

Olanzapine/Fluoxetine Combination in Children and Adolescents With Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: To assess the efficacy and safety of olanzapine/fluoxetine combination (OFC) for the acute treatment of bipolar depression in children and adolescents.

Method: Patients 10 to 17 years of age with bipolar I disorder (BP-I), depressed episode, baseline Children's Depression Rating Scale-Revised (CDRS-R) total score ≥ 40 , Young Mania Rating Scale (YMRS) total score ≤ 15 , and YMRS-item 1 ≤ 2 were randomized to OFC (6/25–12/50 mg/day olanzapine/fluoxetine; $n = 170$) or placebo ($n = 85$) for up to 8 weeks of double-blind treatment. The primary efficacy measure was mean change in CDRS-R using mixed-model repeated-measures methodology.

Results: Baseline-to-week-8 least-squares mean change in CDRS-R total score was greater for OFC-treated patients than for placebo-treated patients (-28.4 versus -23.4 , $p = .003$; effect size = .46), with between-group differences statistically significant at week 1 ($p = .02$) and all subsequent visits (all $p < .01$). Rates of and times to response and remission were statistically significantly greater for OFC- than for placebo-treated patients. The most frequent treatment-emergent adverse events in the OFC group were weight gain, increased appetite, and somnolence.

Mean weight gain at patient's endpoint was significantly greater for OFC- than for placebo-treated patients (4.4 kg versus 0.5 kg, $p < .001$). Treatment-emergent hyperlipidemia was very common among OFC-treated patients. Abnormal increases in hepatic analytes, prolactin, and corrected QT interval (QTc) were also common or very common but generally not clinically significant.

Conclusion: In this study, OFC was superior to placebo, and has been approved by the US Food and Drug Administration (FDA) for the acute treatment of bipolar I depression in patients 10 to 17 years of age. Benefits should be weighed against the risk of adverse events, particularly weight gain and hyperlipidemia.

Clinical trial registration information—A Study for Assessing Treatment of Patients Ages 10-17 with Bipolar Depression; <http://clinicaltrials.gov>; NCT00844857.

Key Words: olanzapine fluoxetine combination, bipolar, depression

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Treatment of the depressive phase of bipolar disorder (BD) in children and adolescents remains a significant unmet medical need. Relative to those diagnosed in adulthood, patients diagnosed with BD during childhood or adolescence have significantly reduced quality of life¹ and greater risk of poorer psychiatric, psychosocial, and health-related outcomes,² including greater risk of suicidal behavior.^{3,4} Inadequate or delayed symptom control in these young patients may have serious impacts on social, emotional, and educational development that can leave this already-vulnerable population even further impaired and disadvantaged. Consequently, rapid and reliable intervention is critical.

Unfortunately, the pharmacological treatment of bipolar depression poses a major therapeutic challenge. Unopposed antidepressant therapy may potentially precipitate manic symptoms,⁵ and although there are multiple medications effective for the treatment of mania, treatment of the

depressive phase of the illness remains understudied in both children and adults, and many frequently used treatments, such as lithium, valproate, and lamotrigine, have limited or no evidence to support their use for the acute treatment of bipolar depression.⁶ At present, only 3 medications are approved for the acute treatment of bipolar depression in adults in the United States by the US Food and Drug Administration (FDA): quetiapine, lurasidone, and olanzapine/fluoxetine combination (OFC). With regard to testing these medications in children and adolescents, 2 randomized, double-blind studies of quetiapine were conducted in patients 10 to 17 years of age diagnosed with bipolar depression, but both studies failed to demonstrate a significant benefit of quetiapine versus placebo in that population.^{7,8} Pediatric trials of lurasidone are still pending.

OFC is a fixed-dose combination capsule, available in generic preparation, which contains the second-generation antipsychotic (SGA) olanzapine and the selective serotonin reuptake inhibitor (SSRI) fluoxetine. Olanzapine and fluoxetine can also be separately co-administered to achieve the same approximate proportions as the fixed-combination OFC capsule.^{9,10} Olanzapine is an effective mood stabilizer¹¹⁻¹³ that appears to enhance the antidepressant action



Clinical guidance is available at the end of this article.

of fluoxetine,^{14,15} as demonstrated in adult studies of treatment-resistant depression, which showed OFC to be superior to fluoxetine alone.¹⁶⁻¹⁸ OFC has also demonstrated rapid and robust improvement of depressive symptoms in adults with bipolar I depression^{19,20} without increasing risk of switch to mania, and was superior to placebo,¹⁹ olanzapine monotherapy,¹⁹ and lamotrigine²¹ during acute treatment.

Although OFC has not previously been studied in patients <18 years of age, its components have been evaluated separately for other indications for which they are now FDA approved. Fluoxetine has been shown to be efficacious for the treatment of major depressive disorder (MDD) in patients 8 to 18 years of age^{22,23} and for obsessive-compulsive disorder in patients 7 to 17 years of age,²⁴ and is generally very well tolerated, with a safety profile similar to that observed in adults.²⁵ Olanzapine has been shown to be efficacious for the treatment of schizophrenia and manic or mixed episodes associated with BD in adolescents 13 to 17 years of age.^{26,27} The most frequent adverse events observed with olanzapine in adolescents included weight gain and somnolence,^{26,27} with adolescent patients likely to gain more weight, experience increased somnolence/sedation, and have greater increases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, prolactin, and hepatic aminotransferase levels than those observed in adults treated with olanzapine.¹⁰ As a result, US labeling for olanzapine warns that clinicians may wish to consider prescribing other medications first in adolescents.¹⁰ Although OFC in children and adolescents would be expected to carry a metabolic risk similar to that of olanzapine monotherapy, the previous lack of an approved medication for the treatment of pediatric bipolar depression supported the need to assess OFC as a possible acute treatment option despite this risk.

The objective of the present study was to assess the efficacy and safety of OFC versus placebo for the treatment of depressive episodes associated with bipolar I disorder (BP-I) in children and adolescents. This study was conducted at the request of the FDA as part of the Pediatric Research Equity Act.

METHOD

Study Patients

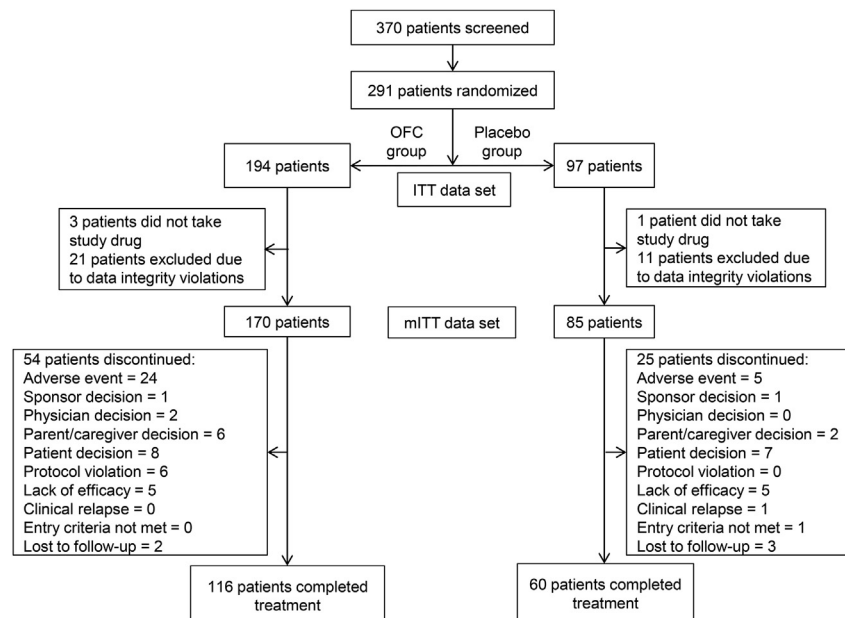
Patients were either inpatients or outpatients, 10 to 17 years of age, who met *DSM-IV-TR*²⁸ criteria for BP-I, current episode depressed, with at least 1 previous manic episode, as confirmed by the Kiddie-Schedule for Affective Disorders–Present and Lifetime (K-SADS-PL).²⁹ Patients also had to have a Children’s Depression Rating Scale–Revised (CDRS-R)³⁰ total score ≥ 40 and a Young Mania Rating Scale (YMRS)³¹ total score ≤ 15 , with YMRS item 1 (Elevated Mood) score ≤ 2 at screening and randomization.

Patients were excluded who had a current or lifetime diagnosis of any of the following according to *DSM-IV-TR* criteria: schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder, delirium, amnesic disorder, substance-induced disorder, mental retardation, substance dependence other than nicotine or caffeine within 30 days before study entry, or a current diagnosis of autism or pervasive developmental disorder. Participants could not be actively suicidal as determined by investigator judgment.

Study Design and Treatment

This was a phase 4, randomized, double-blind, placebo-controlled study conducted between March 2009 and February 2012 at 41 centers in the United States, Mexico, and Russia. Sites were selected based on previous clinical trial experience and experience with pediatric bipolar disorder (PBD). Patients entered a 2- to 45-day screening and washout period during which all psychotropic medications were tapered and discontinued at least 25 hours before

FIGURE 1 Patient disposition. Note: ITT = intent-to-treat; mITT = modified intent-to-treat; OFC = olanzapine/fluoxetine combination.



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