute treatment of bipolar I depression. Tohen et al.[22] reported a 30.4% placebo response rate on the MADRS in the OFC placebo-controlled study for bipolar I depression, and Calabrese et al.[16] reported a 29% placebo response rate on the MADRS in the lamotrigine placebo-controlled study for bipolar I depression. In addition, rates of treatment-emergent mania in this study were low for both treatment groups (OFC, 4.0% vs. LMG, 5.2%).

Treatment differences in illness severity, depressive symptoms, and manic symptoms in favor of OFC over lamotrigine in the present study were significant by week 1. In the previous OFC bipolar I depression study,[22] OFC treatment resulted in significant improvement of depressive symptoms as early as week 1 compared with placebo. In the previous study of lamotrigine for acute bipolar I depression,[16] lamotrigine was titrated up to 50 mg over 2 weeks or to 200 mg over 4 weeks. In that study,[16] lamotrigine (at both doses) significantly differentiated from placebo on MADRS total score after 3 weeks of treatment, and the difference was maintained throughout 7 weeks of treatment.

Dosing in this study was titrated up over 5 weeks for lamotrigine, so the 200 mg/day dose was only received for the last 2 weeks. At least part of the treatment difference in symptom response in this study may, therefore, have been

due to the ability to initiate optimal dosing earlier in the trial with OFC than with lamotrigine. Thus, continued improvement in the lamotrigine group may be apparent with longer duration of the optimal dose. However, at this time, there is no evidence that lamotrigine at 200 mg/day is any more effective than lamotrigine at 50 mg/day for the treatment of acute bipolar I depression.[16] It will be important to determine if treatment differences endure or diminish over the 4.5-month continuation phase of this trial.

The effect size for the primary analysis (CGI-S) was of only modest size (0.26). However, given that this is an effect size comparing 2 active treatments, a large effect size was not anticipated. For comparison, the effect size for the primary analysis in the OFC versus placebo study[22] was 0.68, and in the lamotrigine (200 mg) versus placebo study,[16] it was estimated to be 0.34. Since these effect sizes are calculated against placebo, they are expected to be larger. Interestingly, for the treatment of major depressive disorder, a meta-analysis of fluoxetine versus placebo found the effect size to be only a modest size of 0.30 based on the 17-item Hamilton Rating Scale for Depression total score.[33] Additional studies are needed to determine the clinical relevance of the modest treatment differences between OFC and lamotrigine in patients with bipolar I depression.

OFC safety in this study appeared similar to what has previously been reported for olanzapine in combination with fluoxetine for the treatment of bipolar I disorder.[22] The OFC-treated patients had significantly more mean weight gain and increases in cholesterol and triglycerides compared with lamotrigine-treated patients. These increases must be considered along with potential efficacy advantages in order to make an appropriate risk/benefit assessment. This must be done on an individual-patient basis. For patients treated with OFC who have increases in weight or metabolic parameters that the clinician deems substantial in comparison to the benefits of treatment, alternative therapies should be considered. In light of lamotrigine's weight-neutral profile, lamotrigine is often suggested for treatment of bipolar depressed patients with weight gain, obesity, or metabolic abnormalities.[34] For patients treated with OFC who have increases in weight or metabolic parameters, or both, but for whom the clinician deems continued treatment appropriate, clinicians should address weight and lipid management. Recently, a group of psychiatric and other health care professionals met at the Mount Sinai Conference and published consensus recommendations on the physical health monitoring of patients with schizophrenia, including regular monitoring of body mass index, plasma glucose levels, and lipid profiles.[35] Although these guidelines were made for patients with schizophrenia, many of the recommendations are likely to apply to patients with bipolar disorder as well.

There was a significantly greater incidence of treatment-emergent abnormally high prolactin levels for OFC-treated patients compared with lamotrigine-treated patients. The incidence of abnormally high values in OFC-treated patients in the current study is consistent with the incidence in trials of olanzapine.[36]

Lamotrigine-treated patients had a greater incidence of treatment-emergent suicidal and self-injurious behaviors compared with OFC-treated patients. These observations are consistent with the greater decrease in the suicidal thought item of the MADRS of OFC-treated patients compared with lamotrigine-treated patients. However, these observations are preliminary and require replication to conclusively show a clinically relevant difference between OFC and lamotrigine in decreasing the risk of suicidality in acutely ill patients with bipolar I depression.

This study had a number of potential limitations. As already briefly discussed, lamotrigine-treated patients only received the target 200-mg/day dose for the last 2 weeks of the acute phase of the study owing to the slow dose titration. However, this dose titration was in accordance with the lamotrigine package insert recommendation[15] for dosing in order to minimize the risk of serious rash. This titration is also consistent with the dosing strategy in a previously conducted positive study of lamotrigine in bipolar I depression.[16] In that study, both 50 and 200 mg/day were superior to placebo. In the present study, as in the previous study, patients were receiving 50 mg/day of lamotrigine starting at week 2. An additional limitation of the present study is the lack of a placebo group. This may have led to elevated response rates for one or both treatments. Elevated response rates may have potentially reduced treatment differences.

In summary, OFC therapy produced statistically but modestly greater improvement in overall severity of illness, depressive symptoms, and manic symptoms compared with lamotrigine therapy for patients with acute bipolar I depression. The incidence of treatment-emergent mania was low and not statistically significantly different between the treatment groups. The OFC-treated patients experienced significantly greater weight gain and increases in some metabolic parameters compared with lamotrigine-treated patients, whereas lamotrigine-treated patients had a greater incidence of adverse events related to suicidality and self-harm than OFC-treated patients. Further long-term clinical studies are warranted to confirm and interpret these modest treatment differences.

Drug names: benztropine (Cogentin and others), fluoxetine (Prozac and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax).

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