Prevalence of Obesity and Weight Change During Treatment in Patients With Bipolar I Disorder

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Background: Obesity is a major public health concern in the United States and its prevalence is increasing. Individuals with bipolar disorder tend to be overweight, and their treatment may exacerbate obesity and increase the risk of concurrent medical disease in this population.

Method: This retrospective report from the Pittsburgh Study of Maintenance Therapies in Bipolar Disorder examines the prevalence of overweight (body mass index [BMI] = 25.0–29.9) and obesity (BMI ≥ 30.0) in 50 consecutive subjects with bipolar I disorder (DSM-IV) and evaluates weight change during acute treatment and the first year of maintenance treatment.

Results: At entry into the study, 34 (68%) of the patients in this sample with bipolar disorder were obese or overweight. The prevalence of obesity was high (16 [32%] of the 50 patients in our sample). The number of previous depressive episodes contributed to the likelihood of being overweight or obese at study entry. During the trial, most of the weight gain occurred during acute treatment rather than during maintenance treatment. During acute treatment, the amount of increase of BMI was positively related to the score on the Hamilton Rating Scale for Depression and negatively related to the score on Bech-Rafaelsen Mania Scale. There was a negative relationship between BMI and tendency to gain weight, during both acute and maintenance treatment.

Conclusion: The high prevalence of obesity in subjects with bipolar disorder emphasizes the need for specific treatment strategies and programs for weight control for these individuals. The minimal weight gain during the maintenance phase, the relationship of acute depressive episodes to weight gain, and the fact that stabilization on maintenance medication may facilitate the participation in specific interventions for weight loss provide additional support for the practice of maintenance treatment.

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Obesity is the most common and costly nutritional problem in the United States, and its prevalence is increasing in men and women across all sociodemographic groups.[1] According to the National Health and Nutrition Examination Surveys (NHANES), the prevalence of obesity has increased from 14.5% in the years 1976–1980 to 22.5% in 1988–1994.[2] A recent and more conservative report[1] estimated a slightly lower prevalence, but still confirmed an increase in obesity, from 12% in 1991 to 17.9% in 1998. Obesity and overweight are associated with increased mortality, coronary disease, hypertension, dyslipidemia, diabetes mellitus, gallbladder disease, osteoarthritis, and some cancers.[3–6] The number of annual deaths attributable to obesity among U.S. adults has been estimated to be at least 280,000.[7] Recent evidence suggests that weight gain itself (regardless of baseline weight) increases the risks of medical illnesses and premature death.[8] Moreover, weight gain impairs physical functioning, reduces quality of life,[9] is associated with poor mental health,[10,11] and has a devastating impact on social life.[12] The economic costs of illness associated with obesity and overweight amount to approximately $68 billion per year, and an additional $30 billion per year is spent on weight-reduction programs and special foods.[13] As a result, obesity-related morbidity is estimated to account for 6.8% of U.S. health care costs.[14]

We are not aware of any epidemiologic study of the prevalence of obesity in people with mental disorders, but it is likely that the risk of being obese or overweight among these individuals is greater than in the general population.

Many psychotropic medications have been associated with weight gain. Researchers have investigated the effects of single medications or classes of medications on weight changes, especially during acute treatment.[15–23] However, little attention has been paid to the fact that many variables, in addition to pharmacotherapy, may affect the body weight of patients with bipolar disorder, including bipolar-specific psychiatric symptoms that are associated with changes in eating behaviors and energy expenditure.

We describe the prevalence of obesity and change in weight during acute and maintenance treatment in a group of 50 subjects with bipolar I disorder (DSM-IV) who were treated for at least 12 months following the remission of their index affective episode without developing a recurrence.

METHOD

Maintenance Therapies in Bipolar Disorder Study

The Pittsburgh Study of Maintenance Therapies in Bipolar Disorder (MTBD) is a randomized, controlled, long-term treatment trial comparing interpersonal and social rhythm therapy (IPSRT)[24] with intensive clinical management (ICM) in subjects affected by bipolar I disorder. Both therapies are offered in conjunction with protocol-defined pharmacotherapy algorithms. To enter the study, subjects must have a lifetime diagnosis of bipolar I disorder (confirmed by a Structured Clinical Interview for DSM-IV [SCID]) and be in at least their third affective episode, with the most recent previous episode being no more than 5 years prior to the index episode. Subjects enter in an acute affective episode (manic, depressive, or mixed) and must be 18 to 65 years old. All subjects provide written informed consent.

The study is divided into acute treatment and maintenance treatment. Patients are seen once a week during acute treatment, once every 2 weeks during the first 3 months of maintenance treatment, and then once a month for the remaining 21 months. Patients are considered to have completed acute treatment when they achieve a 4-week period of symptomatic remission defined by a mean Hamilton Rating Scale for Depression (HAM-D)[25] score ≤ 7 and a mean Bech-Rafaelsen Mania Scale (BRMS)[26] score ≤ 7. Once the patients complete acute treatment, they enter maintenance treatment. Pharmacotherapy is provided according to a protocol that has the goal of stabilizing the maximum number of patients on lithium therapy alone. Patients who cannot tolerate lithium receive either divalproex or carbamazepine or a combination of mood stabilizers. Depressed patients who fail to stabilize on lithium therapy or another mood stabilizer alone receive either tranylcypromine or, if they are unwilling to take a monoamine oxidase inhibitor, paroxetine or another antidepressant in addition to their lithium treatment. After 4 weeks of stabilization and prior to the entry to maintenance treatment, an attempt is made to discontinue the antidepressant in a stepwise fashion during a 1-month period. Neuroleptics are given as adjunctive medication to patients with manic or psychotic symptoms who cannot be stabilized with a mood stabilizer alone. During maintenance treatment, neuroleptics can be prescribed for a maximum of 5 days, in the event of prodromal manic symptoms occurring in the absence of a recurrence. Body weight and vital signs are assessed at each visit.

Specific Study Methods

We retrospectively report on 50 individuals consecutively enrolled in the MTBD study from 1991 to 1999 who were treated until remission of their acute symptomatology, completed 12 months of maintenance treatment without developing a recurrence, and had values for height and weight recorded within 2 weeks of starting and completing acute treatment and within 2 months of completing 12 months of maintenance treatment. By design, almost all patients received lithium as a mood stabilizer, both during acute treatment (N = 47) and during maintenance treatment (N = 45). The patients who did not receive lithium received valproate as a mood stabilizer. Some patients (N = 21) were prescribed a neuroleptic during acute treatment, and some (N = 12) were prescribed a neuroleptic at some time in maintenance treatment. Atypical neuroleptics were used only in a small number of subjects (risperidone: N = 4 at some time during acute treatment and N = 2 at some time in maintenance treatment; olanzapine: N = 5 at some time during acute treatment and N = 3 at some time in maintenance treatment). Antidepressants were used in 25 subjects during acute treatment and in 10 individuals during maintenance treatment. Of the 121 subjects who completed acute treatment, 71 were excluded from this sample for the following reasons: 18 subjects had missing values for weight at the timepoints we specified for this report, 14 dropped out before month 12 of maintenance treatment, 33 had a recurrence before month 12 of maintenance treatment, and 6 had recently entered the maintenance treatment. Only 1 subject did not complete acute treatment for reasons related to weight gain. No subject dropped out of maintenance treatment because of concerns related to weight gain.

Body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, was used as the dependent measure in these analyses. For the present study, we adopted the classification of overweight and obesity formalized by the World Health Organization (WHO).[27] This classification uses the same cutoff points reported in the evidence-based clinical guidelines for the identification, evaluation, and treatment of overweight and obesity in adults, published by the National Heart, Lung, and Blood Institute of the National Institutes of Health.[28] Men and women were considered to be underweight if their BMI was less than 18.5, normal weight if their BMI was

Table 1. Demographic and Clinical Characteristics of Study Population (N = 50)[a]

Characteristic	N	%	Mean	SD	Median
Gender					
Female	28	56			
Male	22	44			
Race					
White	46	92			
Nonwhite	4	8			
Marital status					
Married	27	54			
Divorced	3	6			
Separated	1	2			
Single	19	38			
Age, y			37.8	10.6	37.0
Education, y			14.6	2.1	14.0
Age at onset of first depressive episode, y			24.2	9.1	21.5
Age at onset of first manic episode, y			27.8	9.1	26.5
Years since first depressive episode			13.9	9.7	11.5
Years since first manic episode			10.0	8.7	7.5
Baseline 17-item HAM-D score[b]			19.7	5.0	19.0
Baseline 25-item HAM-D score[b]			25.1	5.1	26.0
Baseline BRMS score[c]			22.3	10.2	22.0
No. of previous depressive episodes			7.2	9.6	3.0
No. of previous manic episodes			3.5	4.5	2.0
Acute phase duration, wk			29.9	18.3	22.0
GAF score			49.0	8.1	50.0

[a]Abbreviations: BRMS = Bech-Rafaelsen Mania Scale, GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression.
[b]N = 26 depressed subjects.
[c]N = 24 manic/mixed/cycling subjects.

18.5–24.9, overweight if their BMI was 25.0–29.9, obese class I (moderate) if their BMI was 30.0–34.9, obese class II (severe) if their BMI was 35.0–39.9, and obese class III (very severe) if their BMI was equal to or greater than 40.0.

Table 1 indicates the baseline demographic and clinical characteristics of the 50 subjects who completed acute treatment and 1 year of maintenance treatment.

Statistical Method

Subjects' weight was measured at entry into study, at the end of acute treatment, and after 1 year of maintenance treatment. Body mass index was calculated at each of these points. Each subject was classified as being underweight, normal weight, overweight, or obese based upon BMI values at entry into the study. The amount of weight change was examined and reported during acute and maintenance treatment separately for each of the BMI classifications. To determine if the sample was representative, group t tests and chi-square tests were used to compare the selected sample of 50 with the other 71 subjects who entered but did not reach 1 year of maintenance treatment.

The study sample was compared on mean BMI and clinical and demographic variables with those of the group of patients that was excluded. The only significant differences found were that the excluded subjects were older by 1 year ($t = 2.17$, $df = 119$, $p < .04$), less likely to be married and more likely to be single ($\chi^2 = 17.59$, $df = 4$, $p < .002$), and took longer to remit from the acute episode ($t = 2.18$, $df = 119$, $p < .04$). Restricting the group of excluded subjects to the 33 individuals who had a recurrence before 1 year yielded the same differences except that age was not statistically different ($t = 1.91$, $df = 81$, $p < .06$).

Baseline differences between normal/underweight and overweight/obese subjects were compared using 2-group t tests for continuous measures and chi-square tests for contingency tables for categorical measures. Pearson correlations were used to examine relationships between amount of increase in BMI and baseline measures of severity. Partial correlations were used to examine this relationship while controlling for BMI at entry to the study.

RESULTS

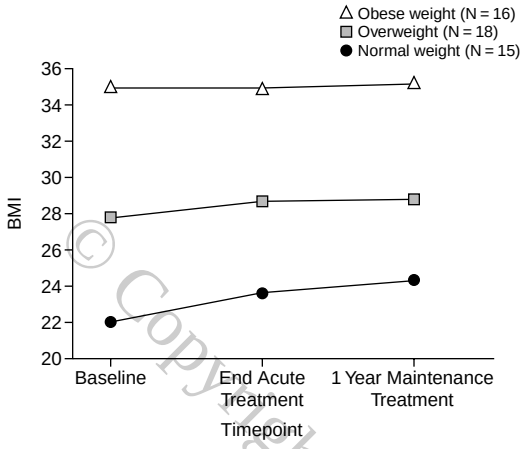
Study Entry Data

At entry into the study, 34 (68%) of the patients were obese or overweight. Sixteen (32%) of the subjects were obese (BMI ≥ 30.0), 18 (36%) were overweight (BMI = 25.0–29.9), 15 (30%) were normal weight (BMI = 18.5–24.9), and 1 (2%) was underweight (BMI < 18.5). Among the 16 obese subjects, 10 (62.5%) met criteria for obesity class I, 4 (25%) met criteria for class II, and 2 (12.5%) met criteria for class III. Comparing the subjects who were overweight or obese at entry to the study with those who were normal or underweight revealed no significant differences for age, ethnicity, age at first manic episode, age at first depressive episode, years since first depressive episode, years since first manic episode, education, marital status, employment, number of previous manic episodes, score on the HAM-D, or duration of index episode. Significant differences between overweight/obese subjects and normal/underweight individuals were found for number of previous depressive episodes (mean = 9.2 vs. 2.8, respectively; $t = 2.28$, $df = 48$, $p < .03$). Men were more likely to be overweight/obese than women ($\chi^2 = 3.45$, $df = 1$, $p < .06$).

Acute Treatment

During acute treatment, 14 subjects (28%) gained at least 5% of their baseline BMI. Six subjects (12%) gained more than 10% and 2 (4%) gained more than 15%. Using a paired t test by BMI classification, we observed that both the normal and overweight groups gained a significant amount of weight during acute treatment (normal weight, $t = 2.25$, $df = 14$, $p < .05$; overweight, $t = 2.96$, $df = 17$, $p < .01$). The median weight gained by normal weight subjects was 4.1% of BMI (5.0 lb). The median weight gained by overweight subjects was 2.9% of BMI (5.5 lb). The obese group experienced no significant weight gain during acute treatment (Figure 1). In terms of category shifts, the single subject who was underweight at study entry switched to normal weight during acute treatment. Three of the 15 subjects who were normal weight at study

Figure 1. Change in Mean Body Mass Index (BMI) During Acute and Maintenance Treatment



entry switched to overweight, and 1 switched to obese class I. Five of the 18 subjects who were overweight at study entry switched to obese class I. One of the 10 subjects who was obese class I at study entry switched to overweight. One of the 2 subjects who was obese class III at study entry switched to obese class II. The remaining individuals did not change BMI classification during acute treatment. There was no relationship between the amount of increase in BMI during acute treatment and age, ethnicity, age at first manic episode, age at first depressive episode, years since first depressive episode, years since first manic episode, education, marital status, employment, number of previous manic episodes, or duration of index episode. There was no correlation between time in acute treatment and amount of increase in BMI ($r = –0.13$, $p = .38$). The increase in BMI was, however, significantly related to the baseline score on the 25-item HAM-D (HAM-D-25) ($r = 0.28$, $p < .05$) and the BRMS ($r = –0.24$, $p < .05$). When baseline BMI was partialled out, the correlations increased to $r = 0.33$, $p < .03$ on the HAM-D-25, and $r = –0.33$, $p < .03$ on the BRMS.

Ten (38%) of the 26 subjects that entered the study in a depressive episode gained more than 5% of their BMI. Two (11%) of the 18 subjects that entered the study in a manic episode gained more than 5% of their BMI. Two (33%) of the 6 subjects that entered the study in a mixed episode gained more than 5% of their BMI. Normal weight patients were significantly ($p < .03$) more likely to gain > 5% of their weight if they entered the study in a depressive episode than if they entered in a manic or mixed episode. All 3 subjects (2 obese and 1 overweight) who lost more than 5% of their BMI during acute treatment entered the study in a manic episode.

None of the 26 patients who entered the study in a depressive episode switched to a manic episode during acute treatment; 1 patient switched to a mixed episode. Among the 18 patients who entered the study in a manic episode, 9 individuals switched to depression and 1 patient switched to a mixed episode. Among the 6 patients who entered the study in a mixed episode, 5 patients switched to depression. Treatment with IPSRT as compared with ICM had no effect on weight.

Maintenance Treatment

During the first 12 months of maintenance treatment, 13 (26%) of the subjects gained more than 5% of their BMI, but only 3 individuals (6%) gained more than 10%. No subject gained more than 15%. There was a significant increase in BMI in the normal weight group only ($t = 3.07$, $df = 14$, $p < .01$), whereas the overweight and the obese groups evidenced no significant weight gain. The median weight gained by normal weight subjects was 3.9% of BMI (5.0 lb) (see Figure 1).

In terms of categorical change, 1 of the 12 subjects who was normal weight at entry to maintenance treatment became overweight. Three of the 17 subjects who were overweight at entry to maintenance treatment became obese class I, whereas 2 subjects returned to normal weight. Three of the 9 subjects who were obese class I at entry to maintenance treatment became obese class II, whereas 2 subjects became overweight. One of the 5 subjects who was obese class II at entry to maintenance treatment became obese class III, whereas 1 subject became obese class I. The subject that was obese class III at entry in maintenance treatment did not change class.

There was no significant relationship between the amount of change in BMI and age, ethnicity, age at first manic episode, age at first depressive episode, years since first depressive episode, years since first manic episode, education, marital status, employment, number of previous manic episodes, duration of index episode, or time in acute treatment. There was no significant difference in mean percentage of weight gain between subjects treated with IPSRT and subjects treated with ICM.

Medications

Table 2 shows the medications that were prescribed during acute and maintenance treatment. The table also shows the mean period of time that patients received those medications. Most of the patients were treated with lithium. Lithium levels were in the normal range for the entire duration of the study. No significant relationship was found between lithium level and weight gain during either acute or maintenance treatment.

During acute treatment, 14 (30%) of the 47 subjects treated with lithium gained at least 5% of their baseline BMI. Six (13%) of the lithium-treated subjects gained more than 10% and 2 (< 1%) gained more than 15%. During maintenance treatment, 11 (24%) of the 45 subjects treated with lithium gained more than 5% of their BMI at

Table 2. Medications and Length of Treatment by Study Phase in 50 Subjects With Bipolar I Disorder[a]

	Acute Treatment				Maintenance Treatment			
	Patients		Duration, d		Patients		Duration, d	
Medication	N	%	Mean	SD	N	%	Mean	SD
Lithium	47	94	200	134	45	90	365	6
SSRIs	12	24	172	136	6	12	366	0
Neuroleptics	21	42	129	126	12	24	216	171
Valproic acid	12	24	135	106	6	12	365	3
Benzodiazepines or other hypnotics	17	34	102	140	12	24	242	154
Tranylcypromine	11	22	124	102	3	6	366	0
TCAs	7	14	118	107	0	0	...	...
Bupropion	2	4	75	57	1	2	366	...
Nonpsychotropic medications	22	44	188	180	28	56	335	296

[a]Abbreviations: SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

the start of maintenance treatment, but only 2 individuals (< 1%) gained more than 10%. No subject gained more than 15%.

DISCUSSION

In these analyses, we examined the prevalence of overweight and obesity in a series of individuals being treated for bipolar I disorder and explored the effects of acute and maintenance pharmacotherapy on weight change. Our research incorporates the newly adopted definitions of overweight and obesity[27] with new cutoff points (BMI of 25.0–29.9 for overweight and 30.0 for obesity) based on research evidence that links BMI to adverse health consequences.[29] The classification of overweight and obesity recommended by the WHO corresponds closely to the levels used in the 1995 Dietary Guidelines for Americans.[30] The previous BMI cutoffs of 27.8 for men and 27.3 for women were, instead, based on a purely statistical definition (85th percentile from NHANES II).[31] The relationship of BMI to body fat differs by ethnicity, age, and gender, but separate BMI cutoff points for overweight and obesity are considered unnecessary. At identical levels of BMI, women will have more body fat than men,[32] but morbidity and mortality increase with increasing BMI in a similar fashion for both men and women.[33,34]

For the purposes of this article, we considered the weight values recorded within 2 weeks of starting acute treatment, within 2 weeks of completing acute treatment, and within 2 months of completing 12 months of maintenance treatment. Although we obtained weight measurements at multiple timepoints throughout the study, these values were linear over time. We, therefore, decided that it was possible to represent changes in weight across the study period accurately and concisely by reporting data for these 3 specific timepoints only.

We found that 68% of the patients in our sample were overweight or obese at entry into the study. Although the prevalence of overweight was comparable with that of adults in the United States, which is itself a reason for major concern, the prevalence of obesity (BMI ≥ 30) was even higher than U.S. norms (32.0% vs. 17.9%).[1,2] Consistent with trends observed in the general population, men were more likely to be overweight/obese than women at entry to our study.[2] However, no significant gender difference was found for weight gain during any phase of our research.

We observed a relationship between BMI and risk for weight gain in both acute and maintenance treatment. During acute treatment, normal weight and overweight patients gained weight, whereas obese patients did not. During maintenance treatment, normal weight subjects were significantly more likely to gain weight, whereas overweight and obese patients were not. Among the patients treated with lithium, 30% gained more than 5% of their BMI during acute treatment. Six subjects (13%) gained more than 10% and 2 (< 1%) gained more than 15%. During maintenance treatment, 11 (24%) of the 45 subjects treated with lithium gained more than 5% of their BMI at the start of maintenance treatment, but only 2 individuals (< 1%) gained more than 10%. No subject gained more than 15% during the first year of maintenance treatment.

Our findings support the hypothesis that patients with bipolar disorder are at risk for gaining weight, particularly during acute treatment, until a plateau is reached over time for that episode. We speculate that repeated exposure to acute episodes of depression and to acute courses of treatment for bipolar depression may confer an additive risk of weight gain. In fact, we found that a greater number of prior depressive, but not of manic, episodes is associated with an increased likelihood of being overweight or obese at study entry and that the severity of the acute episode significantly affected the change in BMI during acute treatment, with the HAM-D score being positively related to weight gain and the score on the BRMS being negatively related to weight gain.

Although we did not measure them directly, we hypothesize that medication effects interact with other factors to determine actual weight changes in subjects with bipolar illness. Our clinical experience suggests that the relationship between bipolar episodes and weight gain can be influenced both by the medication treatment and by changes in variables such as appetite, diet, and energy expenditure. These latter characteristics are greatly influenced by both the polarity and the acuity of an episode. For instance, a patient is likely to experience a precipitous decline in appetite and an increase in energy in the acute phase of a manic episode, both of which return to normal as the episode resolves. Also, because depressive episodes generally last longer than manic episodes, patients are exposed to longer periods of aggressive pharmacologic treatment, which may play a role in the relationship between weight gain and polarity of acute episodes.

Limitations of the present study must be acknowledged. The study sample did not permit an evaluation of the effects of medications, other than lithium, on weight gain. Although most of the patients were taking stable doses of lithium throughout the study, other medications were prescribed at different doses, in different combinations, for different periods of time, and in the absence of a control group taking no medications. Further studies are needed to clarify whether the weight-specific effects of medications like the atypical neuroleptics, which were prescribed only in a very small percentage of our patients, vary with specific clinical variables such as the phase of the illness when the medications are prescribed and the initial weight of the patient. Our study was nonblind and retrospective. Additional variables that could influence weight (e.g., smoking and exercise) were not evaluated.

The fact that we observed a relationship between BMI and number of previous depressive episodes and between increase in BMI and severity of the current depressive episode provides another line of support for the practice of continuing pharmacotherapy beyond acute treatment in this population. Only 3 patients in our sample gained more than 10% of their BMI during 1 year of maintenance treatment and no subject gained more than 15% of their BMI. Weight gain during maintenance treatment was significant only for normal weight patients. Effective maintenance treatment should reduce the number of acute episodes an individual will experience, which in turn reduces the likelihood of weight gain with a concomitant decrease in the risk of concurrent medical disease. Furthermore, after patients are stabilized on maintenance medication, they may be better able to participate in specific interventions for weight loss,[35] including behavior therapy, caloric restriction, dietary changes, and exercise.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), divalproex (Depakote), olanzapine (Zyprexa), paroxetine (Paxil), risperidone (Risperdal), tranylcypromine (Parnate), valproic acid (Depakene and others).

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