Bipolar Disorder, Obesity, and Pharmacotherapy-Associated Weight Gain

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Background: Bipolar disorder, overweight, and obesity are each national public health problems. Overweight and obesity also appear to be related to mood disorders, and patients with bipolar disorder, in particular, may be at greater risk for overweight and obesity than individuals in the general population. This risk may be due to factors associated with the illness itself and/or with medications used to treat bipolar disorder.

Method: We conducted a MEDLINE literature search of all English-language articles (1966–2002) using the keywords *lithium, olanzapine, valproate, valproic acid, divalproex sodium, carbamazepine, lamotrigine, obesity, weight,* and *bipolar disorder*. We augmented this search with manual review of relevant references. Our focus was on studies examining the prevalence of overweight and obesity in bipolar disorder, the risk and magnitude of weight gain associated with medications used to treat bipolar disorder, and the prevention and treatment of overweight and obesity in patients with bipolar disorder.

Results: Forty-five studies were reviewed. Patients with bipolar disorder appear to be at greater risk than the general population for overweight and obesity. Comorbid binge-eating disorder; the number of depressive episodes; treatment with medications associated with weight gain, alone or in combination; excessive carbohydrate consumption; and low rates of exercise appear to be risk factors for weight gain and obesity in patients with bipolar disorder.

Conclusions: More research is required to identify the impact of specific risk factors for overweight and obesity in patients with bipolar disorder. These data could be used to develop better weight gain prevention and treatment programs for those with bipolar disorder. Therapeutic options include dietary counseling, use of mood stabilizers with lower propensities for weight gain, and combination pharmacotherapy with medications that have weight loss properties.

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Although weight gain, overweight, and obesity frequently complicate the treatment of bipolar disorder, the relationship among bipolar disorder, obesity, and pharmacotherapy-associated weight gain remains unclear. Like bipolar disorder, overweight and obesity are each national public health problems in their own right. The National Heart, Lung, and Blood Institute guidelines define overweight as a body mass index (BMI) of ≥ 25 kg/m^2 but < 30 kg/m^2, obesity as a BMI of ≥ 30 kg/m^2, and extreme obesity as a BMI of ≥ 40 kg/m^2.[1] The prevalence of obesity has increased from 23% to 31% in the U.S. adult population in just the last 5 years.[2] The prevalence of overweight has also increased during this time frame, from 56% to 65%. Extreme obesity, in turn, has increased in prevalence from 3% to 5%.[2] These alarming trends are also evident among U.S. children and adolescents.[3] For example, the prevalence of overweight in 4722 children surveyed in 1999 and 2000 was 16% among 12- to 19-year-old children, 15% among 6- to 11-year-old children, and 10% among 2- to 5-year-old children.[3] These prevalence rates represented increases of 5%, 4%, and 3%, respectively, compared with the period 1988 through 1994. These increasing prevalence rates are alarming since obesity and overweight are associated with increased mortality, cardiovascular disease, type II diabetes, osteoarthritis, and some forms of cancer.[4]

A number of lines of evidence suggest that overweight and obesity are themselves related to mood disorders. Obesity and mood disorders share many features, including phenomenological similarities, such as overeating, physical inactivity, and weight gain; high comorbidity with one another and with eating disorders, particularly binge-eating disorder; and increased morbidity and mortality from cardiovascular disease and type II diabetes. In

addition, they share genetic predisposition; biological abnormalities involving thyroid abnormalities, abnormal lipid and glucose metabolism, and hypothalamic-pituitary-adrenocortical, sympathoadrenal, and central monoaminergic dysregulation; and response to medications that selectively enhance central serotonergic, noradrenergic, and/or dopaminergic neurotransmission (S.L.M.; S. Malhotra, M.D.; E. B. Nelson, M.D., manuscript submitted). This body of evidence suggests that patients with bipolar disorder may be at greater risk than individuals in the general population for overweight and obesity.

Many pharmacologic agents are associated with weight gain. Overweight and obesity in patients with bipolar disorder may, therefore, be caused or exacerbated by treatment with specific psychotropic agents associated with weight gain.[5,6] Psychotropic drug–associated weight gain is related not only to increased morbidity from overweight and obesity, but also to patient distress and treatment nonadherence.[7,8] To further understand the relationships among bipolar disorder, overweight and obesity, and pharmacotherapy-associated weight gain, we review in this article studies examining the prevalence of overweight and obesity in bipolar disorder, data regarding the risk and magnitude of weight gain associated with medications used to treat bipolar disorder, and the limited number of studies examining the prevention or treatment of overweight or obesity in bipolar disorder.

We conducted a MEDLINE literature search of all English-language articles (1966–2002) using the keywords *lithium, olanzapine, valproate, valproic acid, divalproex sodium, carbamazepine, lamotrigine, obesity, weight,* and *bipolar disorder.* We augmented this search with manual review of relevant references. Forty-five studies were reviewed.

OVERWEIGHT AND OBESITY IN BIPOLAR DISORDER

Four studies have examined the prevalence and risk factors associated with overweight and obesity in clinical populations of patients with bipolar disorder.[9–12] Elmslie et al.[9] compared the prevalence of overweight and obesity in 89 euthymic outpatients with bipolar disorder with the prevalence in a reference group of 445 age- and sex-matched community control subjects in New Zealand. Most patients (87%) were receiving pharmacologic maintenance treatment. The authors found that female patients had significantly higher prevalence rates of overweight (44% vs. 25%) and obesity (20% vs. 13%) than female community control subjects. Although there was no significant difference in the rates of overweight between male patients (29%) and control subjects (43%), male patients had significantly higher rates of obesity (19% vs. 10%). Significantly more patients receiving antipsychotic medications were obese compared with patients not receiving these agents. Because this study was cross-sectional, it was not possible to determine whether the higher prevalence of obesity among patients treated with antipsychotics was due to these agents, or whether antipsychotic treatment may have been associated with greater illness severity, which, in turn, may have been associated with a greater risk of obesity.

In a follow-up study, Elmslie et al.[10] examined differences in nutrient intake and physical activity in the same patient and community control subjects. Mean total energy intake was significantly higher in female bipolar patients compared with community controls. In addition, total daily sucrose intake and percentage of energy derived from carbohydrates were significantly higher in both male and female patients, as were total fluid intake and intake of sweetened beverages. Patients also reported significantly fewer episodes of physical activity compared with the reference subjects. Because of the wide variety of medication combinations and regimens, the number of patients treated within any specific medication category was too small to allow comparisons for medication contributions to these determinants. However, female patients receiving antipsychotic medications alone or in combination with other agents had significantly higher overall sugar intake compared with other patients. The authors also speculated that dry mouth and thirst (45% of patients were receiving lithium alone or with an antipsychotic) might have led to increased use of beverages high in caloric content.

McElroy et al.[11] assessed the prevalence of overweight and obesity in 644 outpatients with bipolar disorder (I, II, and not otherwise specified) in both the United States and Europe. On the basis of BMI calculations, 31% were overweight, 21% were obese, and 5% were extremely obese. Some evidence showed that there may have been cultural contributions to weight gain. For example, American patients had significantly higher mean BMIs and significantly higher rates of obesity and extreme obesity than European patients. The higher prevalence of obesity in U.S. compared with European patients was not associated with a higher prevalence of atypical antipsychotic use among U.S. patients. Male patients had significantly higher rates of overweight than female patients, whereas female patients had significantly higher rates of extreme obesity than male patients. Compared with general population estimates available at the time of this study, the patients with bipolar disorder in this cohort had significantly different BMI distributions. Female bipolar patients had higher rates of obesity and extreme obesity but lower rates of overweight than the reference population. Male bipolar patients had higher rates of overweight and obesity, but not extreme obesity, than reference men.

Among the bipolar cohort, significant associations were found between overweight, obesity, and extreme obesity and age, annual income, comorbid binge-eating disorder, hypertension, arthritis, diabetes mellitus, exer-

Table 1. Randomized, Controlled Trials of Lithium Reporting Weight Change

Study	N	Design	Duration	Mean Change (kg)	% of Patients With Weight Gain > 5% Baseline
Bowden et al, 2000[15]	90	Placebo-controlled vs divalproex	1y	…	Lithium: 13 Placebo: 7
Tohen et al, 2002[16]	214	vs olanzapine	1y	Lithium: –1 Olanzapine: 2	…
Peselow et al, 1980[17]	21	Placebo-controlled	1y	Lithium: 4 Placebo: 1	Lithium: 62 Placebo: 16
Coxhead et al, 1992[18]	16	vs carbamazepine	1y	Lithium: 4 Carbamazepine: –3	…

Symbol: … = no data.

cise habits, and coffee consumption.[11] Current BMI and weight were positively correlated with the number of psychotropics associated with weight gain to which patients had been exposed.

Fagiolini et al.[12] examined the prevalence of overweight and obesity in 50 consecutive patients with bipolar I disorder (DSM-IV) and followed weight change during acute and maintenance treatment for up to 1 year. At study entry, 36% of patients were overweight and 32% were obese. Patients who were overweight or obese at initial evaluation had significantly more depressive episodes compared with patients who were normal weight (30% of the sample) or underweight (2%). Men were also significantly more likely to be overweight or obese than women.

During acute treatment, normal and overweight patients were significantly more likely to gain weight compared with obese patients. During maintenance treatment, patients of normal weight, but not overweight or obese patients, were more likely to gain weight. Most patients received lithium as their primary mood stabilizer. Among these patients, 30% gained > 5% of their baseline BMI during acute treatment, and 25% did so during maintenance treatment. On the basis of their findings, Fagiolini et al.[12] hypothesized that repeated depressive episodes and repeated courses of pharmacotherapy for depressive episodes may interact to increase the risk of weight gain in patients with bipolar disorder.

The results of these studies indicate that the overall prevalence of overweight and obesity in patients with bipolar disorder was higher than in control populations. Different patterns of obesity emerged according to gender across the studies. Overweight and obesity were also associated with comorbid binge-eating disorder, the number of episodes of depression, increased caloric intake, and reduced physical activity. Because of the design of these studies, the contribution of medications could not be clearly delineated.

THYMOLEPTIC MEDICATIONS AND WEIGHT GAIN

Mood-stabilizing agents form the cornerstone of acute and long-term treatment of bipolar disorder. Although a large body of clinical literature exists attesting to the problem of weight gain associated with many of these agents,[13] there are relatively few long-term controlled trials providing specific data regarding mean weight change and the proportion of patients displaying significant weight gain over time. Moreover, as described earlier in the article, there may be important drug–disease state interactions (e.g., recurrent depressive episodes requiring repeated exposure to medications associated with weight gain) that contribute to weight gain specifically in patients with bipolar disorder.[12,14] Thus, data from randomized, controlled trials are an important source from which to determine risks of weight gain attributable to specific agents since weight gain is a problem in the general population and in patients with bipolar disorder irrespective of medication effects. On the other hand, prospective, randomized, controlled trials have not controlled for the potential effects of preexisting psychotropic medications that were discontinued at the time of study enrollment. This is an important consideration since discontinuation of medications associated with weight gain could artificially suggest more subsequent weight loss during randomized treatment.

Since weight gain and obesity are primarily long-term treatment issues, we review in the following sections the available data regarding weight gain from maintenance and relapse prevention trials. We did not include studies of acute treatment trials because of their comparative brevity (e.g., ranging from 3–6 weeks in duration).

Lithium

The randomized, controlled trials providing data regarding weight changes associated with lithium are presented in Table 1.[15–18] Three studies provided data regarding mean weight gain in patients receiving lithium for up to 1 year.[16–18] In 2 of these studies, mean weight gain among lithium-treated patients was 4 kg.[17,18] However, in 1 study, patients lost an average of 1 kg.[16] The incidence of weight gain > 5% from baseline was reported in only 2 trials and ranged from 13%[15] to 62%.[17] In both studies, significantly more patients receiving lithium gained > 5% body weight from baseline than patients receiving placebo.

Table 2. Long-Term Naturalistic Studies of Lithium Reporting Weight Change

Study	N	Duration (y)	Mean Change (kg)	% of Patients With Weight Gain > 10 kg	% of Patients With Weight Gain > 5 kg
Vestergaard et al, 1988[19]	471	Up to 7	4	21	…
Vestergaard et al, 1980[20]	237	0.5–17	…	20	…
Vendsborg et al, 1976[21]	70	2–10	…	64	…
Kerry et al, 1970[22]	8	1–6	11.5	20	…
Schou et al, 1970[23]	100	1–2	…	…	11
Grof et al, 1973[24]	74	1	Responders: 6.5 Nonresponders: 1	…	20
Mathew et al, 1989[25]	117	Mean = 4.7	1	…	…

Symbol: … = no data.

In open-label, naturalistic outcome studies of bipolar patients receiving lithium, weight gain was more common and substantial.[19–25] These studies are summarized in Table 2. The greater weight gain observed in naturalistic settings may be due to the use of concomitant medications associated with weight gain, higher rates of psychiatric and medical comorbidity, nonsystematic weight recording, variability due to illness state, variance in baseline BMI, and longer durations of follow-up. It was not clear how many patients in the studies summarized in Table 2 were receiving other psychotropic medications associated with weight gain in addition to lithium or for how long.

A number of studies attempted to identify predictors of weight gain. High baseline weight was a strong predictor of subsequent weight gain in 2 studies.[19,21] Moreover, Vendsborg et al.[26] found that fat cell number (obtained from biopsy) but not fat cell size was positively correlated with lithium-induced weight gain. Two studies reported that most weight gain occurred during the first 1 to 2 years of lithium treatment and then tended to stabilize.[19,22] The study by Mathew et al.[25] was the only one not to find a significant increase in weight from baseline. In fact, they reported that 24% of patients lost weight. Among patients who gained weight, young age and male sex were significant predictors of weight gain. In contrast, Vestergaard et al.[19] observed greater weight gain in women compared with men. Vestergaard et al. also found that weight gain was significantly associated with the concomitant administration of antidepressants but not antipsychotics.[19] Vendsborg et al.[21] reported an association between weight gain and thirst, consistent with the observations of Elmslie et al.[10]

Several mechanisms may account for lithium-induced weight gain. Lithium appears to exert insulin-like activity on carbohydrate metabolism in some patients, leading to increased glucose absorption into adipocytes.[21,27–31] This insulin-like effect may stimulate appetite indirectly; in addition, lithium may have direct appetite-stimulating effects in the hypothalamus.[8,21,32] Relieving thirst by consuming high-calorie beverages has been proposed as a third mechanism.[20,21,33] Weight gain from fluid retention and edema has also been demonstrated.[20,33,34]

Valproate

There are only 2 long-term, randomized, controlled trials of divalproex in the treatment of bipolar disorder (Table 3).[15,35] In the 1-year study by Bowden et al.,[15] incidence of weight gain greater than 5% from baseline was significantly more common in patients receiving divalproex (21%) compared with placebo (7%). Mean weight gain in this study, however, was not reported. In the second study, a 47-week maintenance study comparing divalproex with olanzapine, patients receiving divalproex displayed significantly less mean weight gain (1 kg) compared with patients receiving olanzapine (3 kg) in the intent-to-treat analysis.[35] Among study completers, weight gain occurred rapidly among the olanzapine-treated patients who gained weight, but more slowly among patients gaining weight on divalproex treatment. At the end of the trial, there were no significant differences in mean weight gain among patients remaining in the study (completers) in the 2 treatment groups. In addition, significantly more patients receiving olanzapine (25%) reported weight gain as a bothersome side effect compared with patients receiving divalproex (12%). It is possible that weight gain could have contributed differentially to study dropout in either treatment group, but this is not clear from the study results. No clinical predictors of weight gain were identified in these 2 studies.

Weight gain has been reported as a side effect in a number of valproate trials in patients with epilepsy, with prevalence ranging from 4% to 71%.[41] This wide range is most likely due to differences in trial design (monotherapy vs. adjunctive therapy), duration, and study populations (e.g., adults vs. children, males vs. females). Because of these differences, it is difficult to extrapolate these findings in patients with epilepsy to patients with bipolar disorder treated with valproate. Moreover, there may be important differences between patients with epilepsy and bipolar disorder in predisposition toward weight gain. Of concern are reports of valproate-induced weight gain leading to metabolic syndrome in women with epilepsy.[42]

As with lithium, a number of mechanisms have been proposed for valproate-induced weight gain. These include direct appetite stimulation by valproate or a metabo-

Table 3. Long-Term, Randomized, Controlled Trials of Valproate, Olanzapine, Carbamazepine, and Lamotrigine Reporting Weight Change

Study	N	Design	Duration	Mean Change (kg)	% of Patients With Weight Gain > 5% Baseline
Valproate					
Bowden et al, 2000[15]	187	Placebo-controlled vs lithium	1 y	…[a]	Divalproex: 21 Placebo: 7
Tohen et al, 2001[35]	123	vs olanzapine	47 wk	Divalproex: 1 Olanzapine: 3	…
Olanzapine					
Tohen et al, 2002[16]	217	vs lithium	1 y	Olanzapine: 2 Lithium: –1	…
Tohen et al, 2001[35]	125	vs divalproex	47 wk	Olanzapine: 3 Divalproex: 1	…
Tohen et al, 2001[36]	51	Combination vs monotherapy[b]	18 mo	Combo: 2 Mono: –2	…
Carbamazepine					
Coxhead et al, 1992[18]	16	vs lithium	1 y	Carbamazepine: –3 Lithium: 4	…
Joffe et al, 1986[37]	24	Placebo-controlled	≤ 14 wk	Carbamazepine: 2 Placebo: 0	…
Lamotrigine					
Calabrese et al, 2000[38]	182	vs placebo	6 mo	Lamotrigine: 1.1 Placebo: –0.3	…
Calabrese et al, 2001[39]	463	vs lithium, placebo	18 mo	Lamotrigine: –2.2 Lithium: 4.2 Placebo: 1.2	…
Bowden et al, 2001[40]	175	vs lithium, placebo	18 mo	…	…

[a]Percentages of patients with weight gain > 5% from baseline were 21% for divalproex and 7% for placebo.
[b]Combination = olanzapine with divalproex or lithium, monotherapy = divalproex or lithium.
Symbol: … = no data.

lite at the hypothalamus,[41,43–45] increased thirst and subsequent quenching by calorie-rich beverages,[43,44] and impaired fatty acid metabolism.[44]

Olanzapine

Three long-term trials of olanzapine in the treatment of patients with bipolar disorder have been reported that provide data regarding weight gain (Table 3).[16,35,36] As previously described, olanzapine was associated with significantly greater mean weight gain in a 1-year trial compared with lithium[16] (Table 1) and a 47-week trial compared with divalproex.[35] Tohen et al.[16] compared olanzapine with lithium in a 1-year maintenance trial in patients with bipolar I disorder. Prior to randomization, 532 patients were treated with the combination of olanzapine and lithium on an open-label basis for 6 to 12 weeks, with a mean weight gain of 3 kg. During the blinded monotherapy maintenance phase of the trial, patients receiving olanzapine experienced a significantly higher mean weight gain (2 kg) compared with patients receiving lithium (–1 kg). In addition, significantly more patients receiving olanzapine (30%) gained ≥ 7% of baseline body weight compared with patients receiving lithium (10%). Similarly, fewer patients receiving olanzapine (9%) experienced a weight loss of ≥ 7% baseline body weight compared with patients receiving lithium (19%).

A third, 18-month, trial compared the combination of olanzapine plus lithium or divalproex with placebo plus lithium or divalproex in patients initially responding to the combination in a 6-week trial.[36] Patients receiving the combination reported significantly higher rates of weight gain (26%) compared with patients receiving monotherapy with lithium or divalproex (7%). There was no significant difference in the proportion of patients within the monotherapy group reporting weight gain from lithium (5%) and divalproex (8%). Patients in the combination therapy group also experienced significantly greater mean weight gain (2 kg) compared with the monotherapy group (–2 kg). Mean weight gain in patients receiving lithium or divalproex as monotherapy was not presented separately.

No predictors of olanzapine-associated weight gain were identified in these long-term trials. In 2 long-term outcome studies in patients with schizophrenia, better response and low baseline BMI predicted greater weight gain.[46,47] In addition, nonwhite race was associated with greater weight gain in the second study.[47] Notably, weight gain was not dose related.

Olanzapine appears to produce weight gain in a substantial proportion of patients with bipolar disorder and other psychiatric disorders via direct appetite stimulation.[48] Fadel et al.[49] recently reported that antipsychotics associated with weight gain (e.g., olanzapine, clozapine, risperidone, and chlorpromazine) produced activation of orexin neurons in the lateral hypothalamic/perifornical area as reflected by Fos expression in rats compared with antipsychotics associated with low risk of weight gain

(e.g., ziprasidone, fluphenazine, haloperidol). The risk of weight gain was directly proportional to the degree of Fos induction. Other proposed mechanisms underlying olanzapine-induced weight gain include H_1 and 5-HT_{2C} receptor antagonism.[50,51]

Carbamazepine

Only 2 randomized, controlled long-term trials of carbamazepine reported weight change data.[18,37] The first study, a lithium comparison trial, is reviewed above (Table 1).[18] Joffe et al.[37] compared weight change in 24 patients with bipolar disorder or major depression randomly assigned to carbamazepine or placebo for the treatment of manic or depressive episodes (Table 3). Patients with major depression, but not with mania, experienced a significant increase in body weight compared with placebo.

There are also comparatively few data regarding carbamazepine-associated weight gain in epilepsy trials.[41] Weight gain has been reported as a side effect in 2% to 14% of patients in randomized, controlled trials.[41] Mattson et al.[52] reported weight gain (defined as > 5.5 kg) in 8% of patients receiving carbamazepine compared with 20% of those receiving valproate in a long-term comparison trial in patients with epilepsy. There may be important differences between patients with epilepsy and bipolar disorder in predisposition toward weight gain. In addition to appetite stimulation, fluid retention and edema have been reported as mechanisms of carbamazepine-induced weight gain.[53]

Lamotrigine

Lamotrigine has been studied in 3 randomized, controlled, long-term trials in patients with bipolar disorder (Table 3).[38–40] In a 6-month relapse prevention study in 182 patients with rapid-cycling bipolar disorder (I and II), there was no significant difference in mean weight change between patients completing the trial who received lamotrigine (1.1 kg) versus placebo (–0.3 kg).[38] In the first 18-month maintenance trial, the mean change in body weight at week 76 was 1.2 kg for patients receiving placebo, –2.2 kg for lamotrigine, and 4.2 kg for lithium.[39] The differences in weight change were significant between the lamotrigine and lithium groups. The proportion of patients who experienced ≥ 7% increase in body weight from baseline to final study visit was 7% for the lamotrigine group, 10% for lithium, and 6% for placebo. Data regarding mean weight change in the second 18-month maintenance trial have not yet been presented.[40] However, the proportion of patients experiencing ≥ 7% increase in body weight from baseline to endpoint was 11% for the lamotrigine group, 10% for lithium, and 6% for placebo.

In a pooled analysis from randomized, placebo-controlled trials of lamotrigine in epilepsy involving 92 patients, there were no significant differences in weight changes between lamotrigine and placebo.[54] Biton et al.[55] compared the incidence and magnitude of body weight change in monotherapy epilepsy clinical trials comparing lamotrigine (N = 65) and valproate (N = 68). After 32 weeks of treatment, mean weight gain associated with lamotrigine (0.5 kg) was significantly less than that associated with valproate (5 kg). In addition, significantly more patients treated with valproate experienced weight gain of > 4 kg (62%) and > 10% of baseline weight (38%) compared with patients treated with lamotrigine (12% and 8%, respectively).

PREVENTION AND TREATMENT OF WEIGHT GAIN IN BIPOLAR DISORDER

There are few studies of the prevention or treatment of weight gain in patients with bipolar disorder. The only study that specifically addressed prevention of weight gain in bipolar disorder was an open comparison of healthy eating advice with no dietary advice in 50 patients (25 per group) beginning lithium treatment.[56] For patients randomly assigned to receive healthy eating advice, a dietary history was obtained at baseline following British Dietetic Guidelines. Specific dietary changes were recommended on an individual basis from dietary information gathered. The dietary advice emphasized decreasing consumption of calorie-rich food and beverages and food high in fat content, while increasing intake of fiber-rich carbohydrate foods. After 6 months of treatment, the mean weight change was significantly different between the healthy advice group (–1.7 kg) and the control group (1.9 kg). In addition, 20% of the control group gained > 5 kg, whereas only 4% of the dietary advice group gained > 5 kg. Interestingly, dietary advice significantly reduced weight gain in women, but not men. There was no correlation between weight gain and baseline BMI, age, lithium dose or concentration, or other psychotropic medications.

Littrell et al.[57] conducted a similar study in 12 patients with schizophrenia beginning treatment with olanzapine. Patients were randomly assigned to a dietary intervention group (N = 6; 3 men, 3 women) or standard care (N = 6; 3 men, 3 women) and followed for 4 months. The intervention group participated in a 1-hour weekly class consisting of a modular educational program on nutrition and exercise. After 4 months, patients in the intervention group gained significantly less weight (0.5 kg) compared with patients in the standard care group (3 kg). Men gained significantly more mean weight in both the intervention (men, 4 kg; women, –0.5 kg) and standard care (men, 6 kg; women, –1 kg) groups. The promising results of this pilot study are being extended in a larger ongoing project.

Two medications are currently approved by the U.S. Food and Drug Administration for the long-term treat-

ment of obesity, sibutramine[58] and orlistat.[59] There are no successful reports of the use of either agent in the treatment of obesity in patients with bipolar disorder. Hilger et al.[60] treated 8 patients (schizophrenia, N = 4; bipolar disorder, N = 2; major depressive disorder, N = 2) with orlistat, 360 mg/day, coupled with dietary counseling for 8 weeks and observed a mean decrease in body weight of 6% from baseline and a mean BMI reduction of 2 kg/m^2. There were no clinically relevant changes in plasma levels of haloperidol, clozapine, clomipramine, desipramine, or carbamazepine in this small cohort.

Sibutramine blocks both the serotonin and norepinephrine transporters, pharmacologic mechanisms that suggest antidepressant activity.[61] Another antidepressant, bupropion, has been recently shown to produce significantly greater weight loss as a mean percentage of baseline (5%) compared with placebo (1%) in an acute 8-week trial in 50 overweight and obese women.[62] Use of either of these agents could provide a dual therapeutic effect on depressive symptoms and weight gain in patients with bipolar disorder. On the other hand, their use also poses the risk of switch induction or cycle acceleration in some patients.

Topiramate, an antiepileptic agent associated with dose-related weight loss, has been reported to produce weight loss in overweight and obese bipolar patients.[63–66] McElroy et al.[63] reported a mean weight loss of 6 kg and mean decrease in BMI of 6% from baseline in 37 bipolar patients treated adjunctively with topiramate (mean dose = 425 mg/day) for 1 year. Chengappa et al.[64] treated 3 patients with bipolar I disorder and type II diabetes mellitus with topiramate, 300 to 400 mg/day, in combination with antipsychotics, valproate, or carbamazepine. In addition to improved mood stabilization, these patients lost 16% to 21% of their baseline body weight and achieved significantly better glycemic control. In a second, larger case series of 18 bipolar patients treated with adjunctive topiramate (mean maximum dose = 210 mg/day), Chengappa et al.[65] reported a mean weight loss of 4 kg after 5 weeks of treatment. Lastly, Gordon and Price[66] described an 11-kg weight loss over 3 months in an obese bipolar patient treated adjunctively with topiramate, 200 mg/day, and another obese bipolar patient who lost 7 kg in 2 months after topiramate, 300 mg/day, was added to her regimen.

Morrison et al.[67] treated 19 children aged 10 to 18 years who had experienced significant weight gain during treatment with olanzapine, risperidone, quetiapine, or valproate with the hypoglycemic agent metformin (500 mg t.i.d.). Of the 19 patients, 15 lost weight. The mean weight loss was 1 kg after 8 weeks and 3 kg after 12 weeks. Metformin was well tolerated with no significant side effects.

Two open-label reports described specific treatments for olanzapine-associated weight gain.[68,69] Ball et al.[68] evaluated the effectiveness of a Weight Watchers program for 21 patients (7 men, 4 women) with schizophrenia who had gained substantial weight since beginning treatment with olanzapine compared with a group of patients with schizophrenia who were matched by age, sex, weight, BMI, and symptom severity, but who did not participate in the program. Only 11 (52%) of the 21 patients completed the Weight Watchers program. There were no significant differences in mean BMI from baseline to endpoint between patients who completed the study in each group. However, men in the Weight Watchers group had a significant mean decrease of 3 kg compared with men in the control group. On the basis of preclinical observations that amantadine prevented antipsychotic-induced weight gain,[69] Floris et al.[70] treated with amantadine (mean dose = 175 mg/day) 12 patients (2 with bipolar disorder) who had experienced a mean weight gain of 7 kg since beginning olanzapine therapy. Weight gain ceased almost immediately following addition of amantadine in all 12 patients. Mean weight loss after 6 months was 3.5 kg, and all but 1 of the patients lost weight. Cavazzoni et al.[71] examined the efficacy of nizatidine, a histamine H_2 antagonist, in the prevention of weight gain in 175 patients with schizophrenia treated with olanzapine for up to 16 weeks. Patients were randomly assigned to nizatidine, 300 mg/day; nizatidine, 600 mg/day; or placebo at the initiation of treatment with olanzapine. Patients receiving nizatidine, 300 mg/day, gained significantly less weight than patients receiving placebo at weeks 3 and 4 of treatment, but these differences were no longer statistically significant at week 16.

For patients with bipolar disorder and comorbid binge-eating disorder, a number of treatment options supported by findings from randomized, controlled trials in binge-eating disorder are available. These include the selective serotonin reuptake inhibitors fluvoxamine,[72] sertraline,[73] fluoxetine,[74] and citalopram[75] and topiramate.[76] In addition, venlafaxine,[77] sibutramine,[78] and topiramate[79,80] have been reported to have efficacy in the treatment of obesity associated with binge-eating disorder in open trials and case reports.

DISCUSSION

From the studies reviewed, it appears that patients with bipolar disorder are at greater risk for obesity than individuals in the general population. The reasons why patients with bipolar disorder are at greater risk for obesity are presently unclear. A number of biological, demographic, socioeconomic, and behavioral mechanisms may underlie this risk. For example, depressive and mixed episodes are associated with activation of the hypothalamic-pituitary-adrenal axis resulting in increased levels of cortisol.[81,82] Acute or repeatedly sustained cortisol elevations are associated with obesity and insulin resistance.[81] Patients with bipolar disorder are also more likely to be

Table 4. Proposed Strategies for Preventing and Treating Obesity in Bipolar Disorder

Diagnostic assessment
Psychiatric comorbidity: binge-eating disorder, substance use disorders
Medical comorbidity: baseline body mass index, blood pressure, fasting glucose, triglycerides, lipids
Family history: obesity, type 2 diabetes mellitus, hypertension, cardiovascular disease
Prevention
Healthy diet
Minimum weekly exercise regimen
Treatment
Consider choice of pharmacotherapy for bipolar disorder based on evidence of efficacy from randomized, controlled trials and side effects
Pharmacotherapy: orlistat, sibutramine, topiramate, metformin

single, unemployed, and permanently disabled, all demographic risk factors for limited access to health care resources, poor self-care, obesity, and increased mortality.[83–87] Patients with bipolar disorder may be less likely to exercise and adhere to healthy diets, particularly when depressed. Symptoms of bipolar depression such as hyperphagia, lethargy, and hypersomnia may also directly contribute to increased energy intake with diminished activity.

Bipolar disorder is frequently comorbid with substance use disorders and binge-eating disorder.[88–90] Although it is likely that the presence of these comorbid disorders increases the risk of obesity, the magnitude of the contribution of these associated syndromes has not been well studied. Finally, there may be important illness-treatment interactions. For example, patients with bipolar disorder and comorbid binge-eating disorder may be particularly vulnerable to the appetite-stimulating effects of some agents. The association between depressive episodes and weight gain[12] may be due to biological and behavioral changes from depression or to the appetite-stimulating effects of some antidepressants. No clinical trials have examined the potential relationship between changes in mood symptoms and changes in weight. For example, normalization of weight as a consequence of resolving mania or depression could be a secondary effect of treatment. Although there are very limited data available, there is no evidence that weight gain associated with any agent is dose-related. Lastly, there may be pharmacogenetic risk factors for weight gain that act independently or as shared risk factors for illness vulnerability.[47,91] For example, Reynolds et al.[51] found a significant association between the –759 5-HT_{2C} receptor polymorphism and antipsychotic-induced weight gain in patients with schizophrenia.

There has been little systematic research regarding the prevention and treatment of psychotropic drug–induced weight gain in bipolar disorder. Ideally, preventive strategies would be based on identified risk factors for weight gain. In the absence of such data, efforts to educate patients about the components of a healthy diet and the need for exercise constitute an obvious first step in the prevention of weight gain (Table 4). Diagnostic assessment for personal and family psychiatric and medical histories of comorbid conditions associated with obesity may also help in the formulation of preventive strategies and guide laboratory evaluation and pharmacologic treatment recommendations (Table 4). Most studies reporting weight loss with specific agents, e.g., topiramate,[63–66] in patients with bipolar disorder have been clinical trials examining the efficacy of these agents in treating mood symptoms. To date, no randomized, controlled clinical trials have specifically addressed the efficacy of medications to treat obesity in patients with bipolar disorder. Until such trials are conducted, medications with efficacy in producing weight loss, such as orlistat, sibutramine, topiramate, and metformin, may be useful for some patients. The choice among these agents requires consideration of their side effects, possible effects on mood symptoms, and drug interactions with other agents that are being used to manage bipolar illness.

CONCLUSIONS

Bipolar disorder and many of the medications used in its treatment appear to be risk factors for overweight and obesity. The impact of psychiatric comorbidity (e.g., binge-eating disorder[11]), course of illness (e.g., number of depressive episodes[12]), illness-treatment interactions,[12] and other risk factors has not been well delineated. Combinations of medications associated with weight gain appear to convey at least an additive risk for weight gain in patients experiencing weight increases. Similarly, the strategies to prevent weight gain specific to patients with bipolar disorder have only begun to be studied, as have weight loss treatments in these patients.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), citalopram (Celexa), clomipramine (Anafranil and others), clozapine (Clozaril and others), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), metformin (Metaglip and others), nizatidine (Axid and others), olanzapine (Zyprexa), orlistat (Xenical), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), sibutramine (Meridia), topiramate (Topamax), venlafaxine (Effexor), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, amantadine, bupropion, and nizatidine are not approved by the U.S. Food and Drug Administration for weight loss; carbamazepine, clozapine, divaloprex sodium, and olanzapine are not approved for the maintenance treatment of bipolar disorder; citalopram, fluoxetine, sertraline, and venlafaxine are not approved for the treatment of binge-eating disorder; metformin is not approved for the treatment of obesity and weight loss; and topiramate is not approved for the treatment of binge-eating disorder and weight loss.

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