Long-Term Weight Gain in Patients Treated With Open-Label Olanzapine in Combination With Fluoxetine for Major Depressive Disorder

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Objective: Patients with major depressive disorder (MDD) treated with olanzapine in combination with fluoxetine (OFC) demonstrate robust improvement in their depressive symptoms. Treatment with olanzapine may impact a patient's weight; thus, long-term weight gain and potential predictors (e.g., age and gender) and correlates (e.g., cholesterol and glucose levels) of weight gain were investigated in OFC-treated patients with MDD.

Method: Outpatients who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, diagnostic criteria for MDD were included (N = 549) in the current analyses of this 76-week, open-label study (February 2000 to July 2002). Maximum, endpoint, and potentially clinically significant (PCS; ≥ 7% increase from baseline) weight gain; time to PCS weight gain; and predictors and correlates of weight change were assessed. Patients were treated once daily with oral olanzapine (6, 12, or 18 mg) plus fluoxetine (25, 50, or 75 mg) capsules. Statistical significance for all tests was based upon $p \leq .05$.

Results: Mean baseline-to-endpoint weight change was 5.6 ± 6.6 kg (12.3 ± 14.6 lb). Weight gain plateaued by 52 weeks. Fifty-six percent of patients met criteria for PCS weight gain by 76 weeks, and the median time to PCS weight gain was 16 weeks. Low baseline body mass index (BMI), female gender, younger age, and increased fluoxetine dose were predictors of weight gain; olanzapine dose was not. Patients with early (≤ 6 weeks) rapid PCS weight gain were 4.6 times more likely to gain substantial (≥ 15%) weight long-term (weeks 7–76). Changes to endpoint in total cholesterol and systolic blood pressure values were positively correlated with weight change.

Conclusion: Long-term (76 weeks) OFC treatment may lead to a large percentage (56%) of patients meeting criteria for PCS weight gain (≥ 7%). The risk of weight gain may be significantly increased for OFC-treated patients who have a low BMI or who are female, younger, or taking high-dose fluoxetine. It is important that prescribers balance the risk of weight gain with the benefit of treatment for individual patients with depression.

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Some patients who receive treatment with antipsychotics, including the atypical antipsychotic olanzapine, commonly gain weight.[1,2] Observations of weight gain of 1.2 to 11.9 kg have been reported in double-blind, controlled clinical trials examining olanzapine.[3–9] Long-term trial data may be more meaningful than short-term data because patients with psychiatric disorders often require maintenance therapy to prevent relapse. Examination of long-term effects (up to 3 years) of olanzapine on body weight has demonstrated a mean weight change for olanzapine-treated patients of 6.3 kg, with approximately 26% of patients losing or gaining no weight, 44% gaining > 0 to 10 kg, 22% gaining > 10 to 20 kg, and 9% gaining > 20 kg.[10,11]

For patients with major depressive disorder (MDD), olanzapine in combination with fluoxetine (OFC) treatment has demonstrated sustained improvements in depressive symptoms and a safety profile similar to that of its components.[12] Mean Montgomery-Asberg Depression Rating Scale (MADRS; primary efficacy measure) total scores decreased 11, 18, and 22 points from baseline after 1, 8, and 76 weeks of treatment, respectively. Response (62%) and remission (56%) rates were high. The relapse rate was low (15%).[12]

In a recent study of patients with borderline personality disorder, OFC-treated patients gained statistically significantly less weight than olanzapine-treated patients.[13] Fluoxetine treatment has led to a 52-week statistically significant weight loss (5.8 kg) in patients with type 2 diabetes mellitus,[14] and fluoxetine has been shown to be an effective anorexic agent in obese subjects.[15,16] However, data from 2 OFC studies suggest that treatment with fluoxetine did not prevent treatment-emergent weight

gain in patients treated with olanzapine.[12,17] In these studies, and in comparisons of data from other studies,[10,12,17,18] mean weight change in OFC-treated patients was similar to that observed in olanzapine-treated patients.

Patients with psychiatric disorders, regardless of antipsychotic treatment, have an increased risk for weight gain[19,20] and a greater prevalence of being overweight or obese than individuals without a psychiatric disorder.[21,22] Weight gain during treatment with psychotropic agents can lead to poor self-esteem, social withdrawal, and poor treatment compliance.[23] Moreover, increased weight is considered one of the risk factors for glucose dysregulation, type 2 diabetes mellitus, hypertension, and dyslipidemia.[24,25] The current analyses were conducted to examine weight change (including predictors of weight gain) in OFC-treated patients with MDD to provide information that may help physicians make risk-benefit decisions (weight gain vs. efficacy) regarding OFC treatment.

METHOD

Subjects

A total of 651 patients who met diagnostic criteria for MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), entered the study. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version (SCID-CV),[26] and the MDD specifiers in the SCID-I, Research Version,[27] confirmed the diagnosis of MDD. Patients were also required to have a Clinical Global Impressions-Severity of Illness scale[28] score of ≥ 3. At the end of the screening period, 560 patients continued to meet inclusion criteria and were enrolled in the study (study code F1D-MC-HGIP). Patients were included (549 of 560) in the current weight analyses if they had at least 1 acceptable dose of OFC (olanzapine/fluoxetine: 6/25, 6/50, 6/75, 12/25, 12/50, 12/75, 18/25, 18/50, or 18/75 mg/day), had a baseline weight assessment, and had at least 1 postbaseline weight assessment. All patients were aged 18 years or older and had signed a written informed consent form prior to participating in the study. Pregnant or lactating women were excluded. Ethics committees at each site, in accordance with the Declaration of Helsinki, approved the protocol. Potential treatment-emergent adverse events were explained to patients.

A large number of patients (144 of 549, 26.2%) were considered to have treatment-resistant depression (TRD), as determined by individual investigators on the basis of patient history of treatment failure with at least 2 different classes of antidepressant.[12] Treatment-resistant depression was a variable tested for effect (risk) on weight change and was found not to be statistically significant ($p = .800$). Therefore, analyses differentiating TRD from non-TRD patients were excluded.

Study Design

This 76-week, open-label trial was conducted at 40 outpatient investigative sites in the United States, Canada, Australia, Italy, Belgium, Poland, and Turkey. The starting dose was 6 mg of olanzapine in combination with 25 mg of fluoxetine. Thereafter, the dose could be adjusted, according to the investigator's clinical judgment, within a dose range of olanzapine 6, 12, or 18 mg/day in combination with fluoxetine 25, 50, or 75 mg/day. Olanzapine and fluoxetine were administered as separate capsules, taken together once daily in the evening. Data were collected from February 2000 to July 2002. In general, concomitant medications with primarily central nervous system activity were not allowed.

Assessment

Weight and other vital signs were assessed at every visit (weeks 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 52, 60, 68, and 76). Laboratory assessments were performed at baseline and at weeks 12, 24, 36, 52, 68, and 76 or upon early discontinuation. Spontaneously reported adverse events were recorded at every visit.

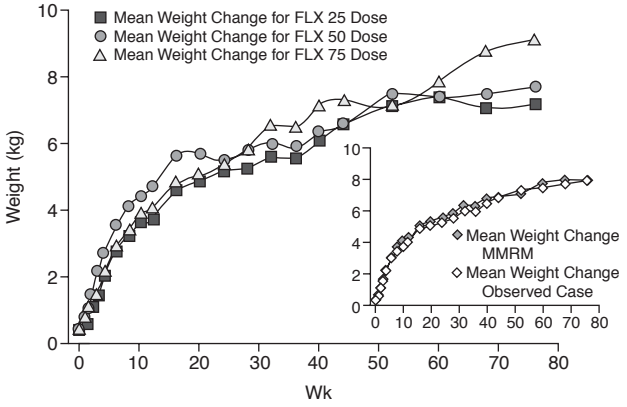
Statistical Methods

SAS version 8.2 (SAS Institute, Cary, N.C.) was used for all statistical analyses. In analyses of laboratory analytes and blood pressure measures, only patients with a baseline and at least 1 postbaseline measure were included. Endpoint refers to a patient's endpoint (i.e., the time at which the patient discontinued or completed the study). All hypotheses were tested at a 2-tailed significance level of $p \leq .05$.

Graphs of postbaseline weight measurements were created using observed cases (OCs). With the OC analyses, only patients with a weight observed at a given visit contributed to the mean weight change at that visit. Additionally, a likelihood-based mixed-model repeated-measures (MMRM) analysis was performed. For patients who discontinued prior to study end, the MMRM analysis modeled each patient's weight at each visit after discontinuation, contributing data to the mean weight change values at subsequent study visits. The linear model for the MMRM analysis included terms for the investigator and time in study and assumed an unstructured variance-covariance matrix. Mixed-model repeated-measures findings were similar to those of OCs (Figure 1); thus, for simplification, discussion focuses on the OC results.

An analysis-of-variance model evaluated changes in weight from baseline to maximum postbaseline weight. Multivariate logistic regression, using a stepwise approach, was used to identify significant predictors of weight change and potentially clinically significant (PCS) weight gain. Potentially clinically significant weight gain was defined as a ≥ 7% increase from baseline.[8,29,30] A Kaplan-Meier plot assessed time to PCS weight gain. The

Figure 1. Mean Weight Change From Baseline Over Time by Modal Fluoxetine Dose Among Outpatients With Major Depressive Disorder[a]



[a]Means in the main figure are based upon observed cases (e.g., only patients with a weight observed at 76 weeks contributed to the mean weight change at 76 weeks). Observed-case results without breaking out by fluoxetine dose are presented in the inset figure along with a likelihood-based MMRM analysis, in which the weight of a patient who discontinued prior to study endpoint contributed to subsequent study visit mean weight change values (see the Statistical Methods section).

Abbreviations: FLX 25 = fluoxetine 25 mg/d, FLX 50 = fluoxetine 50 mg/d, FLX 75 = fluoxetine 75 mg/d, MMRM = mixed-model repeated measures.

Table 1. Demographic and Baseline Illness Characteristics of 549 Outpatients With Major Depressive Disorder

Variable	Mean (incidence)	SD	Median
Age, y	43.2	12.1	43.6
Women, %	(66.7)	NA	NA
White, %	(89.4)	NA	NA
Antipsychotic-naive, %	(86.5)	NA	NA
Weight, kg	79.8	21.9	76.0
Body mass index, kg/m^2	28.3	7.1	27.3
MADRS total score	31.7	7.1	32.0

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable.

Table 2. Distribution of Olanzapine in Combination With Fluoxetine Dosing in 549 Outpatients With Major Depressive Disorder

Dose, mg/d[a]	N	%
6/25	219	39.9
6/50	138	25.1
6/75	77	14.0
12/25	13	2.4
12/50	28	5.1
12/75	42	7.7
18/25	2	0.4
18/50	8	1.5
18/75	22	4.0

[a]Olanzapine dose (numerator) in combination with fluoxetine dose (denominator).

Cox proportional hazards model was used to determine whether early rapid weight gain was a predictor of substantial long-term weight gain. Early rapid weight gain was defined as a ≥ 7% increase from baseline within the first 6 weeks of treatment. Substantial long-term weight gain was defined as a ≥ 15% gain from baseline throughout the remainder of the study (weeks 7–76), using the same baseline (visits 1–2) for each category. Categorical data were evaluated with the Fisher exact test.

A treatment-emergent PCS increase in nonfasting (random) glucose level was defined as a baseline result less than 140 mg/dL that increased to at least 200 mg/dL postbaseline.[31] A treatment-emergent PCS increase in total cholesterol level was defined as a baseline result less than 200 mg/dL that increased to at least 240 mg/dL.[32]

Each patient was assigned to a dose group on the basis of their modal dose. The modal dose for each patient was calculated after deleting all but acceptable, protocol-defined OFC doses (6/25, 6/50, 6/75, 12/25, 12/50, 12/75, 18/25, 18/50, and 18/75 mg of olanzapine in combination with fluoxetine). In the event that more than 1 dose was most frequently used for a patient, the highest dose was selected.

RESULTS

Table 1 summarizes patient demographics and baseline illness characteristics. At baseline, 95% of patients had a MADRS total score of ≥ 19, denoting at least a moderate severity of illness. Fifty percent of patients had a baseline MADRS total score of ≥ 32. Among the patient population, 86.5% were antipsychotic-naive.

Table 2 provides a patient distribution by modal dose taken during the study. A large proportion of patients had a modal dose that was the lowest available olanzapine dose (6 mg/day, 79.0% of patients) given in combination with their fluoxetine treatment. In combination with 6 mg/day of olanzapine, the most commonly provided fluoxetine dose was the lowest dose available (25 mg/day, 39.9% of patients). In combination with 6 mg/day of olanzapine, 39.1% of patients had a modal dose of either 50 or 75 mg/day of fluoxetine.

The cumulative patient study discontinuation rate for any reason was 30.8% at 12 weeks, 47.9% at 24 weeks, 67.8% at 52 weeks, and 74.0% at 76 weeks. The cumulative patient study discontinuation rate due to adverse events was 12.9% at 12 weeks, 18.9% at 24 weeks, 23.9% at 52 weeks, and 24.8% at 76 weeks. Table 3 summarizes the incidence of the reasons for discontinuation across the entire 76-week study. Weight gain was the most common adverse event reported as reason for discontinuation (8.2% of the total study patients). Three patients (0.6%) discontinued due to hyperglycemia or diabetes (Table 3). Two of these patients had diabetes mellitus at baseline and baseline glucose values of > 200 mg/dL.

Table 3. Reasons for Study Discontinuation Among 549 Outpatients With Major Depressive Disorder

Variable	N	%
Adverse event total[a]	136	24.8
Weight gain	45	8.2
Hyperglycemia	2	0.4
Diabetes mellitus	1	0.2
Other adverse event	88	16.0
Other[b]	270	49.2
Total	406	74.0

[a]Any *Medical Dictionary for Regulatory Activities* (MedDRA)-preferred event term (MedDRA MSSO, Reston, Va., Version 7.0) for which at least 1 patient had an occurrence and which is related to a risk factor for metabolic syndrome (obesity, triglycerides, high-density lipoprotein cholesterol, lipids, blood pressure, glucose, metabolic disturbances, and insulin alterations) is listed as a subcategory under the "Adverse event total" category. All other adverse events are summarized under the subcategory "Other adverse event."
[b]All non-adverse event–related reasons for discontinuation are summarized within the "Other" category and include lack of efficacy, lost to follow-up, patient/physician decision, protocol violation, satisfactory response, and sponsor decision.

Table 4. Mean and Median Change From Baseline to Endpoint for Weight, Nonfasting Glucose, Total Cholesterol, and Blood Pressure Values Among Outpatients With Major Depressive Disorder

		Median Change to	Change to Endpoint	
Variable[a]	N	Endpoint	Mean	SD
Weight, kg[b]	549	5.0	5.6	6.6
Nonfasting blood glucose, mg/dL	487	3.0	7.4	34.9
Total cholesterol, mg/dL	488	9.8	12.7	34.3
DBP (supine), mm Hg	549	0.0	0.9	10.4
DBP (standing), mm Hg	549	0.0	0.5	10.5
SBP (supine), mm Hg	549	0.0	1.3	14.7
SBP (standing), mm Hg	549	0.0	0.1	15.6

[a]Overall within-group endpoint weight, nonfasting blood glucose, and total cholesterol changes were statistically significant ($p < .0001$).
[b]Weight change in pounds: median change (11.0 lb), mean ± SD change to endpoint (12.3 ± 14.6 lb).
Abbreviations: DBP = diastolic blood pressure, SBP = systolic blood pressure.

Table 4 presents mean weight change from baseline to endpoint for the 549 patients included in the analyses. Of these 549 patients, 56% gained ≥ 7% of their baseline weight, a threshold frequently used to define PCS weight gain.[8,29,30] Mean baseline-to-endpoint weight change was 5.6 ± 6.6 kg (12.3 ± 14.6 lb). Mean baseline-to-maximum weight change was 7.5 ± 6.1 kg (16.5 ± 13.4 lb). Figure 1 displays the mean weight change from baseline in patients over the course of the 76-week study. Since olanzapine dose was not a predictor of weight change, and fluoxetine dose was a statistically significant predictor of weight change (Table 5; only statistically significant predictors are included in the table because of the stepwise statistical approach), Figure 1 displays mean weight change by modal fluoxetine dose. For completeness, the overall weight gain data are displayed in the Figure 1 inset using both OC and MMRM methodology.

Table 5. Predictors of Weight Change With Olanzapine in Combination With Fluoxetine Treatment Among Outpatients With Major Depressive Disorder

Variable (N = 548)[a]	Estimate[b,c]	SE	p Value[c]	OR[d]
Endpoint weight change[e]				
Baseline BMI, kg/m^2	–0.083	0.037	.0262	NA
Gender (female)	1.191	0.557	.0329	NA
Age, y	–0.051	0.022	.0179	NA
Fluoxetine dose, mg/d	0.048	0.013	.0003	NA
Variable (N = 549)				
PCS weight gain[e,f]				
Baseline BMI, kg/m^2	–0.070	0.014	.0001	0.933
Gender (female)	0.241	0.097	.0126	1.619
Age, y	–0.017	0.008	.0298	0.983
Fluoxetine dose, mg/d	0.017	0.005	.0002	1.017
Race (non-white)	–0.352	0.151	.0202	0.495

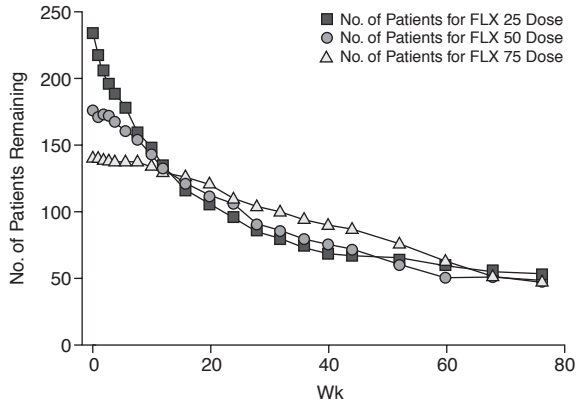
[a]One patient was not included in the predictor modeling for the endpoint weight change variable because her weight gain of 60.8 kg (134 lb) was an extreme outlying observation that exerted an excessive (statistically inappropriate) influence on the model parameter estimates and their statistical significance.
[b]Estimate is the mathematical weighting of each variable in the regression model.
[c]$p < .05$ suggests that the variable is a predictor of weight change. Negative estimates suggest that, as the variable increases, the likelihood of weight gain (PCS weight gain) decreases; positive estimates suggest that, as the variable increases, the likelihood of weight gain (PCS weight gain) increases.
[d]The OR provides the odds that PCS weight gain will occur for each unit increase in the variable. ORs are not applicable for endpoint weight change because it is a continuous variable.
[e]As part of the stepwise methodology for these analyses, the following independent variables were dropped from the full model, as their p values were > .1 (not statistically significant predictors of weight change): endpoint weight change: race (non-white), olanzapine dose (mg/d), baseline MADRS total score, and antipsychotic-naive designation; PCS weight gain: olanzapine dose (mg/d), baseline MADRS total score, and antipsychotic-naive designation.
[f]PCS weight gain is a ≥ 7% increase from baseline.
Abbreviations: BMI = body mass index, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, OR = odds ratio, PCS = potentially clinically significant.

Figure 1 suggests that, while weight gain generally plateaued for patients treated with 25 or 50 mg/day of fluoxetine during weeks 52 to 76, some patients treated with 75 mg/day of fluoxetine appeared to continue to gain weight after 52 weeks of exposure. The percentages of patients with PCS weight gain were 48%, 62%, and 62% for the 25-, 50-, and 75-mg fluoxetine groups, respectively. The apparent trend of continued weight gain after 52 weeks for patients in the 75-mg group was not due to individual outliers or dropout of low weight gain patients.

Figure 2 presents the number of patients remaining in the study over time by fluoxetine dose. Across all patients and doses, there were no statistically significant weight change differences between time points after 52 weeks ($p > .10$ for all comparisons), suggesting that, on average, weight gain plateaued by week 52 (Figure 1).

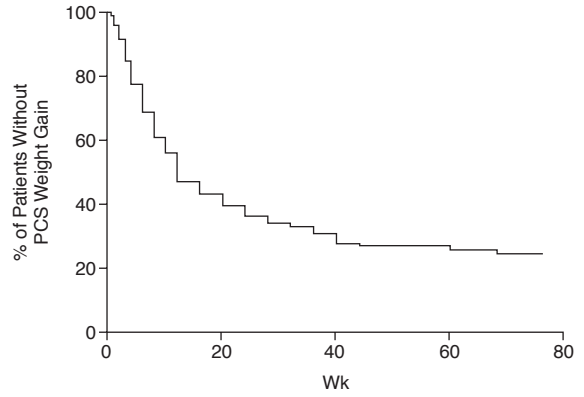
On the basis of Kaplan-Meier modeling for the current study population, an estimated 25% of all patients in the study (dose groups combined) would have PCS weight gain after 8 weeks, and an estimated 75% of patients would have PCS weight gain if they all continued to the

Figure 2. Number of Outpatients With Major Depressive Disorder Remaining in the Study Over Time by Fluoxetine Dose[a]



[a]Figure 2 illustrates dropout rates according to dose group as though patients began the study in the dose group to which they were retroactively assigned. However, all patients actually started at a dose of 25 mg of fluoxetine.
Abbreviations: FLX 25 = fluoxetine 25 mg/d, FLX 50 = fluoxetine 50 mg/d, FLX 75 = fluoxetine 75 mg/d.

Figure 3. Estimated Time to Potentially Clinically Significant (PCS) Weight Gain Among Outpatients With Major Depressive Disorder[a,b]

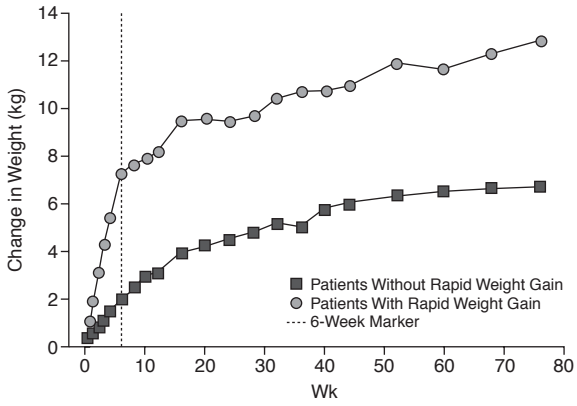


[a]PCS weight gain is a ≥ 7% increase postbaseline.
[b]This graph is a Kaplan-Meier survival curve with the y-axis 0 to 1 survival probability converted to percent of patients without PCS weight gain.

end of the study (Figure 3). For those patients with PCS weight gain, it took, on average, an estimated 16 weeks to gain the PCS weight (i.e., the median time to PCS weight gain was 16 weeks).

For patients taking OFC, several variables were examined as potential predictors of endpoint weight change: baseline body mass index (BMI), gender, age, fluoxetine dose, race, olanzapine dose, baseline MADRS total score, and antipsychotic-naive status. Of these variables, BMI,

Figure 4. Mean Weight Change From Baseline for Outpatients With Major Depressive Disorder With and Without Rapid Weight Gain[a,b]



[a]Rapid weight gain was defined as ≥ 7% weight gain from baseline within the first 6 weeks of treatment.
[b]N = 99 for patients with rapid weight gain; N = 357 for patients without rapid weight gain.

gender, age, and fluoxetine dose were statistically significant predictors of weight change (Table 5). The findings suggest that greater weight gain was experienced in patients who had lower baseline BMIs or who were younger or taking higher doses of fluoxetine. Women gained more weight than men.

For the logistic regression analysis, statistically significant predictors of PCS weight gain were baseline BMI, gender, age, fluoxetine dose, and race; patients with low baseline BMIs who were younger, female, white, or taking a higher fluoxetine dose were at greater risk of PCS weight gain (Table 5). On the basis of the odds ratios, as baseline BMI increased by 1 unit (kg/m^2), the likelihood of PCS weight gain declined by 6.7%. For each year increase in age, the likelihood of PCS weight gain declined by 1.7%. In contrast, for each 1-mg/day increase in fluoxetine dose, the likelihood of PCS weight gain increased by 1.7%, which would be a 42.5% increase in likelihood for a 25-mg/day increase in fluoxetine dose. Women and whites had a 61.9% and 49.5% greater risk of PCS weight gain than men and non-whites, respectively.

Among the study patients, 99 (22%) of 456 rapidly gained a PCS amount of weight (≥ 7% gain from baseline during the first 6 weeks of treatment); the sample size for this analysis was reduced from 549 because the analysis required both a baseline weight and a postbaseline weight at week 7 or later. A statistically significantly greater percentage of patients with early rapid PCS weight gain experienced substantial long-term weight gain (≥ 15% gain from baseline throughout weeks 7 to 76 of the study) compared with patients with no early PCS weight gain (58% vs. 18%; $p < .0001$). Figure 4 summarizes mean weight change for patients with and without rapid weight

gain. Patients who exhibited PCS weight gain in the first 6 weeks were 4.6 times more likely to exhibit substantial weight gain over the subsequent 70 weeks ($p < .0001$).

Table 4 summarizes mean and median changes from baseline to endpoint for weight, nonfasting blood glucose, total cholesterol, and blood pressure values. Correlation analyses for endpoint change in weight compared to total cholesterol (N = 488), nonfasting glucose (N = 487), and blood pressure (N = 549) values demonstrated that, unlike random glucose level, which was not significantly correlated with weight change, increased total cholesterol level ($p < .0001$, $r = 0.18$) was positively correlated with weight gain. While increased systolic blood pressure (supine; $p = .0002$, $r = 0.16$) was positively correlated with weight gain, there was no statistically significant correlation with diastolic blood pressure. The systolic blood pressure versus weight change correlation was low (standing; 0.14), and the mean ± SD change in endpoint systolic blood pressure was only 0.1 ± 15.6 mm Hg (standing).

Endpoint analyses of treatment-emergent PCS change in weight and levels of cholesterol and nonfasting glucose suggest that there was no correlation between either PCS weight gain and PCS total cholesterol levels or PCS weight gain and PCS random glucose levels. Similar incidences of PCS cholesterol levels were observed in patients without PCS weight gain (4.9%) as in patients with PCS weight gain (8.2%; $p = .44$). Similar incidences of PCS nonfasting glucose levels were observed in patients without PCS weight gain (2.2%) as in patients with PCS weight gain (1.1%; $p = .45$).

DISCUSSION

Time Course, Predictors, and Correlates of Weight Change

The mechanism(s) of how weight gain may occur during olanzapine treatment is unknown, although some hypotheses have been speculated: direct effect on central serotonergic (particularly via 5-HT_{2C} receptors) or histaminergic systems or indirect effect via reproductive hormones, triglycerides, leptin, corticosterone, prolactin, or ghrelin, which may contribute to weight regulation pathways.[1] Although underlying mechanisms are not well understood, weight gain while on olanzapine treatment is beginning to be characterized. Data from previous long-term olanzapine studies demonstrated that weight gain during olanzapine treatment was most rapid in the initial 12 to 15 weeks of treatment and then plateaued after approximately 39 weeks, with weight remaining stable thereafter.[9–11] Current findings suggest that, with OFC, weight gain most rapidly increased in the first 15 weeks, but did not plateau until approximately 52 weeks of treatment, particularly in those patients who were taking high-dose fluoxetine. Importantly, risk of substantial weight gain is greatly reduced among patients who do not exhibit PCS weight gain in the first 6 weeks.

Findings from the current study of OFC treatment and multiple studies examining olanzapine treatment strongly support that weight gain is not olanzapine dose dependent[10,11,33–35] and that low baseline BMI is a statistically significant predictor for weight gain.[1,10,11,33,35,36] Additionally, early rapid weight gain in OFC-treated patients statistically significantly increased the likelihood of substantial long-term weight gain, which has also been observed for olanzapine monotherapy.[10] The finding in this study that race was not predictive of weight gain is in contrast to an earlier study of olanzapine monotherapy[33] that found race to be a statistically significant predictor for weight gain. Among the olanzapine studies cited above (with some variance of degree), younger age, better clinical response, increased appetite, male gender, and nonwhite race were statistically significant predictors of increases in weight for olanzapine-treated patients. Among the olanzapine studies examining predictors of treatment-emergent weight gain, some differences in findings occurred. These differential findings may be due to differences in treatment groups (size and patient makeup), study design and duration, or whether fluoxetine was added to olanzapine treatment.

In support of current observations, no statistically significant correlation between treatment-emergent weight change in patients taking olanzapine and change in blood glucose levels,[10,37] including fasting glucose levels,[38] was observed in other studies. Although triglyceride levels were not assessed in this study, total cholesterol levels were measured. There was a statistically significant positive correlation between changes in endpoint weight and changes in endpoint total cholesterol levels, which has been observed with olanzapine treatment in another study.[37] However, the correlation was low (0.18). Additionally, in another study, increases in body weight in patients treated with olanzapine were not statistically significantly correlated with increases in cholesterol levels.[2] Thus, although increases in total cholesterol levels have been seen in patients treated with olanzapine, weight gain was not always positively correlated with such increases. Nevertheless, increasing weight should alert the physician to the possibility of elevations in cholesterol levels.

The current data suggest that some OFC-treated patients, depending on risk factors, may have an increased need for a weight management program. If weight gain is a concern, changing the olanzapine dose is unlikely to have an effect, while lowering the fluoxetine dose may be beneficial.

Benefit-Risk Assessment

Unsuccessfully treated MDD (including patients who respond to treatment but are not in remission) is associated with extensive social and economic costs that

include loss of function and quality of life, lost work productivity, and increased use of health services.[39,40] These costs are particularly high in cases of TRD.[41,42] Moreover, unsuccessfully treated depression is associated with suicidality.[43] Worldwide, of the approximately 1 million suicides per year, approximately 60% occur during a depressive mood disorder.[43] These observations highlight the importance of successful treatment of depression.

Olanzapine in combination with fluoxetine has been demonstrated to be efficacious for TRD,[12,18] bipolar disorder,[17] and borderline personality disorder,[13] but is currently approved to treat only depressive episodes associated with bipolar disorder. During a small, double-blind study, depressed patients who received OFC showed statistically significantly greater symptom improvement within a week of treatment compared with depressed patients who received olanzapine or fluoxetine monotherapy.[18] Moreover, during a large open-label study, a 67.7% reduction in symptomatology was maintained for up to 76 weeks in depressed patients.[12] A large proportion of these patients had well-controlled symptomatology on the lowest dose (25 mg) of fluoxetine in combination with olanzapine;[12] therefore, the potential increased risk of weight gain with high-dose fluoxetine would not be a factor for these patients.

Behavioral interventions, such as diet and exercise, have been demonstrated to have a positive effect on preventing or reducing weight gain in patients with mental illness who are taking olanzapine.[44–47] For example, education classes focused on nutrition, exercise, and healthy living led to statistically significant differences in mean weight change in patients with schizophrenia or schizoaffective disorder treated with olanzapine for 6 months versus those treated with olanzapine without the education class (0.06-lb loss vs. 9.57-lb gain, respectively).[45] In another study of olanzapine, which also included other atypical antipsychotics, the mean weight change after 12 weeks was a 6.4-lb gain for patients without and a 6.0-lb loss for patients with behavioral intervention.[47] Thus, for many patients taking olanzapine, behavioral intervention may attenuate treatment-emergent weight change.

Pharmacologic intervention may be an alternate method for weight control. The novel anticonvulsant topiramate added to olanzapine in bipolar patients controlled weight gain without loss of efficacy.[48] The H_2 antagonist nizatidine also may be associated with weight reduction without loss of efficacy in patients treated with olanzapine,[49,50] although this may not hold true for long-term treatment.[51] Other drugs, such as metformin,[52] amantadine,[53,54] and reboxetine,[55] have demonstrated attenuation of treatment-emergent weight change in patients taking olanzapine. Although none of these treatments have been evaluated in OFC-treated patients, if OFC is efficacious in a patient who is gaining weight, and behavioral interventions have failed, pharmacologic intervention may be an option to help with weight control.

Although treatment-emergent adverse events such as weight gain can lead to compliance issues, efficacy also has an impact on treatment compliance. A study of attitudes toward weight gain associated with medication found that patients would be willing to gain 5.7 kg (12.6 lb; likely an underestimation based upon study limitations) for treatment of a serious psychiatric condition.[56] This finding may explain the relatively low incidence (8.2%) of discontinuation due to weight gain in the current long-term study, which had a mean maximum weight change of 7.5 kg and a relatively large percentage of patients with PCS weight gain. This finding suggests that some weight gain, if it could not be controlled by behavioral or pharmacologic intervention, would be acceptable to some patients and physicians if the efficacy benefits were evident. Overall, the benefits of symptom control may outweigh the risks of weight gain. Since weight gain can lead to health problems, the patient and physician should make decisions on the basis of both potential benefits and risks.

Limitations of Data

There are limitations to stating that low BMI is a predictor of PCS weight gain, since PCS weight gain is based upon gaining a percentage of baseline weight, and patients with lower baseline weight need to gain less weight to reach this threshold (e.g., a patient weighing 50 kg would need to gain 3.5 kg, while a patient weighing 100 kg would need to gain 7 kg). Mean baseline BMI for the current population was 28.3 kg/m^2; thus, these patients were generally considered overweight.

The study is limited by the lack of controls that would allow comparisons to be made, although the open-label design adds the benefit that it closely mirrors typical clinical practice. A further limitation is that the current study design did not incorporate fixed doses. Therefore, patients could be exposed to higher fluoxetine doses after their initial 25-mg dose, and modal doses were used for the purpose of retrospectively grouping patients. Thus, patients in the 25-mg group may have been exposed to 25 mg of fluoxetine longer than patients in the 75-mg group were exposed to 75 mg of fluoxetine, and a patient within a dose group could have been exposed longer to that dose than someone else in the same dose group. Despite this limitation, the OC data, which at a given time point only examine patients with the same length of overall study drug exposure, suggest that study completers gained more weight in the 75-mg group compared to the other dose groups (Figure 1).

Since modal dose was used to group patients, dropout rates (Figure 2) for patients in the 50- and 75-mg dose groups would not register early in the study because the groups comprised people who remained in the study long enough to be included in the higher dose groups. That is, the patients received the higher dose for more days than

they received the 25-mg starting dose. Thus, though Figure 2 appears to show a greater early dropout rate for the patients in the 25-mg group, this is simply a result of the method used to group the patients. Although the overall dropout rates were 31% at 12 weeks and 74% at 76 weeks, these are not unusual rates for these lengths of time in a study of MDD, particularly with a significant proportion of TRD patients.[57,58]

Random glucose levels were collected for assessment of potential glucose dysregulation, which is a less accurate method than collecting fasting glucose levels. Thus, maximum increase in glucose values should be interpreted with caution. An additional limitation of this study is the lack of data on triglyceride levels. As triglyceride levels were not collected for this patient population, any correlation with weight change cannot be assessed.

CONCLUSION

Comparing olanzapine with OFC clinical trial data demonstrates that weight gain is not statistically significantly different between olanzapine- and OFC-treated patients.[59] High-dose fluoxetine in combination with olanzapine may increase the likelihood of weight gain in some patients. Weight gain most rapidly increased in the first 15 weeks of treatment, and rapid early weight gain increased the likelihood of long-term substantial weight gain. While there is potential for weight gain with OFC treatment, findings to date indicate that OFC provides robust, rapid, and sustained symptom control for depressed patients. The potential benefits for a patient with depression may outweigh any weight gain risk, particularly if a behavioral weight intervention program can be maintained. When prescribing OFC, it is important that physicians balance the risk of weight gain against the benefit of treatment efficacy for each individual patient.

Drug names: amantadine (Symmetrel), fluoxetine (Prozac and others), metformin (Fortamet, Glucophage, and others), nizatidine (Axid and others), olanzapine (Zyprexa), topiramate (Topamax).

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