Weight Gain During Treatment of Bipolar I Patients With Olanzapine

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Background: Body weight increase during long-term treatment with olanzapine in schizophrenia patients is well documented, but weight gain and its association with other medical measures are less well evaluated in bipolar disorder patients.

Method: We analyzed data from a 3-week, randomized, placebo-controlled trial of olanzapine for acute mania in DSM-IV bipolar I patients, followed by open continuation treatment with olanzapine up to a year. We examined factors associated with increased body mass index (BMI), including ratings of clinical change and selected physiologic measures.

Results: Among 113 subjects treated with olanzapine for a mean ± SD of 28.6 ± 19.9 weeks, BMI increased from a baseline mean of 28.8 ± 6.2 kg/m^2, by 7.9 ± 10.8% ($p < .001$), into the obese range (31.0 ± 6.1 kg/m^2). Initial BMI change (first 3 weeks of drug exposure) predicted final BMI increases (Spearman rank correlation $r_s = 0.32$, $p < .001$). History of longer illness ($p = .006$) and lifetime substance abuse ($p = .02$) were associated with below-median BMI increases. BMI increased much more among 40 subjects achieving symptomatic recovery than in the 73 who did not (by 11.9 ± 13.2% vs. 5.3 ± 7.7%; $p = .004$), with correspondingly longer olanzapine exposure (44.7 ± 11.8 vs. 19.7 ± 17.7 weeks; $p < .001$) at similar doses. On average, serum cholesterol increased 4.8 times more (17.5% vs. 3.6%) and endpoint cholesterol levels were newly 240 mg/dL or greater 3.6 (95% CI = 1.5 to 8.0) times more frequently in subjects with above-median BMI gain, who also experienced significantly larger increases in systolic and diastolic blood pressure, pulse rates, and nonfasting serum glucose than low–BMI-gain subjects.

Conclusions: Weight gain associated with long-term olanzapine treatment for mania was common, substantial, time-dependent, predicted by initial increases, and temporally associated with significant changes in cardiovascular and metabolic measures in bipolar I patients with prolonged illness and already-high basal BMI. An association of weight gain with favorable clinical response probably reflects longer olanzapine treatment.

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Weight gain is common and sometimes substantial during treatment of patients with antipsychotic agents, particularly clozapine and olanzapine.[1–4] In a meta-analysis of studies of schizophrenia patients, an average gain of 9.3 lb (4.2 kg) over a hypothetical 10-week period in 7 trials of olanzapine was higher than with any other antipsychotic except clozapine.[1] Among bipolar disorder patients, too, weight was reported to increase during olanzapine treatment in several studies.[5–11] For example, in a recent trial, 57 mania patients gained an average of 8.8 lb (4.0 kg) within 12 weeks of olanzapine treatment.[11]

Greater clinical improvement has been associated, albeit inconsistently, with greater weight gain in psychotic patients treated with olanzapine.[1,12,13] This association is less well documented in bipolar disorder patients, and its significance is unclear.[4,14,15] Indeed, little is known about correlations of weight changes in bipolar disorder patients treated with olanzapine with risk factors for potential later development of medical disorders associated with obesity. Potential effects of long-term treatments on medical risk factors are particularly important, since in bipolar disorder patients, certain chronic illnesses with high morbidity risk, such as type 2 diabetes, may occur at increased rates,[16,17] independent of treatment or obesity, and since most bipolar disorder patients require indefinitely prolonged maintenance treatment. Moreover, bipolar disorder reportedly is associated with increased

mortality rates of cardiovascular, pulmonary, endocrine, and other stress-sensitive medical disorders.[18–21]

In view of this background, we analyzed data from a randomized, controlled trial involving 113 bipolar I subjects treated initially for acute mania and then continued in open-label treatment with olanzapine up to a year, with discretionary addition of benzodiazepines, fluoxetine, or lithium allowed.[6] A preliminary account of this first long-term experience with olanzapine in bipolar I patients included an estimated 36.3% risk of weight gain of ≥ 7% over baseline weight during open-label treatment for an average of 6.6 months.[14] We now report more extensively on the timing and extent of increases in weight and body mass index (BMI) during long-term treatment with olanzapine and their temporal association with changes in selected clinical, physiologic, and metabolic measures.

METHOD

Subjects and Assessments

Methods employed are detailed in the primary report of a brief, double-blind, placebo-controlled trial with open continuation of treatment with olanzapine providing data for the present analyses.[6] Institutional review board requirements for this multisite study differed among study locations. Further details of diagnostic and assessment methods are provided in previous reports of this trial,[6] a very similar later trial,[7] and analyses based on their pooled data.[22] All 113 patient-subjects reported here were initially hospitalized for a DSM-IV–defined, acute bipolar I manic episode or mixed state, with an intake score of ≥ 20 on the Young Mania Rating Scale (YMRS).[23] Exclusion criteria included age < 18 or > 65 years; serious, unstable medical illnesses; DSM-IV substance dependence within 3 months; and serious risk of suicide.

Intake assessment was based on the Structured Clinical Interview for DSM (modified for DSM-IV), patient version.[24] Rating scales employed, in addition to the YMRS, included the 21-item Hamilton Rating Scale for Depression (HAM-D),[25] the Clinical Global Impression-Bipolar Version (CGI-BP),[26] and the Positive and Negative Syndrome Scale (PANSS)[27] for psychotic features.

All psychotropic medicines (except benzodiazepines) were gradually discontinued before 1:1 random assignment of 139 patients to olanzapine (N = 70) or placebo (N = 69) for 3 weeks, after which 113 subjects (81.3%) elected to continue for up to 1 year with open-label olanzapine treatment. Only these 113 subjects are included in the present analyses. The permitted daily dosing range for olanzapine was 5 to 20 mg, starting at 10 mg. Subjects were assessed clinically and weighed weekly in the initial 3-week trial, then biweekly through week 12 and monthly thereafter to a maximum of 52 weeks of treatment with olanzapine, with or without open supplementation with lithium carbonate or fluoxetine hydrochloride as required clinically after the initial 3 weeks of controlled treatment.

In the secondary analyses reported here, the primary efficacy measure (not employed in the original trial) was strictly determined initial symptomatic remission, defined a priori as attaining a YMRS total score ≤ 7, HAM-D score ≤ 7, and CGI-BP severity score ≤ 2, with 4 YMRS item scores (irritability, speech, content, and aggressive-disruptive behavior) all ≤ 2 and the remaining 7 YMRS item scores (elevated mood, motor activity, sexual interest, sleep, language-thought disorder, appearance, and insight) ≤ 1.[28] Sustained clinical recovery was defined as such remission sustained continuously for ≥ 8 weeks. For analysis of weight gain and associated changes, basal weight and exposure to olanzapine were timed from first use of olanzapine: either at the beginning of the randomized trial for subjects randomly assigned to olanzapine or on entry into open treatment for subjects initially randomly assigned to placebo. Subjects with ≥ 1 postbaseline assessment were included.

Factors Associated With Weight Gain

Given a lack of literature consensus on how to define high versus low weight gain nonarbitrarily, we distinguished relatively high– versus low–weight-gain subjects by median-split of BMI (weight-to-height ratio in kg/m^2) at endpoint. Using last-observation-carried-forward (LOCF) methods, we identified 57 high– and 56 low–BMI-gain subjects, in an effort to separate subjects with clinically meaningful versus incidental weight gains. We then compared high– versus low–BMI-gain subjects by baseline demographic and clinical characteristics, including initial rating scale scores, use of supplemental medication (benzodiazepine, fluoxetine, or lithium) at any time, clinical endpoints including rates of remission and recovery, rates of rehospitalization, and self-ratings of well-being based on the Medical Outcomes Study Short Form-36 scale (SF-36).[29,30] SF-36 assessments were obtained for physical health and mental/emotional health (with transformed data in the range 0–100 and higher scores indicating better self-rated health status) and a standardized overall summary score (z-score, transformed to have mean = 0 and SD = 1). SF-36 data were obtained at several points during the blinded trial and its extension, but we report only baseline and endpoint (LOCF) data.

We also compared high– versus low–BMI-gain subjects on serum concentrations of total cholesterol (mg/dL), random glucose (mg/dL), supine blood pressure, and resting pulse rate. Laboratory determinations were made at baseline, weekly during the blinded trial, and at irregular, approximately monthly, intervals during the open-label, 49-week extension. Endpoint clinical measures were based on last available observations.

Statistical Analyses

We assessed relative risks (e.g., likelihood of nonremission) by generalized linear regression modeling (GLRM) methods, with binomial family and logarithmic link, to obtain an estimated risk ratio (RR), its 95% confidence interval, and a corresponding z-statistic and p value.[31] We used GLRM methods with Gaussian family for contrasts of single-timepoint continuous measures (e.g., subgroup age at baseline). For categorical contrasts, we examined contingency tables (with χ^2 at stated degrees of freedom [df], or Fisher exact test [p] for tables with < 10 observations/cell). To summarize weight gain, we computed the overall percentage change in BMI expressed as a rate, percentage change/week of exposure to olanzapine. To assess the relative importance of high versus low weight gain versus duration of olanzapine exposure in predicting clinical remission, we used nested-model likelihood-ratio methods. For some correlations of changes in BMI versus time (e.g., early [3-week] vs. endpoint measures) and changes in BMI versus physiologic measures, we employed nonparametric, Spearman rank-correlation methods (r_s) or partial correlation methods. Physiologic changes were determined as observed increases as well as proportions of subjects newly reaching levels considered to exceed normal clinical limits.

We obtained robust standard error estimates for all model-based parameter estimates. For certain specified endpoint contrasts, we used LOCF methods. Averaged continuous data are reported as means with standard deviations (± SD) or 95% confidence intervals except in Figure 3, which shows means and standard errors due to space constraints. Statistical significance required 2-tailed $p < .05$. Analyses employed commercial microcomputer programs (Stata, Stata Corp., College Station, Tex.; and Statview-5, SAS Institute, Cary, N.C.).

RESULTS

Weight Gain and Exposure to Olanzapine

Of the 113 subjects participating in the open-label extension, 45 (39.8%) continued participation until the endpoint at 52 weeks; mean duration of participation was 30.0 ± 19.8 weeks. Consistent with their extended prior illness histories, which were a mean of 14.4 ± 10.0 years from estimated onset of bipolar disorder, the 113 long-term subjects, on average, were already overweight at study entry (mean BMI = 28.5 ± 6.7 kg/m^2), and 30.1% (34/113) were obese (BMI ≥ 30 kg/m^2). Initial BMI correlated significantly with years of bipolar illness (r_s = 0.149, p = .019). During the initial 3 weeks of exposure to olanzapine (N = 59 by randomization and N = 54 by later open treatment following initial randomization to placebo), mean weight increased from 84.0 ± 17.8 to 86.0 ± 17.6 kg, a change of 2.26 ± 2.75%, and BMI increased by 0.77 ± 0.94 kg/m^2 (2.78 ± 3.47%).

Treatment with olanzapine continued for a mean total of 28.6 ± 19.9 weeks (median = 25 weeks; range, 1–52 weeks), with a mean endpoint daily dose of olanzapine of 13.1 ± 5.7 mg (0.155 ± 0.070 mg/kg) that did not differ between high– and low–weight-gain subjects (Table 1). On average, weight gain at endpoint was substantial: body weight had increased by 6.53 ± 8.9 kg (8.0 ± 10.9%), and BMI by 2.17 ± 3.0 kg/m^2 (7.9 ± 10.8%) to 31.0 ± 6.1 kg/m^2 (range, 20.0–48.3 kg/m^2); 50.4% of subjects reached obesity criteria (BMI ≥ 30 kg/m^2), and a third (33.9%) of the subjects experienced increases of BMI of at least 10%. Within 8 weeks of treatment with olanzapine, the mean BMI was in the obese range (≥ 30 kg/m^2; Figure 1). Time trends for changes of both weight and BMI were strongly statistically significant when examined using random-effects modeling methods, with adjustment for baseline levels ($z = 23.8$, $p < .001$ for weight; $z = 22.2$, $p < .001$ for BMI). As expected in acute mania, there was some weight loss early in treatment, presumably due to hyperactivity and decreased food intake, with later increases to baseline values of BMI and steady average increases thereafter (Figure 1). Yet, early increases in BMI within the first 3 weeks of olanzapine treatment were significantly correlated with final BMI measures ($r_s = 0.322$, $p < .001$). Only 19.5% of the 113 subjects did not experience BMI increase during treatment (Figure 2).

As expected, the overall duration of treatment with olanzapine was 69% longer for the 57 high–BMI-gain subjects (35.8 ± 17.9 weeks) than for the 56 low-gain subjects (21.2 ± 19.2 weeks; Table 1). It follows that discontinuation before 12 months of treatment was much less frequent among the high–BMI-gain subjects (47.4% vs. 75.0%; Table 1). Increases in BMI ($r_s = 0.279$, $p < .001$; Figure 1) and percentage change in BMI (r_s = 0.327, $p < .001$, not shown) were robustly correlated with duration of olanzapine treatment. However, total daily doses of olanzapine, expressed as mean mg/day or body weight corrected (mg/kg/day), did not differ between the low– and high–BMI-gain subgroups (Table 1). These observations seem to suggest that the duration of olanzapine treatment was more responsible for greater weight gain than dose. However, dosing was constrained by the study protocol to the range of 5 to 20 mg/day, and at endpoint, 77.1% of subjects received 10 to 20 mg/day.

Correlates of Weight Gain

The high–BMI-gain subgroup had nonsignificantly lower baseline body weight (81.7 ± 14.3 vs. 86.2 ± 20.6 kg) and lower baseline BMI (28.1 ± 4.4 vs. 29.6 ± 7.5 kg/m^2), but more initial obesity (31.6% vs. 28.6% of subjects at BMI ≥ 30 kg/m^2) than the lower-gain subjects (Table 1). These high– and low–BMI-gain subgroups did not differ on any baseline psychiatric rating scale assessments, including YMRS, HAM-D, CGI-BP, and PANSS

Table 1. Characteristics of 113 Bipolar I Manic Patients With Increases in Body Mass Index (BMI) Above Versus Below Median in a Clinical Trial of Olanzapine

Characteristic	BMI Increase		Statistic[a,b]	p
	High (N = 57)	Low (N = 56)		
Male sex, N (%)	29 (50.9)	29 (51.8)	$\chi^2 = 0.01$	.92
Age, mean ± SD, y				
Current	37.4 ± 10.6	39.8 ± 11.0	z = 1.18	.24
At onset	25.5 ± 9.2	22.9 ± 8.5	z = 1.94	.052
Index diagnosis, N (%)			$\chi^2 = 0.20$	.65
Mania	46 (80.7)	47 (83.9)		
Mixed state	11 (19.3)	9 (16.1)		
Medical comorbidities per subject, mean ± SD	1.33 ± 1.8	1.29 ± 1.69	z = 0.15	.88
Substance abuse, N (%)				
Current	6 (10.5)	4 (7.1)	$\chi^2 = 0.40$	.53
Lifetime	31 (54.4)	42 (75.0)	$\chi^2 = 5.25$	.022
Prior morbidity				
In first episode, N (%)	3 (5.3)	3 (5.4)	$\chi^2 = 0.01$	.98
Years ill, mean ± SD	11.8 ± 9.5	17.0 ± 10.0	z = 2.76	.006
No. of episodes, median ± SD	15 ± 78	17 ± 80	z = 0.24	.81
No. of hospitalizations per subject, mean ± SD	0.93 ± 1.3	1.48 ± 2.0	z = 1.83	.067
Rapid cycling, N (%)	20 (35.1)	19 (33.9)	$\chi^2 = 0.02$	.90
Baseline psychiatric ratings, mean ± SD				
CGI-BP severity	4.4 ± 0.75	4.6 ± 0.86	z = 1.40	.16
YMRS	27.2 ± 6.4	28.9 ± 6.1	z = 1.51	.13
HAM-D	13.3 ± 7.0	13.7 ± 6.7	z = 0.31	.76
PANSS total psychosis	69.8 ± 20.3	70.0 ± 17.7	z = 0.05	.96
Olanzapine exposure				
Randomly assigned to olanzapine, N (%)	30 (52.6)	29 (51.8)	$\chi^2 = 0.01$	.93
Discontinued < 12 mo, N (%)	27 (47.4)	42 (75.0)	$\chi^2 = 9.08$	.003
Duration of olanzapine exposure, mean ± SD, wk	35.8 ± 17.9	21.2 ± 19.2	z = 4.16	< .001
Initial daily dose, mean ± SD				
mg	10.1 ± 1.2	9.6 ± 1.7	z = 1.49	.13
mg/kg	0.12 ± 0.02	0.11 ± 0.03	z = 1.62	.11
Final daily dose, mean ± SD				
mg	12.5 ± 6.0	13.7 ± 5.3	z = 1.22	.22
mg/kg	0.15 ± 0.07	0.16 ± 0.07	z = 1.40	.16
Body weight				
Basal weight, mean ± SD, kg	81.7 ± 14.3	86.2 ± 20.6	z = 1.34	.18
Basal BMI (kg/m^2), mean ± SD	28.1 ± 4.4	29.6 ± 7.5	z = 1.31	.19
Initially obese (BMI ≥ 30), N (%)	18 (31.6)	16 (28.6)	$\chi^2 = 0.12$	.73
BMI early % increase/wk[c]	0.76 ± 1.8	0.32 ± 1.1	z = 1.55	.12
Final BMI (kg/m^2), mean ± SD[d]	32.2 ± 5.3	29.5 ± 7.5	…	…
Obese at endpoint, N (%)	38 (66.7)	19 (33.9)	$\chi^2 = 6.47$	.011
BMI final % increase/wk, mean ± SD	0.36 ± 0.29	–0.01 ± 0.55	z = 4.21	< .001

[a]Ordered logistic regression was used to assess CGI-BP ratings, and Poisson analyses (with z) were used for previous hospitalizations and medical diagnoses.
[b]For χ^2 statistics, df = 1.
[c]Initial BMI increase (%/week) during the first 3 weeks of olanzapine treatment.
[d]Statistical significance not examined because endpoint BMI defined the BMI increase subgroups as above versus below median endpoint BMI.
Abbreviations: CGI-BP = Clinical Global Impression-Bipolar Version, HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

scores (Table 1), even though low–BMI-gain subjects, on average, had been ill 44% longer (11.8 ± 9.5 vs. 17.0 ± 10.0 years). The percentage change in BMI during the study was less among subjects with longer illness histories ($r_s = –0.290$, p = .002) and also less among subjects with correspondingly higher initial weight or BMI. These differences are consistent with the possibility that lower initial weight may have been associated with less prior exposure to weight-promoting treatments. High– and low–BMI-gain subgroups differed significantly on lifetime substance use (more with lower BMI), but not on other baseline measures, including age, sex, presenting diagnosis (manic vs. mixed), presence of recent rapid cycling, current medical or substance use comorbidity, prior hospitalizations, or episodes of illness (Table 1).

Clinical Response and Weight Gain

Initial symptomatic remission was attained by 69.9% of subjects (79/113), and 35.4% (40/113) achieved sustained clinical recovery. Such major improvements were more common among subjects with greater increases of BMI and longer exposure to olanzapine (Table 2). Recovery was unrelated to daily doses of olanzapine (mg or mg/kg; data not shown). Only 15% (3 men, 3 women) of the 40 subjects who recovered did so without weight gain. Endpoint BMI increases of those recovering were 2.24

Figure 1. Body Mass Index in Bipolar I Patients Treated With Olanzapine

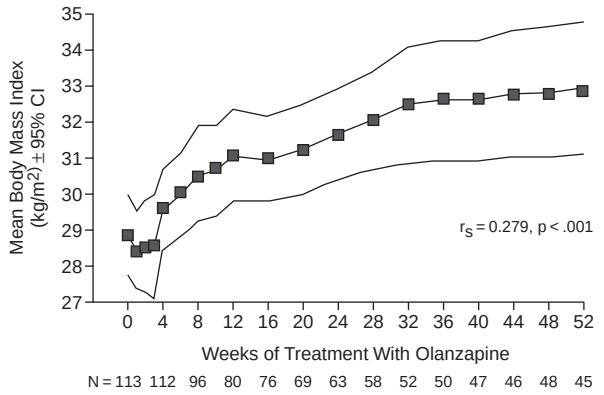
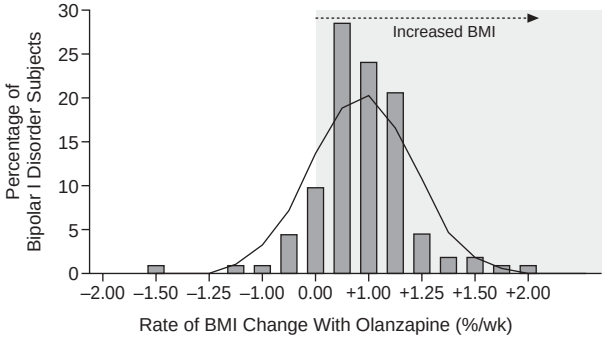


Figure 2. Percentage of Change in Body Mass Index (BMI) per Week in Bipolar I Patients Treated With Olanzapine[a]



[a]Curve indicates normalized data.

Table 2. Outcomes Among Bipolar I Manic Subjects With Body Mass Index (BMI) Increase Above Versus Below Median During Treatment With Olanzapine up to 12 Months

	BMI Increase			
Outcome	High (N = 57)	Low (N = 56)	z	p
Clinical outcomes, N (%)				
Achieved initial symptomatic remission[a]	44 (77.2)	35 (62.5)	1.67	.095
Recovered[b]	28 (49.1)	12 (21.4)	2.86	.004
Rehospitalized	11 (19.3)	9 (16.1)	0.45	.66
Treatment augmentation, N (%)[c]				
Benzodiazepine	30 (52.6)	36 (64.3)	–1.24	.21
Fluoxetine	9 (15.8)	5 (8.9)	1.08	.28
Lithium	11 (19.3)	5 (8.9)	1.52	.13
SF-36 scores[d]				
Physical health				
Baseline	53.2 ± 9.3	50.7 ± 10.4	1.34	.18
Improvement[e]	–0.57 ± 8.8	3.57 ± 9.3	1.08	.28
Emotional health				
Baseline	33.7 ± 11.2	37.4 ± 13.4	–1.56	.12
Improvement[e]	6.90 ± 14.3	0.81 ± 15.1	2.19	.032
Overall Summary (z-score)[f]				
Baseline	1.84 ± 1.30	1.60 ± 1.40	0.91	.37
Improvement[e]	1.15 ± 1.60	0.58 ± 1.80	2.64	.010

[a]Defined as Young Mania Rating Scale (YMRS) total score ≤ 7, Hamilton Rating Scale for Depression score ≤ 7, and Clinical Global Impressions-Bipolar Version severity score ≤ 2, with 4 YMRS item scores (irritability, speech, content, and aggressive-disruptive behavior) all ≤ 2 and the remaining 7 YMRS item scores (elevated mood, motor activity, sexual interest, sleep, language-thought disorder, appearance, and insight) ≤ 1.
[b]Defined as remission sustained continuously for ≥ 8 weeks.
[c]Open treatment supplements as allowed by protocol and required clinically.
[d]Medical Outcomes Study, general health and vigor self-assessment subscale,[30] as transformed mean ± SD scores. For baseline and change, respectively, N = 55 and N = 36 with high BMI increase; N = 54 and N = 34 with low BMI increase.
[e]Change-from-baseline contrast between high– and low–BMI-gain subgroups, adjusted for baseline levels.
[f]Overall SF-36 self-ratings expressed as standardized (z) scores (mean = 0, SD = 1).

times larger, on average, than in the 73 subjects who did not recover (11.9 ± 13.2% vs. 5.3 ± 7.7%), and their exposure to olanzapine was 2.27 times longer (44.7 ± 11.8 vs. 19.7 ± 17.7 weeks; z = 9.02, p < .001). Patients with above-median endpoint increases in BMI were somewhat more likely to achieve initial symptomatic remission (77.2% vs. 62.5%) and 2.29 times more likely to reach sustained clinical recovery (49.1% vs. 21.4%) than those with lesser increases (Table 2).

Neither rehospitalization rates (19.3% vs. 16.1%) nor rates of treatment supplementation with a benzodiazepine, fluoxetine, or lithium differed significantly between high– and low–BMI-gain subjects (Table 2). For example, subjects with versus without lithium augmentation had BMI percentage changes at endpoint of 7.8 ± 8.3% versus 7.5 ± 11.2%, respectively (z = 0.16, p = .87). Of note, however, clinical recovery was less frequent among patients given benzodiazepines (3/20 [15.0%] vs. 37/93 [40.0%]; χ^2 = 4.42, df = 1, p = .035).

SF-36 data were available for 109/113 subjects (96%) at baseline and 70/113 (62%) at endpoint. Not surprisingly, at baseline, superior self-rated mental/emotional health summary scores were associated with greater YMRS-assessed mania symptom severity (r_s = 0.271, p = .004) and with lower initial HAM-D depression scores (r_s = –0.249, p = .009). In contrast, correlations of baseline SF-36 physical health self-ratings and overall summary scores with both YMRS and HAM-D scores at baseline were small and nonsignificant (data not shown).

High–BMI-gain subjects with longer exposure to olanzapine reported substantially greater improvements than low–BMI-gain subjects on SF-36 self-ratings on both the mental/emotional health subscale and overall summary z-scores. For the SF-36 mental/emotional health subscale, change-from-baseline scores in the high– versus low–BMI-gain subgroups were 6.9 ± 14.3 versus 0.8 ± 15.1, respectively (adjusted for baseline SF-36 scores, this difference was significant: z = 2.19, p = .032; Table 2).

Similarly, SF-36 overall summary scores also showed greater improvement in the high–BMI-gain group (1.15 ± 1.6 vs. 0.58 ± 1.8; adjusted for baseline scores, z = 2.64, p = .010; Table 2). Changes in SF-36 ratings of physical well-being were unrelated to increases in BMI (Table 2) or duration of olanzapine treatment (data not shown).

Association of Weight Gain and Clinical Outcome With Olanzapine Exposure

To assess the relative importance of the associations of weight gain and duration of olanzapine treatment with symptomatic remission, we carried out a trivariate modeling analysis with BMI gain and days of olanzapine treatment as explanatory factors. To obtain an interpretable risk ratio, we formed high– and low–drug exposure subgroups by median-split on days of olanzapine exposure. These 2 subgroups, together with the high– versus low–BMI-gain subgroups, defined a 4-way (2 × 2) categorization of the 113 subjects in prolonged, open-label treatment. We then carried out nested regression analyses, with clinical remission as the outcome and high versus low BMI gain and high versus low olanzapine exposure as explanatory factors.

The results of this modeling regarding remission were as follows: for olanzapine exposure, RR = 6.13 (95% CI = 2.49 to 15.1; z = 3.94, p < .001), and for high– versus low–BMI-gain, RR = 1.43 (95% CI = 0.86 to 2.38; z = 1.39, p = .160). We then dropped BMI gain from the model and estimated the unadjusted RR for olanzapine exposure (median-split) alone; this estimate was RR = 6.88 (95% CI = 2.89 to 16.3; z = 4.37, p < .001). The second model (olanzapine exposure only) did not differ significantly from the first 2-factor model in explanatory power (likelihood-ratio test, $\chi^2 = 2.42$, df = 1, p = .120). These results indicate that, although both factors were strongly correlated with clinical response, the dominant factor related to clinical remission was duration of olanzapine treatment and that the addition of the weight gain factor did not appreciably enhance explanatory power.

Changes in Physiologic Measures

Percentage increases in pulse rate, systolic and diastolic blood pressure, serum total cholesterol concentration, and nonfasting (random) glucose levels all were significantly greater among subjects with above-median increases in BMI (Table 3) and correspondingly longer exposures to olanzapine (Table 1). The low–BMI-gain subgroup had significantly higher baseline systolic and diastolic blood pressure and pulse rates (Table 3), in association with a nonsignificantly greater baseline body weight and BMI (Table 1). In contrast, baseline serum levels of cholesterol and glucose were similar in the high– and low–BMI-gain subgroups (Table 3).

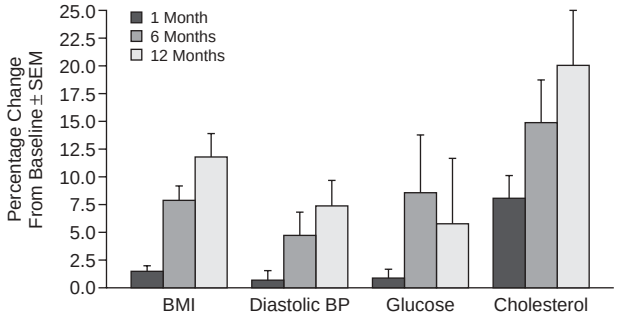
Table 3. Medical Measures Among Bipolar I Subjects With Body Mass Index (BMI) Increase Above Versus Below Median During Treatment With Olanzapine up to 12 Months

	BMI Increase			
Outcome Measure[a]	High (N = 57)	Low (N = 56)	z[b]	p
Systolic BP				
Baseline, mm Hg	114 ± 16.3	123 ± 15.7	2.75	.006
Final, mm Hg	125 ± 12.4	122 ± 13.8	1.57	.12
Change, %	13.1 ± 26.7	–0.5 ± 13.2	3.19	.001
Newly ≥ 140 mm Hg, N (%)[c]	24 (42.1)	17 (30.4)	1.28	.20
Diastolic BP				
Baseline, mm Hg	73.5 ± 9.3	78.5 ± 9.7	2.83	.005
Final, mm Hg	79.4 ± 9.3	78.2 ± 9.4	0.70	.48
Change, %	9.42 ± 16.7	–0.84 ± 16.6	2.75	.006
Newly ≥ 90 mm Hg, N (%)[c]	27 (47.4)	20 (35.7)	1.25	.21
Pulse rate				
Baseline, beats/min	75.9 ± 10.5	79.9 ± 9.8	2.11	.035
Final, beats/min	79.6 ± 12.8	78.8 ± 10.5	0.39	.69
Change, %	6.91 ± 22.6	–0.26 ± 15.8	1.97	.049
Newly ≥ 100 beats/min, N (%)[c]	18 (31.6)	18 (32.1)	0.06	.95
Total serum cholesterol				
Baseline, mg/dL	184 ± 43.2	182 ± 42.3	0.16	.87
Final, mg/dL	210 ± 46.7	186 ± 43.1	2.81	.00
Change, %	17.5 ± 28.8	3.6 ± 16.9	3.14	.002
Newly ≥ 240 mg/dL, N (%)[c]	22 (38.6)	6 (10.7)	3.23	.001
Nonfasting serum glucose				
Baseline, mg/dL	103.0 ± 29.5	109.9 ± 41.6	1.01	.31
Final, mg/dL	106.4 ± 32.3	98.6 ± 28.4	1.37	.17
Change, %	7.06 ± 28.0	–4.25 ± 27.6	2.17	.030
Newly ≥ 130 mg/dL, N (%)[c]	10 (17.5)	9 (16.1)	0.21	.83

[a]Baseline, final, and change data shown as mean ± SD. Baseline data were measured at study entry; change data indicate percentage change from initial to last observation.
[b]Statistics (z) and corresponding p values were estimated using generalized linear regression modeling methods.
[c]Cases newly reaching widely accepted clinical norm values for each index. Risk ratios (RRs) for the high– versus low–BMI-gain subgroups ranked as follows: cholesterol newly ≥ 240 mg/dL, RR = 3.67 (95% CI = 1.53 to 7.99; z = 2.98, p = .003); systolic BP newly ≥ 140 mm Hg, RR = 1.40 (CI = 0.84 to 2.35); diastolic BP newly ≥ 90 mm Hg, RR = 1.20 (CI = 0.76 to 1.87); random glucose newly ≥ 130 mg/dL, RR = 1.05 (CI = 0.46 to 2.44); and pulse newly ≥ 100 beats/min, RR = 0.99 (CI = 0.58 to 1.70); for all but cholesterol, RRs were not significantly different from 1.0 (p values of .20 to .95).
Abbreviation: BP = blood pressure.

Since some of the preceding risks may reflect cumulative long-term changes in this long-ill and already overweight sample of bipolar disorder patients, we also considered risks of newly exceeding upper limits of standard clinical norms after 8.1 and 4.7 months of olanzapine treatment in the high– and low–BMI-gain subgroups, respectively (Table 1). Notably, for total cholesterol, the risk of newly reaching or surpassing 240 mg/dL was 3.6-fold greater for the high– than low–BMI-gain subjects (RR = 3.6, 95% CI = 1.5 to 7.9; z = 2.98, p = .003; Table 3). The risk of systolic blood pressure values newly at or above 120 mm Hg also was substantial (RR = 1.40; 95% CI = 0.84 to 2.35), but not statistically significant. For diastolic blood pressure and random glucose concentra-

Figure 3. Change From Baseline in Physiologic Measures in Bipolar I Patients Treated With Olanzapine



Abbreviations: BMI = body mass index, BP = blood pressure.

tions, but not pulse rate, there were also nonsignificantly higher rates of newly abnormally elevated values at endpoint (Table 3).

From baseline to the last available observation, the percentage increases in cholesterol were 4.8 times greater among the high–BMI-gain subjects (17.5% vs. 3.6%), and final cholesterol levels newly reached ≥ 240 mg/dL in 38.6% (22/57) of high–BMI-gain versus 10.7% (6/56) of low–BMI-gain subjects (adjusted for baseline cholesterol level, RR = 3.81, 95% CI = 1.44 to 10.1; z = 2.69, p = .001). Diastolic blood pressure increased by 9.42%, on average, in the high–BMI-gain subgroup, compared with a decrease of 0.84% in the low–BMI-gain subgroup. For systolic blood pressure (13.1% vs. –0.54%), pulse rate (6.9% and –0.26%), and nonfasting glucose levels (7.1% and –4.2%), the high–BMI-gain subgroup experienced substantial increases, whereas, on average, the low–BMI-gain subjects had small decreases; these differences were statistically significant (Table 3).

Percentage increases in BMI were correlated with percentage increases in blood pressure, pulse rate, and serum cholesterol levels, with mean levels of all of these measures increasing over rising months of treatment (Figure 3). These data, taken together (Table 3, Figure 3), suggest that both weight gain and extended exposure to olanzapine may represent contributing risk factors for the changes in physiologic measures recorded at endpoint in this high-risk group of already-overweight patients.

Exposure to lithium, fluoxetine, or benzodiazepines was not significantly associated with weight gain (Table 2). These exposures also were unassociated with increases in any of the physiologic measures just described (data not shown).

Other Adverse Events

Data on some 50 categories of adverse events reported by study subjects at each assessment were categorized for severity (data not shown). Rates of any adverse event occurring at any time during treatment with olanzapine did not differ between the high– and low–BMI-gain subgroups (38/57 [66.7%] vs. 38/56 [67.9%] overall), nor was there a difference between these subgroups in the number of complaints per subject rated "severe" (1.8 ± 3.3 vs. 1.8 ± 3.1). However, specific complaints reported significantly more often in the high–BMI-gain subgroup were somnolence (42.1% vs. 16.1%; $\chi^2 = 9.26$, df = 1, p = .002) and increased appetite (19.3% vs. 3.6%; Fisher p = .016).

DISCUSSION

In these data obtained from 113 bipolar I subjects in an olanzapine treatment trial for up to 52 weeks (all but the initial 3 weeks open-label; mean exposure = 28.6 ± 19.9 weeks), it is clear that meaningful clinical responses were achieved by a substantial proportion of the participants, including initial symptomatic remission by 70% (79/113) and sustained clinical recovery (remission sustained for at least 2 months) by 35% (40/113). However, nearly 80% of subjects experienced weight gain during olanzapine treatment, and one third gained at rates above 1%/week during follow-up (Figure 2). BMI increased by an average of 7.9% at endpoint, and the criterion for obesity (30 kg/m^2) was met or exceeded by 50% of the already-overweight subjects by 2 months of olanzapine treatment. These BMI increases were strongly correlated with the duration of olanzapine treatment, but not with the constrained range of doses permitted or with use of adjunctive psychotropic medicines. Several important physiologic measures also increased substantially in temporal association with weight gain, including blood pressure, pulse rates, nonfasting serum glucose, and especially serum cholesterol (Table 3, Figure 3).

Several important features and limitations of these analyses bear highlighting. Limitations include a patient sample with many years of illness, lack of blinded observations during long-term treatment with olanzapine, nonparticipation in long-term treatment by only 19% of eligible subjects, and completion of a full year of treatment by only 39% of those entered in the initial controlled trial. These study characteristics may limit generalizability of our findings.

A striking observation is that, at baseline, most subjects were already overweight, following an average of over 14 years of bipolar illness and presumably prolonged exposure to various psychotropic medicines. Subjects presented with a mean BMI value (29 kg/m^2) just below the obesity criterion of 30 kg/m^2, and initial BMI was significantly correlated with years of illness. The high initial BMI values are consistent with results of several investigations reporting strong association of weight gain with prolonged treatment with various agents with proven antimanic, antipsychotic, or mood-stabilizing effective-

ness.[1,3,4,32] Despite already high body weights at baseline, weight increases observed in bipolar disorder patients in this study were similar to those found during long-term olanzapine treatment of patients diagnosed with schizophrenia, including the possibility of lesser increases at later times.[1,2,4] These observations indicate that previous weight gain or obesity does not protect against further increases during long-term treatment of bipolar disorder patients with olanzapine.

Of further potential clinical significance, several cardiovascular or metabolic risk factors, including increased blood pressure, pulse rate, cholesterol, and, more variably, glucose levels, also showed time-dependent increases during extended olanzapine treatment. For total cholesterol, the percentage of subjects reaching or exceeding 240 mg/dL was, significantly, 3.6 times higher in the high–BMI-gain subgroup (38.6%) than in the low–BMI-gain subgroup (10.7%; Table 3). For attaining newly abnormally elevated systolic and diastolic blood pressure and nonfasting glucose, the high/low–BMI-gain contrast was in the same direction, though it fell short of statistical significance (Table 3). The percentage increases in these physiologic indices from baseline levels were quite consistently correlated with percentage increases in BMI over time, suggesting that longer exposure to olanzapine and greater weight gain may have contributed to the increases observed in these indices.

The present findings also suggest that it may be possible clinically to predict relatively large later weight gains by early increases in weight or BMI within the initial weeks of olanzapine treatment (Table 1, Figure 1). Among patients who developed above-median increases in BMI, the rate of increase in BMI by week 3 of treatment with olanzapine was already 2.4 times greater than among low–BMI-gain subjects (0.76% vs. 0.32%/week), and these rates remained much higher after up to a year (mean = 6.75 ± 4.95 months) of continuous exposure to olanzapine (0.36% vs. –0.01%/week at endpoint; Table 1). These early increases in BMI were strongly correlated with later increases ($r_s = 0.322$, $p < .001$) and therefore seem to be predictive of potentially unfavorable long-term increases in body weight (Figure 1).

We also found consistent evidence that clinical responses over time, including attaining strictly defined, initial symptomatic remission and sustaining this for at least 2 months (sustained clinical recovery), were associated with increases in body weight during olanzapine treatment (Table 2). Weight gain and attainment of clinical recovery were both highly time-dependent. A similar association between treatment outcome and weight gain also has been observed previously among olanzapine-treated patients diagnosed with schizophrenia.[1,12,13] This finding and others analyzed above suggest that this relationship may be mediated by a common factor—duration of treatment. We propose that weight gain is a consequence of drug exposure–by-time, and that it may also be correlated with medication adherence, but that dose of olanzapine (within typical clinical limits) is a less important correlate of weight gain.

Participating subjects experiencing substantial weight gain, compared with subjects with smaller weight gain, tended to assess their mental/emotional health as being improved, but their physical health as being unchanged, based on SF-36 self-ratings (Table 2). These physical health self-ratings in the high–BMI-gain subgroup appear to be inconsistent with the observed tendencies toward adverse changes in several physiologic and metabolic indices experienced by such patients within several months of olanzapine treatment (Table 3). Yet, substantial weight gain, itself, may be perceived as undesirable by some patients, and its potential effects on long-term treatment adherence remain to be tested.

Olanzapine can be highly effective both in the treatment of acute mania and for preventing manic and depressive relapses up to 1 year after recovery from acute mania[5–11] and is the first antipsychotic to be U.S. Food and Drug Administration–approved for these indications.[32] However, olanzapine and many other agents employed to treat bipolar disorder patients are associated with later risks of weight gain that must be considered critically and weighed against the benefits of the treatments.[32] Potential long-term consequences of weight gain and increases in other cardiovascular risk factors are of particular concern in patients diagnosed with bipolar disorder. Such patients appear to be at increased risk of cardiovascular disease, type 2 diabetes, and other comorbid medical illnesses in which emotional distress and weight gain can be contributing risk factors.[15–21] These considerations highlight the need for comprehensive medical management of psychiatric patients who require sustained, long-term treatment with any antipsychotic or mood-altering agents that contribute to weight gain and potentially deleterious associated physiologic and metabolic changes, so as to limit their potential long-term, adverse health effects.

In conclusion, our findings indicate that weight gain was very common and often substantial in recovering bipolar I manic patients treated with olanzapine for an average of nearly 7 months. Later weight gain was largely anticipated by increases observed within the first few weeks of treatment and correlated strongly with duration of olanzapine exposure. Weight gain was also associated with clinical recovery and improved self-assessed general health and vigor (SF-36 scores); however, these associations may well be coincidental since both changes in weight (or BMI) and indices of clinical improvement depended on duration of treatment. The correlations found between weight gain and physiologic or metabolic measures that increased with duration of olanzapine treatment support the need for larger, prospective studies of weight gain during long-term antipsychotic treatment of bipolar

disorder patients and its clinical consequences, as well as for renewed efforts to limit weight gain associated with long-term use of many agents now employed in the long-term care of bipolar disorder patients.[32]

Drug names: clozapine (Clozaril, Fazaclo, and others), fluoxetine (Prozac and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa).

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