Obesity in Patients With Bipolar Disorder: A Biopsychosocial-Behavioral Model

Jennifer E. Wildes, Ph.D.;
Marsha D. Marcus, Ph.D.; and Andrea Fagiolini, M.D.

Objective: We provide a model to explicate how factors representing different levels of analysis (i.e., biology, psychology, sociodemographics, and behavior) interact to influence the onset and maintenance of obesity in bipolar disorder.

Data Sources: We conducted MEDLINE (1966–2005) and PsycInfo (1872–2005) searches of all English-language articles using the keywords *obesity*, *body weight*, *weight gain*, and *metabolic syndrome* combined with *bipolar disorder*, *depression*, *atypical depression*, *binge eating*, and *pharmacotherapy*.

Study Selection: Studies were selected if they provided data regarding (1) the prevalence of obesity in patients with bipolar disorder, (2) correlates of obesity in patients with bipolar disorder, or (3) evidence that a clinical feature(s) or correlate(s) of bipolar disorder is associated with obesity. Ninety-two studies were reviewed.

Data Synthesis: Obesity is prevalent in patients with bipolar disorder and is associated with increased medical morbidity and poorer psychiatric outcome. Variables that may interact to influence the onset and maintenance of obesity in bipolar disorder include genetic factors, neurotransmitter abnormalities, atypical depression, eating behaviors, pharmacotherapy, age, gender, socioeconomic status, and physical inactivity.

Conclusions: Although the exact causes of obesity in bipolar disorder undoubtedly vary across patients, the etiologic cascade, which includes biological, psychological, and sociodemographic variables, ultimately directly or indirectly affects levels of physical activity and eating behavior, leading to obesity in this population. Behavioral interventions aimed at targeting physical inactivity and overeating in bipolar disorder patients are needed, as are better screening and treatment for binge eating. Finally, there is a clear need for ongoing research to explicate the causes and consequences of obesity across levels of analysis.

(J Clin Psychiatry 2006;67:904–915)

Received Aug. 24, 2005; accepted Nov. 22, 2005. From Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

Supported in part by National Institute of Mental Health grants MH030915 and MH029618 (Dr. Fagiolini).

Dr. Fagiolini is a consultant for Pfizer and Bristol-Myers Squibb and has received honoraria from and is a member of speakers/advisory boards for Pfizer, Bristol-Myers Squibb, Eli Lilly Italy, and Shire. Drs. Wildes and Marcus report no additional financial or other relationships relevant to the subject of this article.

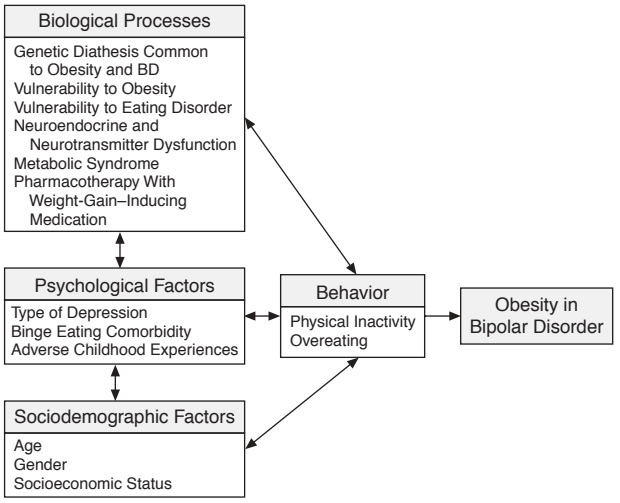
Corresponding author and reprints: Jennifer E. Wildes, Ph.D., Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213 (e-mail: wildesje@upmc.edu).

There is increasing interest among researchers and clinicians in the relationship between mood disorders, particularly bipolar disorder (BD), and obesity. Clinical research has suggested that more than half of all treatment-seeking BD patients are overweight or obese.[1] Yet, little is known about the mechanisms involved in the onset and maintenance of obesity in BD. Most of the research in this area has examined the iatrogenic effects of medications used to treat BD.[2–5] Although weight-related effects of psychotropic medications (e.g., lithium, second generation antipsychotics, anticonvulsants) may account for weight gain in some individuals with BD, the co-occurrence of obesity and BD was observed long before the advent of current medications,[6] and it is highly unlikely that all changes in weight observed in BD patients are induced by drug treatment. Other risk factors such as genetic predisposition, course of illness, and psychiatric comorbidity are undoubtedly involved in the onset and maintenance of obesity in BD.

Kendler[7] addressed the problem of explaining complicated medical and psychiatric phenomena in a recent article calling for a new philosophical framework for psychiatry. Specifically, he noted that all major psychiatric conditions are complex and multifactorial. Thus, although it may be tempting to search for big, simple etiologic explanations, the reality is that all major psychiatric phenomena arise from multiple, interacting etiologic pathways or "levels of analysis."[7(p435)] The task for psychiatry is to adopt an "integrative pluralism"[7(p437)] approach, whereby scientists seek to understand how these multiple etiologic pathways interact to produce psychopathology.

Accordingly, there are multiple parameters at different levels of analysis that may influence the development

Figure 1. Biopsychosocial-Behavioral Model of Obesity in Bipolar Disorder



of obesity in BD. These include biological processes (e.g., genetic predisposition, biological dysfunction, treatment with weight-gain–inducing medications), psychological factors (e.g., family environment, phenomenology of depressive symptoms, psychiatric comorbidity), and sociodemographic factors (e.g., age, socioeconomic status), some or all of which impact behaviors (i.e., inactivity, overeating) proximal to the onset and maintenance of overweight. A summary of these variables and their hypothesized interactions is presented in Figure 1.

To obtain relevant articles for the present review, we conducted MEDLINE (1966–2005) and PsycInfo (1872–2005) searches of all English-language articles using the keywords *obesity*, *body weight*, *weight gain*, and *metabolic syndrome* combined with *bipolar disorder*, *depression*, *atypical depression*, *binge eating*, and *pharmacotherapy*. We also examined the reference sections of all identified articles and literature reviews. Studies were selected if they (1) described the prevalence of obesity (or a related condition, e.g., metabolic syndrome) in patients with BD, (2) described correlates of obesity (or a related condition) in patients with BD, (3) provided evidence that a clinical feature or correlate of BD is associated with obesity (e.g., evidence that individuals with atypical depression are at increased risk for overweight), (4) provided evidence of an interaction between 1 or more levels of analysis associated with obesity in BD (e.g., weight-gain–inducing medications [biological factor] increase thirst resulting in increased consumption of high calorie beverages [behavior]), or (5) helped to explain the presence of an obesity correlate in patients with BD (e.g., binge eating as a mechanism for regulating negative affect in BD). We also compared studies of obesity and BD with respect to biological processes, psychological factors, sociodemographic factors, and behavior. Ninety-two studies were reviewed.

OBESITY IN BIPOLAR DISORDER: THE SCOPE OF THE PROBLEM

Obesity is common in patients with BD. Prevalence estimates indicate that up to 68% of treatment-seeking BD patients are overweight or obese.[1] Moreover, there is evidence that BD patients are at increased risk for overweight and obesity relative to normal population samples and other psychiatric control groups. For example, Elmslie and colleagues[8] compared rates of overweight, obesity, and abdominal obesity in 89 euthymic BD outpatients and 445 age- and sex-matched controls. They found that female BD patients had significantly higher rates of overweight (44% vs. 25%), obesity (20% vs. 13%), and abdominal obesity (59% vs. 17%) than female controls; male BD patients also had higher rates of obesity (19% vs. 10%) and abdominal obesity (58% vs. 35%) than controls. Similarly, McElroy and colleagues[1] concluded a recent review of the relationship between obesity and mood disorders by observing that some subtypes of mood disorder appear to be more strongly associated with overweight and obesity than others. The subtypes most strongly associated with obesity included depression with atypical features, depression with juvenile onset, and BD.

Research also suggests that many medical correlates of obesity, including impaired glucose tolerance,[9] diabetes mellitus,[10,11] and death from cardiovascular disease,[12] are prevalent in patients with BD. Of note are recent findings that indicate that point prevalence rates of the "metabolic syndrome" (defined in the third report of the National Cholesterol Education Program [NCEP ATP III][13] as having 3 or more of the following aberrant physical characteristics: [1] abdominal obesity, [2] hypertriglyceridemia, [3] low high-density lipoprotein cholesterol [HDL-C], [4] high blood pressure, and [5] fasting hyperglycemia) are elevated in patients with BD relative to point prevalence rates for the general U.S. population. For example, Basu and colleagues[14] reported that 42% of a sample of 33 patients with schizoaffective disorder-bipolar type met NCEP ATP III criteria for the metabolic syndrome as compared to 24% of the general U.S. population at the time of the study. Likewise, Fagiolini et al.[15] found that 30% of a sample of 171 BD patients met NCEP ATP III criteria for the metabolic syndrome. Forty-nine percent of patients met the criterion for abdominal obesity, 41% met the criterion for hypertriglyceridemia, 23% met the criterion for abnormal HDL-C, 39% met the criterion for hypertension, and 8% met the criterion for diabetes mellitus. These findings have important implications for the medical treatment of patients with BD.

There is evidence that the convergence of cardiovascular risk factors represented by the metabolic syndrome confers additional risk for disease above and beyond the individual risk factors.[13] Indeed, studies have documented that the metabolic syndrome is associated with up to 5-fold increased risk of mortality due to coronary heart disease[16] and up to 9-fold increased risk of developing type 2 diabetes mellitus.[17]

Obesity frequently complicates treatment for patients with BD. Weight gain is a common factor in medication discontinuation,[18] and studies have documented that obesity is associated with increased medical morbidity[19] and poorer psychiatric outcome. For example, in a study of 644 BD outpatients, McElroy et al.[20] found that obese (body mass index [BMI] = 30.0–39.9) and "extremely obese" (BMI ≥ 40.0) patients were 2 to 3 times as likely as patients who were normal weight (BMI ≤ 24.9) or overweight (BMI = 25.0–29.9) to have current hypertension and diabetes mellitus; extremely obese patients also were more likely to have arthritis. Similarly, Fagiolini and colleagues[21] found that obese patients with bipolar I disorder had significantly more previous depressive and manic episodes than nonobese patients. Obese patients also presented with more severe and difficult-to-treat index affective episodes and were more likely than nonobese patients to experience a depressive recurrence following acute treatment. Finally, 2 recent studies have suggested a relationship between obesity and suicidal ideation and behavior in patients with BD.[15,22] Specifically, Fagiolini and colleagues[22] reported a positive correlation between BMI and history of suicide attempts in 175 patients with bipolar I disorder. They also found that BD patients who met criteria for the metabolic syndrome and BD patients with abdominal obesity were significantly more likely than BD patients without these medical comorbidities to report a history of suicide attempt(s).[15]

EXPLAINING OBESITY IN BIPOLAR DISORDER

Levels of Analysis

Because the sequence of events leading to obesity in BD is complex, it is unlikely that all aspects of a hypothetical model will have equal salience for all BD patients. Different processes may interact with parameters at different levels of analysis for individual patients, resulting in numerous pathways leading to obesity in BD. Accordingly, it becomes virtually impossible to explicate every one of the manifold factors that may be involved in the onset and maintenance of obesity in BD. To provide further clarification, we present a hypothetical case as an example. We will return to this case over the course of the article as a means of illustrating how biological processes, psychological factors, sociodemographic factors, and behavior might interact to influence the onset and maintenance of obesity in a single BD patient.

Case Example

Ms. B is a 45 year-old single, white woman with a 20-year history of BD. On presentation, she is 5 ft 3 in tall and weighs 195 lb (BMI = 34.5). Although Ms. B completed a bachelor's degree in biology and worked as a laboratory technician for 15 years, she is currently unemployed and receives Social Security benefits. She lives alone and does not have any children.

Like the majority of BD patients, Ms. B's bipolar illness is dominated by periods of clinical and subclinical depression. During depressive episodes, Ms. B reports that she has "no energy" and sleeps for 12 to 14 hours per day. She also describes that she feels hungry "all the time," frequently snacking on breads, cereals, and fast foods. Ms. B experienced a particularly severe depressive episode approximately 5 years ago during which she had a "nervous breakdown" at work and requested that her psychiatrist help her apply for disability. Ms. B identifies at least 15 separate depressive episodes over the past 20 years, each lasting between 3 and 9 months.

Ms. B also describes a history of clinically significant manic symptoms with onset during her late 20s. She reports that these symptoms last approximately 7 to 8 days and include elevated mood, decreased sleep, impulsive behavior, grandiosity, and pressured speech. Although she states that she feels "good" and is "more social" during these manic episodes, Ms. B notes that she frequently "gets [her]self into trouble," particularly with respect to spending money and sexual promiscuity. Ms. B is unsure of the total number of manic episodes she has experienced over the course of her life, but estimates that they have occurred at least 10 times since their onset.

Ms. B reports that she has been overweight "my whole life" and that both of her parents (who are now deceased) had weight problems. She describes that as a child, she had a preference for sweets and "junk" foods (e.g., candy, potato chips) and that she never enjoyed sports or other physical activities. Ms. B reports onset of "binge" eating episodes when she was in high school. Specifically, Ms. B describes that as a sophomore she began experiencing sporadic "out of control" eating episodes during which she would consume unusually large quantities of food (e.g., 1 half gallon of ice cream, a 9" × 11" sheet cake from a local bakery) in a circumscribed period of time (i.e., 1–2 hours). These binge eating episodes increased in frequency to 2 to 3 times per week after Ms. B entered college. Ms. B denies any history of compensatory behaviors (e.g., self-induced vomiting, laxative abuse). She reports that the binge eating episodes "come and go" depending on her mood and life circumstances and that she is particularly vulnerable to out-of-control eating at times when she feels lonely, anxious, or depressed. Ms. B notes that she has experienced a recent increase in the frequency of her binge eating episodes during the years since she stopped working. She has few friends and enjoys a

limited number of social activities, preferring to stay at home and watch television. Ms. B reports an average of 1 to 2 binge eating episodes per week for the past 3 years.

Ms. B's symptom history is consistent with diagnoses of bipolar I disorder and binge eating disorder; however, her eating disorder has never been diagnosed or treated. Ms. B has been treated with numerous psychotropic medications over the years including lithium, divalproex, olanzapine, risperidone, amitriptyline, trazodone, clonazepam, lorazepam, and mirtazapine. She is currently taking lithium, risperidone, and mirtazapine. Ms. B reports a weight gain of at least 40 lb in the years since she began pharmacotherapy.

BIOLOGICAL PROCESSES

Genetic Predisposition

Numerous genetic processes may contribute to the development of obesity in patients with BD. Early conceptual models[23] hypothesized that a common genetic diathesis might underlie the 2 conditions such that genes that predispose patients to BD might also predispose them to obesity. There is evidence that rates of BD are elevated in family members of obese individuals. Black and colleagues[24] obtained family history data from 88 morbidly obese patients presenting for vertical banded gastroplasty and 33 healthy controls. They found significantly higher lifetime rates of depression (18% vs. 4%), BD (3% vs. 0%), and antisocial personality disorder (3% vs. 0%) in the first-degree relatives of the morbidly obese probands as compared to the relatives of control subjects.

Investigators also have identified several potential candidate genes for a genetic relationship between obesity and BD. For example, Philibert et al.[25] reported that HOPA (also known as thyroid receptor-associated protein 230) polymorphisms were associated with increased risk for both obesity and depression in a cohort of 112 Iowa adoptees. Likewise, Comings and colleagues[26] found significant correlations between a human obesity gene polymorphism (D7S1875) and BMI, depression, and anxiety in a sample of 211 men and women. Finally, Chagnon et al.[27] employed model-based genetic linkage analyses to test the hypothesis that antipsychotic-induced weight gain in BD is the result of genetic susceptibility. They found a suggestive linkage on chromosome 12q24, indicating that the pro-melanin-concentrating hormone (PMCH) gene may be involved in the onset of treatment-related obesity in BD. Interestingly, no linkage signals were detected for obesity alone, leading the authors to speculate that the PMCH gene is specifically related to antipsychotic-induced weight gain.

Personal and family history of obesity also may help to explain why some BD patients are at increased risk for weight gain and obesity. There is considerable evidence that genetic variables play a role in the development of obesity.[28] Moreover, among BD patients, personal and family vulnerability to obesity may place individuals at risk for weight gain in the presence of other known obesity risk factors (e.g., weight-gain–inducing medications, atypical depressive symptoms, decreased physical activity, overeating). Likewise, personal and family history of obesity may influence the development of these obesity risk factors. For example, personal and family history of obesity are likely to be risk factors for the development of binge eating in patients with BD. Community studies have reported that rates of childhood and parental obesity are elevated in women with bulimia nervosa relative to women with other psychiatric conditions and healthy controls.[29,30] There also is evidence that women with binge eating disorder are more likely to have a history of childhood obesity as compared to women with non–eating-related psychiatric disorders.[29]

Finally, genetic processes may influence other potential obesity-related risk factors, leading to weight gain in patients with BD. For example, there is evidence that genetic mechanisms play a role in the development of atypical depression and binge eating.[31,32] Genetic processes also may influence personal preferences for food and activity[33–35] and neurobiological abnormalities known to be associated with obesity and eating disorders.[36,37]

Biological Perturbations

Although we were unable to locate any studies that have directly examined the relationship between the biology of obesity (or a related disorder) and the biology of BD, several common neuroendocrine and neurotransmitter abnormalities have been associated with these conditions. This research should be interpreted with caution, as most studies have failed to control for mood and weight when assessing biological correlates of obesity and BD. In addition, the absence of prospective research in this area makes it impossible to determine whether biological dysfunction antedates the onset of obesity and BD or develops as a result of these conditions or the medications used to treat them. Nevertheless, biological abnormalities that may help to explain the development of obesity in BD include dysregulation of the central serotonin and dopamine systems,[38–42] increased norepinephrine turnover,[38,43] and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis.[36,44,45]

Interestingly, some research suggests that certain biological correlates of obesity are more strongly associated with BD than with unipolar depression. For example, Rybakowski and Twardowska[46] performed a combined dexamethasone/corticotropin-releasing hormone test on 16 patients with bipolar depression and 24 patients with major depressive disorder. They found significantly higher cortisol concentrations during acute depressive episode in BD patients as compared to patients with unipolar depression. Remitted BD patients also dem-

onstrated higher cortisol concentrations (assessed 30–60 minutes after corticotropin-releasing hormone infusion) than patients with remitted major depressive disorder. Based on these findings, the authors conclude that HPA axis dysregulation is significantly more pronounced in individuals with bipolar affective illness than in those with unipolar depression.

Clinical studies suggest that patients with BD are at elevated risk for abdominal obesity as compared to individuals with unipolar depression[1] and normal controls.[8] These findings may be explained in part by the presence of HPA axis hyperactivity in BD. In particular, there is evidence that hypercortisolemia is associated with abdominal obesity in depressed individuals. For example, Weber-Hamann et al.[47] classified 22 postmenopausal women with major depressive disorder as "hypercortisolemic" (free cortisol concentration > 25 nmol/L; N = 11) or "normocortisolemic" (N = 11) based on salivary assessment of free cortisol. They found significantly higher intra-abdominal fat deposits in the hypercortisolemic patients as compared to the normocortisolemic patients. These findings are consistent with those of Thakore and colleagues,[48] who reported that intra-abdominal fat and waist-to-hip ratio were positively correlated with plasma cortisol in 7 premenopausal women with major depression.

Neurotransmitter abnormalities also may influence obesity-related behaviors in patients with BD. For example, decreased cerebrospinal fluid serotonin metabolite levels have been shown to predict decreased satiety and increased carbohydrate consumption in obese women with abdominal obesity.[38] Decreased central serotonin functioning and HPA axis hyperactivity also have been associated with binge eating and bulimia nervosa.[49]

Finally, there is considerable interest in the relation among depression (including bipolar depression), obesity, and the metabolic syndrome. Prospective research has demonstrated that depressive symptoms predict onset of the metabolic syndrome in healthy, middle-aged women.[50] Moreover, biological studies have identified several characteristics of the metabolic syndrome, including glucose intolerance and insulin resistance,[51,52] hypertriglyceridemia,[15] decreased HDL-C,[53] and abdominal obesity,[1] in samples of BD patients. What remains unclear is whether the metabolic syndrome is a cause or a consequence of overweight and obesity in patients with BD. Prospective studies are needed to elucidate the timing of obesity and metabolic syndrome onset in BD patients and the biological mechanisms that may contribute to these processes.

Pharmacotherapy With Weight-Gain–Inducing Medications

There is considerable interest in the association between obesity and psychotropic medications used to treat BD. Although an extensive review of this relationship is beyond the scope of the current article (for more thorough reviews, see Keck and McElroy[2] and Nemeroff[3]), several recent findings are noteworthy. In particular, studies of BD outpatients have found that BMI is positively correlated with the number of weight-gain–inducing medications to which a patient has been exposed[20] and the specific types of medications to which a patient has been exposed.[8] For example, in a study of 89 BD outpatients, Elmslie and colleagues[8] found that patients who were treated with antipsychotic medications were significantly more obese than patients who were treated with other drug combinations or no pharmacotherapy. Interestingly, there was no association between the length of time a patient had been on his or her current medication regimen and BMI or obesity.

Researchers have identified several attributes that appear to increase a patient's risk of gaining weight during pharmacotherapy. These include female gender, low pretreatment BMI, eating under stress, narcissistic personality traits, premorbid or family history of obesity, and dramatic weight fluctuations during adulthood.[54,55] Although several studies have shown that personal or family history of obesity is associated with increased risk for weight gain during phamacotherapy,[54] at least one recent investigation suggests that normal weight and overweight patients are at greater risk for medication-induced weight gain than obese patients. Fagiolini and colleagues[56] examined the effects of acute and 12-month maintenance pharmacotherapy on weight change in 50 outpatients with bipolar I disorder. They found that normal weight and overweight, but not obese, patients gained a significant amount of weight during acute treatment; only normal weight patients continued to gain weight during maintenance treatment.

There are several pathways by which medication exposure might influence the onset and maintenance of obesity in BD. For example, weight-gain–inducing medications may stimulate appetite via disruption of neurochemical processes in the brain. Lithium has been shown to exert insulin-like activity on carbohydrate metabolism in some patients, which may indirectly stimulate appetite.[2] In addition, both lithium and valproate appear to have direct appetite-stimulating effects at the hypothalamus.[2] Finally, second generation antipsychotic medications (e.g., clozapine, olanzapine) disrupt serotonin, cholinergic, and histamine receptors, which may increase appetite and render adipocytes less efficient at managing fat storage and release.[54,57]

The consumption of high calorie beverages as a means of relieving thirst associated with psychotropic medications is another possible mechanism of drug-induced weight gain in BD. In their study of 89 BD outpatients, Elmslie and colleagues[58] found that female BD patients who were taking antipsychotic medications alone or

in combination with other drugs had significantly higher overall sugar intakes (derived primarily from nonalcoholic beverages) than other patients. Thirst and the consumption of high calorie beverages also have been observed in patients taking mood stabilizers (i.e., lithium and valproate).[2]

Finally, psychotropic medications might interact with other known obesity correlates and risk factors to influence weight gain in patients with BD. As noted above, personal and family history of obesity increases a patient's risk of gaining weight during pharmacotherapy.[54] In addition, it is possible that the appetite-stimulating effects of some psychotropic medications might exacerbate comorbid binge eating or interact with atypical depressive symptoms like hypersomnia and decreased activity to produce weight gain and obesity in BD. Likewise, sedation associated with some psychotropic medications might exacerbate inactivity, also leading to weight gain and obesity in BD.

Case Example

With a BMI of 34.5, Ms. B is "moderately obese" (class I obesity). Several biological processes may be implicated in her weight status. First, Ms. B reports a personal and family history of obesity that may reflect a genetic diathesis for obesity and also may interact with other obesity-related risk factors including weight-gain–inducing medications, atypical depressive symptoms (i.e., hypersomnia, hyperphagia, and decreased energy), and her preference for high calorie foods and sedentary activities (e.g., watching television). Second, heritable factors and neurochemical abnormalities (e.g., decreased central serotonin functioning, HPA axis hyperactivity) may have contributed to Ms. B's atypical depressive symptomatology and binge eating. Of note is the possibility that Ms. B's personal and family history of obesity may have increased her risk for the onset of binge eating in high school. Third, genetic and neurobiological (e.g., decreased serotonin functioning) processes may have contributed to Ms. B's childhood preference for high calorie foods and her dislike of physical activity. Fourth, Ms. B has been treated with numerous psychotropic medications including mood stabilizers (i.e., lithium and divalproex), antidepressants (i.e., mirtazapine and amitriptyline), and second generation antipsychotics (i.e., olanzapine, and risperidone) that have been shown to be associated with weight gain and obesity in BD.[2,3] Moreover, Ms. B's gender and personal and family history of obesity place her at increased risk for weight gain during pharmacotherapy, although her current obesity might suggest that she has reached a plateau with respect to medication-induced weight gain.[56] Finally, it is possible that the appetite-stimulating effects of medications like olanzapine, risperidone, mirtazapine, amitriptyline, lithium, and divalproex might have exacerbated Ms. B's atypical depressive symptomatology and binge eating, leading to increased weight gain and obesity.

PSYCHOLOGICAL FACTORS

Bipolar Depression

Prospective research has shown that depressive symptoms confer increased risk for weight gain and obesity,[1] central adiposity,[59,60] type 2 diabetes mellitus,[61] and the metabolic syndrome.[50] These findings are of particular relevance for patients with BD because these individuals tend to spend the majority of their time experiencing clinical and subclinical depression.[62,63] Moreover, with notable exceptions,[8,20] recent studies have found that depression history is an important correlate of obesity in BD.[21,56] For example, in a study of 50 outpatients with bipolar I disorder, Fagiolini and colleagues[56] found a positive relationship between number of previous depressive, but not manic, episodes and being overweight or obese at study entry. Baseline depression severity also was positively related to increase in BMI during acute pharmacotherapy.

There is evidence that bipolar depression differs from unipolar depression in important ways that may place patients at risk for weight gain and obesity. In particular, research has documented that physical inactivity and psychomotor retardation more frequently characterize the depressive episodes of BD patients than they do unipolar depressed patients[63–66] (but see references 67 and 68). Available data also suggest that "atypical" depressive symptoms, including hypersomnia, hyperphagia (or weight gain), and leaden paralysis (i.e., the physical sensation of having limbs that feel heavy or like lead), are more common in patients with bipolar versus unipolar depression[65,69,70] (but see reference 71). For example, Mitchell and colleagues[65] reported that BD patients scored significantly higher than patients with major depression on measures of leaden paralysis and hypersomnia. Similarly, Benazzi[72] reported that 64% of a sample of 178 patients with atypical depression met criteria for bipolar I or bipolar II disorder.

Community studies provide support for a relationship between atypical depressive symptoms and overweight and obesity.[73,74] For example, Kendler et al.[32] characterized the depression profiles of 1029 female-female twin pairs from the Virginia Twin Registry. They found that women with atypical depression had significantly higher mean body mass indices than women with mild or severe "typical" depression.

Kendler and colleagues[32] also assessed BMI in the co-twins of women with atypical and mild and severe "typical" depression. They found that BMI was significantly elevated in the co-twins of women with atypical depression. BMI also was elevated in co-twins of women with mild typical depression, but this effect was about half as

large as that reported for the atypical depression group. Kendler and colleagues reported similar findings in another study using the Virginia Twin Registry. Specifically, Sullivan et al.[74] found that membership in an atypical depression "class" (characterized by depressed mood, anhedonia, appetite and weight increase, agitation, and worthlessness/guilt) was strongly predictive of a co-twin's adjusted (for age and gender) BMI in a sample of 2927 male-male and male-female twin pairs.

Binge Eating Comorbidity

The association of binge eating, i.e., aberrant overeating accompanied by a feeling of loss of control, with both obesity and mood disorders has been well documented.[75,76] Clinical studies have shown that 23% to 46% of individuals seeking obesity treatment report binge eating.[77,78] There also is evidence that binge eating and binge eating disorder are associated with weight gain, as well as obesity onset and severity.[75,79]

Available data suggest that binge eating is prevalent in patients with BD. Kruger and colleagues[80] reported that 38% of a sample of 61 BD patients engaged in recurrent episodes of binge eating, and 13% met diagnostic criteria for binge eating disorder. Similarly, Ramacciotti et al.[81] found that 27% of a sample of 51 patients with bipolar I disorder met criteria for a current or lifetime diagnosis of bulimia nervosa (N = 5) or binge eating disorder (N = 9).

Research also suggests that binge eating is associated with obesity and medical and psychiatric morbidity in patients with BD. McElroy and colleagues[20] found that 13.5% of obese BD patients and 50% of "extremely obese" BD patients had a self-reported lifetime history of binge eating disorder, as compared to 4.9% of normal-weight BD patients. Moreover, ongoing research in our lab has shown that after controlling for obesity, BD patients who engage in weekly binge eating are more likely to have at least 1 current medical or psychiatric comorbidity than BD patients who do not engage in recurrent binge eating (J.E.W.; A.F.; T. Salopek, M.S.W.; M.D.M., unpublished data, June 2006).

Little is known about the mechanisms that may explain the relationship among binge eating, obesity, and BD. One hypothesis is that that binge eating and BD share common pathophysiologic factors that increase the likelihood of their co-occurrence.[82] This theory is supported by epidemiologic data indicating that binge eating and BD, particularly soft spectrum and subthreshold BD, co-occur more frequently than would be expected by chance alone,[83–85] as well as research demonstrating phenomenological, longitudinal, biological, and treatment response similarities between eating disorders and BD.[82] There also is evidence that genetic variables play a role in the development of both binge eating[86,87] and BD,[88] and family history research suggests that binge eating and BD may have common familial causal factors.[89]

Another hypothesis is that binge eating serves a functional role in regulating negative affect. There is evidence that negative affect plays a role in the onset and maintenance of binge eating. A recent meta-analysis of studies examining risk and maintenance factors for eating disorder pathology found that negative affect was a significant predictor of both the onset of eating disordered behaviors and the maintenance of binge eating.[90] Moreover, some research suggests that affective instability, which characterizes bipolar spectrum disorders,[91] may be an especially potent predictor of binge eating. Greenberg and Harvey[92] assessed depressive symptoms, biphasic mood shifts (i.e., shifts between elated and depressed mood), dietary restraint, and binge eating in a sample of 73 female undergraduates. They found that the interaction of biphasic mood shifts and dietary restraint accounted for all of the variance in the relation among depression, dietary restraint, and binge eating. Finally, binge eating is one of the diagnostic criteria for borderline personality disorder,[93] a condition characterized by affective instability that is frequently (mis)-diagnosed in patients with BD.[94]

In addition to affective instability, research suggests that atypical depressive symptoms and certain biological correlates of BD (e.g., HPA axis hyperactivity, decreased central serotonin functioning) are associated with binge eating.[32,49] Hence BD patients whose depressive episodes are characterized by atypical depressive symptoms, or patients with certain types of biological dysfunction, may be at elevated risk for the onset of binge eating and obesity. Kendler et al.[32] assessed atypical depressive symptoms and binge eating in their sample of 1029 female-female twin pairs. They found a significantly higher lifetime prevalence of bulimia nervosa (19%) in women with atypical depression as compared to women with severe and mild "typical" depression (15.6% and 6.6%, respectively). Kendler and colleagues[32] also reported that co-twins of women with atypical depression were at nearly 3 times greater lifetime risk for bulimia nervosa relative to co-twins of women with mild depression, suggesting that there may be a genetic relationship between atypical depression and binge eating.

Finally, some research suggests that binge eating onset precedes BD onset in patients with comorbid eating- and mood-related psychopathology (but see Ramacciotti et al.[81]). Kruger et al.[80] reported that the onset of binge eating disorder antedated the onset of affective disorder by an average of 7 years in their sample of 8 patients with comorbid bipolar I or bipolar II disorder and binge eating disorder. These findings suggest that binge eating may be a marker for the presence of affective instability prior to the onset of BD. Indeed, studies of obese individuals indicate that binge eating is associated with increased risk for psychiatric and medical morbidity. In particular, research has shown that relative to obese individuals who

do not binge eat, obese binge eaters have higher rates of Axis I and Axis II psychopathology,[75,95,96] greater health dissatisfaction,[77] lower self-esteem,[97] more cognitive features of disordered eating,[98] and higher body mass indices[99] and are more likely to seek treatment.[100] Binge eating also may help to explain why many BD patients are already overweight or obese when they present for treatment,[56] as well the association between obesity and BD symptom severity.[21]

Adverse Childhood Experiences

Community studies have indicated that childhood adversity (i.e., physical, sexual, and emotional abuse and neglect) is associated with increased body weight and risk of obesity during adolescence and adulthood.[101–103] For example, in a 10-year prospective study of 1258 9- to 10-year-old children, Lissau and Sorensen[102] found that children who were rated by their school health service as "dirty and neglected" were 9.8 times more likely to be obese in young adulthood than averagely groomed children. Likewise, Williamson and colleagues[103] found that adults who reported physical, sexual, or emotional abuse during childhood were 0.6 to 4.0 kg heavier on average than adults who did not report childhood abuse. Frequent verbal abuse and frequent physical abuse with injury were most strongly associated with adult obesity in this study.

Available data suggest that 36% to 49% of BD patients have a history of childhood abuse or neglect.[104,105] There are several pathways by which this childhood adversity might contribute to obesity in BD. For example, general population studies have documented an association between childhood abuse and increased risk for binge eating[29]; indeed, binge eating has been hypothesized to mediate the relationship between childhood sexual abuse and adult obesity.[106] In addition, there is evidence that adverse childhood experiences are associated with indices of BD illness severity including earlier age at BD onset, increased comorbidity on Axes I, II, and III, rapid cycling, and a higher rate of lifetime suicide attempts.[104,105] Of particular relevance to the development of obesity in BD is the relationship of childhood adversity to "reverse neurovegetative symptoms" (i.e., hypersomnia, hyperphagia, weight gain). Specifically, Levitan and colleagues[107] reported that having a history of childhood physical or sexual abuse was associated with a significantly higher lifetime risk of experiencing reverse neurovegetative symptoms in a sample of 8116 depressed patients. Finally, some authors have hypothesized that traumatic experiences, including childhood abuse, might result in psychobiological disturbances, which could be related to weight gain and obesity.[106] For example, reduced serotonin activity has been associated with increased rates of childhood physical and sexual abuse in samples of women with bulimia nervosa[108] and borderline personality disorder.[109]

Case Example

Ms. B reports an extensive depression history (15 previous depressive episodes) and atypical depressive symptoms that may be directly related to her current weight status and may also interact with other obesity-related risk factors (e.g., personal and family history of obesity, weight-gain–inducing medications). In addition, Ms. B reports current and past binge eating that is exacerbated by negative affect and may also be related to her atypical depressive symptomatology.

SOCIODEMOGRAPHIC FACTORS

General population studies have identified several sociodemographic variables that are associated with increased risk for overweight and obesity, including age (individuals 25–60 years of age are at highest risk for weight gain and obesity),[110,111] female gender,[112] and African American ethnicity (for women, but not men).[110–113] Of note are numerous studies indicating an inverse relationship between socioeconomic status (SES) and obesity, especially among women and individuals of white ethnicity.[114,115]

Sociodemographic Factors and Obesity in BD

There is evidence that sociodemographic factors are associated with rates of obesity in patients with BD. For example, McElroy and colleagues[20] reported that overweight, obese, and extremely obese patients were older than normal-weight patients in their sample of 644 BD outpatients. They also found that female BD patients were more likely than male BD patients to be extremely obese; male BD patients were more likely than female BD patients to be overweight. Fagiolini et al.[56] reported similar findings in their sample of 50 patients with bipolar I disorder. In particular, they found that male BD patients were more likely to be overweight or obese than female BD patients. Finally, research supports the presence of an inverse relationship between SES and obesity in patients with BD. McElroy and colleagues[20] found that obese and extremely obese BD patients had significantly lower incomes as compared to normal-weight and overweight BD patients. Similarly, Fagiolini et al.[21] reported that obese BD patients had significantly fewer years of education than nonobese BD patients.

Several theories may be proposed to explain sociodemograhic disparities in the prevalence of overweight and obesity in patients with BD. First, older patients may be at greater risk for weight gain and obesity due to a longer history of bipolar illness and treatment with multiple weight-gain–inducing medications. Second, female BD patients may be at greater risk for extreme obesity due to gender differences in the prevalence of psychiatric factors related to weight gain and obesity. In particular, research has shown that atypical depressive

symptoms[72,116,117] (but see reference 71) and binge eating[118–121] are significantly more common in women than in men. Finally, several mechanisms may be involved in driving the inverse relationship between SES and obesity in patients with BD. General population studies indicate that women of higher SES, in particular, are more likely to diet and to engage in physical activity, behaviors that have been shown to reduce weight gain and obesity.[114] In addition, there is evidence that downward mobility (i.e., a decrease in SES over one's lifetime) is associated with obesity[114] and BD,[122,123] although the direction of these effects has yet to be elucidated. Finally, family history may play a role in the relationship among SES, obesity, and BD. Sobal and Stunkard[114] noted that the SES of parents is one of the best predictors of SES in their grown children; parental overweight, which may be associated with parental SES, also has been shown to predict obesity in grown children.[28]

Case Example

Ms. B's age, gender, and SES all place her at risk for weight gain and obesity. Her 20-year history of BD, exposure to numerous psychotropic medications, atypical depressive symptoms, and comorbid binge eating all may have influenced or been influenced by these sociodemographic factors. Moreover, as a white woman, Ms. B's low SES, as evidenced by her downward mobility, unemployment, and receipt of Social Security benefits, likely places her at risk for continued weight gain and obesity. For example, like many individuals on a fixed income, Ms. B relies primarily on canned and processed foods, and the availability of fresh fruits and vegetables is limited in her neighborhood. Likewise, there are few recreational facilities or parks where Ms. B can exercise.

BEHAVIOR

Ultimately, obesity results from an energy imbalance; that is, energy intake must exceed energy expenditure in order for weight gain to occur.[124] This means that behavioral processes (i.e., physical inactivity and overeating) must be involved in virtually every pathway leading to obesity in BD.

Numerous studies have documented the association of reduced physical activity, increased appetite, and a high calorie diet to weight gain and obesity in normal populations,[125,126] as well as individuals with BD.[20,58] For example, McElroy et al.[20] found a significant negative correlation between amount of exercise and BMI in their study of 644 BD outpatients. Similarly, Elmslie et al.[58] reported that their sample of 89 BD outpatients (19% of whom were obese) engaged in significantly fewer episodes of low-to-moderate–intensity and high-intensity physical activity over a 4-week period than 445 age- and sex-matched controls (12% of whom were obese). Elmslie and colleagues[58] also reported that total daily sucrose intake, mean percentage of energy from carbohydrate, and total available carbohydrate were higher in BD patients as compared to the control group. Specifically, BD patients consumed significantly more nonalcoholic beverages, cakes, and sweets than control subjects.

We already have reviewed several mechanisms that may help to explain why sedentary behavior and overeating are prevalent in patients with BD including neurotransmitter and neuroendocrine dysfunctions (e.g., decreased central serotonin functioning, HPA axis hyperactivity), thirst resulting from psychotropic medications, atypical depressive symptoms, comorbid binge eating, and low SES (which is associated with decreased physical activity and less frequent dieting, especially in women[114]). In addition to these direct effects on weight gain in patients with BD, behavioral processes undoubtedly interact with other mechanisms to produce obesity in this population. Of note is the likelihood that a genetic vulnerability to obesity might increase a patient's risk of gaining weight in the presence of a sedentary lifestyle and high calorie diet. Obesity researchers have long noted the importance of focusing on gene-environment interactions in an effort to better understand individual differences in weight gain and obesity.[33] Moreover, general population studies have found that ingestion of a high-fat diet is related to weight gain in women with a familial predisposition to obesity.[33] It also is possible that preferences for high-fat foods and sedentary activities, which are at least partially influenced by genetic factors,[33,34] might lead to increased caloric intake and weight gain in BD. Finally, individuals with a diathesis for BD and obesity may be particularly likely to self-soothe with palatable, high-fat foods.

CONCLUSION

Obesity is prevalent in patients with BD and is associated with increased medical morbidity and poorer psychiatric outcome. Consequently, there is a compelling need for researchers and clinicians to better understand the complex and multifactorial nature of the cascade of events that leads to obesity onset and maintenance in this population. Explication of these etiologic pathways may help us to develop effective interventions aimed at preventing and treating weight gain in BD patients and enhancing the outcome of mood disorder treatment. Although the exact causes of obesity in BD remain unknown, substantial evidence documents the salience of biological, psychological, and sociodemographic variables in the onset and maintenance of obesity. However, as demonstrated by the case example, the relevance of each of these factors within levels of analysis will vary across individuals. Nevertheless, the etiologic cascade, which includes factors such as genetic vulnerability,

atypical depressive symptomatology, pharmacotherapy, and SES, ultimately will directly or indirectly affect levels of physical activity and eating behavior. One task for future research is to develop behavioral interventions aimed at targeting physical inactivity and overeating in patients with BD. There also is a need to incorporate screening and treatment for binge eating problems in patients with BD. Finally, future research targeting a clearer understanding of the causes and consequences of obesity across levels of analysis may lead to better treatments for both obesity and BD.

Drug names: clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), risperidone (Risperdal), trazodone (Desyrel and others).

REFERENCES

1. McElroy SL, Kotwal R, Malhotra S, et al. Are mood disorders and obesity related? a review for the mental health professional. J Clin Psychiatry 2004;65:634–651
2. Keck PE Jr, McElroy SL. Bipolar disorder, obesity, and pharmacotherapy-associated weight gain. J Clin Psychiatry 2003;64:1426–1435
3. Nemeroff CB. Safety of available agents used to treat bipolar disorder: focus on weight gain. J Clin Psychiatry 2003;64:532–539
4. Schwartz TL, Nihalani N, Jindal S, et al. Psychiatric medication–induced obesity: a review. Obes Rev 2004;5:115–121
5. Zimmerman U, Kraus T, Himmerich H, et al. Epidemiology, implications, and mechanisms underlying drug-induced weight gain in psychiatric patients. J Psychiatr Res 2003;37:193–220
6. Kretschmer E. Physique and Character. 2nd ed. New York, NY: Harcourt, Brace, & Company; 1936
7. Kendler KS. Toward a philosophical structure for psychiatry. Am J Psychiatry 2005;162:433–440
8. Elmslie JL, Silverstone JT, Mann JI, et al. Prevalence of overweight and obesity in bipolar patients. J Clin Psychiatry 2000;61:179–184
9. Muller-Oerlinghausen B, Passoth P-M, Poser W, et al. Impaired glucose tolerance in long-term lithium-treated patients. Int Pharmacopsychiatry 1979;14:350–362
10. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes in hospitalized manic-depressive patients. Am J Psychiatry 1999;156:1417–1420
11. Regenold WT, Thapar RK, Marano C, et al. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective disorders independent of psychotropic drug use. J Affect Disord 2002;70: 19–26
12. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844–850
13. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497
14. Basu R, Brar JS, Chengappa KNR, et al. The prevalence of the metabolic syndrome in patients with schizoaffective disorder-bipolar subtype. Bipolar Disord 2004;6:314–318
15. Fagiolini A, Frank E, Scott JA, et al. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord 2005;7:424–430
16. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–2716
17. Laaksonen DE, Lakka HM, Niskanen LK, et al. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 2002;156:1070–1077
18. Sachs GS. Unmet clinical needs in bipolar disorder. J Clin Psychopharmacol 2003;23(suppl 1):2–8
19. Pi-Sunyer FX. Health implications of obesity. Am J Clin Nutr 1991;53 (suppl):1595–1603
20. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002; 63:207–213
21. Fagiolini A, Kupfer DJ, Houck PR, et al. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry 2003;160: 112–117
22. Fagiolini A, Kupfer DJ, Rucci P, et al. Suicide attempts and ideation in patients with bipolar I disorder. J Clin Psychiatry 2004;65:509–514
23. Kretschmer E. Heredity and constitution in the aetiology of psychic disorders. Br Med J 1937;part 2:403–406
24. Black DW, Goldstein RB, Mason EE, et al. Depression and other mental disorders in the relatives of morbidly obese patients. J Affect Disord 1992;25:91–96
25. Philibert R, Caspers K, Langbehn D, et al. The association of a HOPA polymorphism with major depression and phobia. Compr Psychiatry 2002;43:404–410
26. Comings DE, Gade R, MacMura JP, et al. Genetic variants of the human obesity (OB) gene: association with body mass index in young women, psychiatric symptoms, and interaction with the dopamine D_2 receptor (DRD2) gene. Mol Psychiatry 1996;1:325–335
27. Chagnon YC, Merette C, Bouchard RH, et al. A genome wide linkage study of obesity as secondary effect of antipsychotics in multigenerational families of eastern Quebec affected by psychoses. Mol Psychiatry 2004;9:1067–1074
28. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet 1997;27: 325–351
29. Fairburn CG, Doll HA, Welch SL, et al. Risk factors for binge eating disorder: a community-based case-control study. Arch Gen Psychiatry 1998;55:425–432
30. Fairburn CG, Welch SL, Doll HA, et al. Risk factors for bulimia nervosa: a community-based case-control study. Arch Gen Psychiatry 1997;54: 509–517
31. Bulik CM, Sullivan PF, Kendler KS. Genetic and environmental contributions to obesity and binge eating. Int J Eat Disord 2003;33:293–298
32. Kendler KS, Eaves LJ, Walters EE, et al. The identification and validation of distinct depressive syndromes in a population-based sample of female twins. Arch Gen Psychiatry 1996;53:391–399
33. Faith MS, Johnson SL, Allison DB. Putting the behavior into the behavior genetics of obesity. Behav Genet 1997;27:423–439
34. Reed DR, Bachmanov AA, Beauchamp GK, et al. Heritable variation in food preferences and their contribution to obesity. Behav Genet 1997;27: 373–387
35. Wardle J, Guthrie C, Sanderson S, et al. Food and activity preferences in children of lean and obese parents. Int J Obes Relat Metab Disord 2001; 25:971–977
36. Bjorntorp P, Rosmond R. Obesity and cortisol. Nutrition 2000;16: 924–936
37. Steiger H. Eating disorders and the serotonin connection: state, trait, and developmental effects. J Psychiatry Neurosci 2004;29:20–29
38. Ericsson M, Poston WSC, Foreyt JP. Common biological pathways in eating disorders and obesity. Addict Behav 1996;21:733–743
39. Mahmood T, Silverstone T. Serotonin and bipolar disorder. J Affect Disord 2001;66:1–11
40. Sobczak S, Honig A, van Duinen MA, et al. Serotonergic dysregulation in bipolar disorders: a literature review of serotonergic challenge studies. Bipolar Disord 2002;4:347–356
41. Vogel M, Pfiefer S, Schaub RT, et al. Decreased levels of dopamine D-sub-3 receptor mRNA in schizophrenic and bipolar patients. Neuropsychobiology 2004;50:305–310
42. Wang G-J, Volkow ND, Logan J, et al. Brain dopamine and obesity. Lancet 2001;357:354–357
43. Young LT, Warsh JJ, Kish SJ, et al. Reduced brain 5-HT and elevated NE turnover and metabolites in bipolar affective disorder. Biol Psychiatry 1994;35:121–127
44. Vicennati V, Pasquali R. Abnormalities of the hypothalamic-pituitary-adrenal axis in nondepressed women with abdominal obesity and relations with insulin resistance: evidence for a central and a peripheral alteration. J Clin Endocrinol Metab 2000;85:4093–4098

45. Watson S, Gallagher P, Ritchie JC, et al. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. Br J Psychiatry 2004;184: 496–502
46. Rybakowski JK, Twardowska K. The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. J Psychiatr Res 1999;33:363–370
47. Weber-Hamann B, Hentschel F, Kniest A, et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. Psychosom Med 2002;64:274–277
48. Thakore JH, Richards PJ, Reznek RH, et al. Increased intra-abdominal fat deposition in patients with major depressive illness as measured by computer tomography. Biol Psychiatry 1997;41:1140–1142
49. Pope HG Jr, Hudson JI. Is bulimia nervosa a heterogeneous disorder? lessons from the history of medicine. Int J Eat Disord 1988;7:155–166
50. Raikkonen K, Matthews KA, Kuller LH. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? Metabolism 2002;51:1573–1577
51. Mueller PS, Heninger GR, McDonald RK. Insulin tolerance test in depression. Arch Gen Psychiatry 1969;21:587–594
52. Mueller PS, Heninger GR, McDonald RK. Intravenous glucose tolerance test in depression. Arch Gen Psychiatry 1969;21:470–477
53. Glueck CJ, Tieger M, Kunkel R, et al. Hypocholesterolemia and affective disorders. Am J Med Sci 1994;308:218–225
54. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatr Scand 1999;100:3–16
55. Fagiolini A, Novik DM. Bipolar disorder and obesity. Dir Psychiatry 2004;24:257–263
56. Fagiolini A, Frank E, Houck PR, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry 2002;63:528–533
57. Virk S, Schwartz TL, Jindal S, et al. Psychiatric medication induced obesity: an aetiologic review. Obes Rev 2004;5:167–170
58. Elmslie JL, Mann JI, Silverstone JT, et al. Determinants of overweight and obesity in patients with bipolar disorder. J Clin Psychiatry 2001;62: 486–491
59. Lloyd CE, Wing RR, Orchard TJ. Waist to hip ratio and psychosocial factors in adults with insulin-dependent diabetes mellitus: the Pittsburgh epidemiology of diabetes complications study. Metabolism 1996;45: 268–272
60. Raikkonen K, Matthews KA, Kuller LH. Anthropometric and psychosocial determinants of visceral obesity in healthy postmenopausal women. Int J Obes Relat Metab Disord 1999;23:775–782
61. Golden SH, Williams JE, Ford DE, et al. Depressive symptoms and the risk of type 2 diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care 2004;27:429–435
62. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history and the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269
63. Mitchell PB, Malhi GS. Bipolar depression: phenomenological overview and clinical characteristics. Bipolar Disord 2004;6:530–539
64. Beigel A, Murphy DL. Unipolar and bipolar affective illness: differences in clinical characteristics accompanying depression. Arch Gen Psychiatry 1971;24:215–220
65. Mitchell PB, Wilhelm K, Parker G, et al. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. J Clin Psychiatry 2001;62:212–216
66. Parker G, Roy K, Wilhelm K, et al. The nature of bipolar depression: implications for the definition of melancholia. J Affect Disord 2000;59: 217–224
67. Kuhs H, Reschke D. Psychomotor activity in unipolar and bipolar depressive patients. Psychopathology 1992;25:109–116
68. Mitchell P, Parker G, Jamieson K, et al. Are there any differences between bipolar and unipolar melancholia? J Affect Disord 1992;25: 97–105
69. Akiskal HS, Walker P, Puzantian VR, et al. Bipolar outcome in the course of depressive illness. J Affect Disord 1983;5:115–128
70. Fabrega H Jr, Mezzich JE, Mezzich AC, et al. Descriptive validity of DSM-III depressions. J Nerv Ment Dis 1986;174:573–584
71. Robertson HA, Lam RW, Stewart JN, et al. Atypical depressive symptoms and clusters in unipolar and bipolar depression. Acta Psychiatr Scand 1996;94:421–427
72. Benazzi F. Prevalence and clinical features of atypical depression in depressed outpatients: a 467-case study. Psychiatry Res 1999;86: 259–265
73. Hasler G, Pine DS, Gamma A, et al. The associations between psychopathology and being overweight: a 20-year prospective study. Psychol Med 2004;34:1047–1057
74. Sullivan PF, Prescott CA, Kendler KS. The subtypes of major depression in a twin registry. J Affect Disord 2002;68:273–284
75. Yanovski SZ. Binge eating disorder and obesity in 2003: could treating an eating disorder have a positive effect on the obesity epidemic? Int J Eat Disord 2003;34(suppl):S117–S120
76. Yanovski SZ, Nelson JE, Dubbert BK, et al. Association of binge eating disorder and psychiatric comorbidity in obese subjects. Am J Psychiatry 1993;150:1472–1479
77. Bulik CM, Sullivan PF, Kendler KS. Medical and psychiatric morbidity in obese women with and without binge eating. Int J Eat Disord 2002;32: 72–78
78. Marcus MD. Binge eating in obesity. In: Fairburn CG, Wilson GT, eds. Binge Eating: Nature, Assessment, and Treatment. New York, NY: Guilford Press; 1993:77–96
79. Grissett NI, Fitzgibbon ML. The clinical significance of binge eating in an obese population: support for BED and questions regarding its criteria. Addict Behav 1996;21:57–66
80. Kruger S, Shugar G, Cooke, RG. Comorbidity of binge eating disorder and the partial binge eating syndrome with bipolar disorder. Int J Eat Disord 1996;19:45–52
81. Ramacciotti CE, Paoli RA, Marcacci G et al. Relationship between bipolar illness and binge-eating disorders. Psychiatry Res 2005;135: 165–170
82. McElroy SL, Kotwal R, Keck PE Jr, et al. Comorbidity of bipolar and eating disorders: distinct or related disorders with shared dysregulations? J Affect Disord 2005;86:107–127
83. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–151
84. Lewinsohn PM, Shankman SA, Gau JM, et al. The prevalence and comorbidity of subthreshold psychiatric conditions. Psychol Med 2004;34: 613–622
85. Wittchen H-U, Muhlig S, Pezawas L, et al. Natural course and burden of bipolar disorders. Int J Neuropsychopharmacol 2003;6:145–154
86. Bulik CM, Sullivan PF, Kendler KS. Heritability of binge-eating and broadly defined bulimia nervosa. Biol Psychiatry 1998;44:1210–1218
87. Reichborn-Kjennerud T, Bulik CM, Tambs K, et al. Genetic and environmental influences on binge eating in the absence of compensatory behaviors: a population-based twin study. Int J Eat Disord 2004;36: 307–314
88. Kelsoe JR. Arguments for the genetic basis of the bipolar spectrum. J Affect Disord 2003;73:183–197
89. Mangweth B, Hudson JI, Pope HG, et al. Family study of the aggregation of eating disorders and mood disorders. Psychol Med 2003;33: 1319–1323
90. Stice E. Risk and maintenance factors for eating pathology: a meta-analytic review. Psychol Bull 2002;128:825–848
91. Perugi G, Akiskal HS. The soft bipolar spectrum redefined: focus on the cyclothymic, anxious-sensitive, impulse-dyscontrol, and binge-eating connection in bipolar II and related conditions. Psychiatr Clin North Am 2002;25:713–737
92. Greenberg BR, Harvey PD. Affective lability versus depression as determinants of binge eating. Addict Behav 1987;12:357–361
93. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
94. Akiskal HS, Bourgeois ML, Angst J, et al. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord 2000;59(suppl 1):5–30
95. Marcus MD, Wing RR, Ewing L, et al. Psychiatric disorders among obese binge eaters. Int J Eat Disord 1990;9:69–77
96. Specker S, de Zwaan M, Raymond N, et al. Psychopathology in subgroups of obese women with and without binge eating disorder. Compr Psychiatry 1994;35:185–190
97. Webber EM. Psychological characteristics of binging and nonbinging obese women. J Psychol 1994;128:339–351
98. Hsu LK, Mulliken B, McDonagh B, et al. Binge eating disorder in extreme obesity. Int J Obes Relat Metab Disord 2002;26:1398–1403
99. Ricca V, Mannucci E, Moretti S, et al. Screening for binge eating disorder in obese outpatients. Compr Psychiatry 2000;41:111–115

100. Fitzgibbon ML, Stolley MR, Kirschenbaum DS. Obese people who seek treatment have different characteristics than those who do not seek treatment. Health Psychol 1993;12:342–345
101. Johnson JG, Cohen P, Kasen S, et al. Childhood adversities associated with risk for eating disorders or weight problems during adolescence or early adulthood. Am J Psychiatry 2002;159:394–400
102. Lissau I, Sorensen TIA. Parental neglect during childhood and increased risk of obesity in young adulthood. Lancet 1994;343:324–327
103. Williamson DF, Thompson TJ, Anda RF, et al. Body weight and obesity in adults and self-reported abuse in childhood. Int J Obes Relat Metab Disord 2002;26:1075–1082
104. Garno JL, Goldberg JF, Ramirez PM, et al. Impact of childhood abuse on the clinical course of bipolar disorder. Br J Psychiatry 2005;186: 121–125
105. Leverich GS, McElroy SL, Suppes T, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biol Psychiatry 2002;51:288–297
106. Gustafson TB, Sarwer DB. Childhood sexual abuse and obesity. Obes Rev 2004;5:129–135
107. Levitan RD, Parikh SV, Lesage AD, et al. Major depression in individuals with a history of childhood physical or sexual abuse: relationship to neurovegetative features, mania, and gender. Am J Psychiatry 1998; 155:1746–1752
108. Steiger H, Gauvin L, Israel M, et al. Serotonin function, personality-trait variations, and childhood abuse in women with bulimia-spectrum eating disorders. J Clin Psychiatry 2004;65:830–837
109. Rinne T, Westenberg HGM, den Boer JA, et al. Serotonergic blunting to meta-chlorophenylpiperazine (m-CPP) highly correlates with sustained childhood abuse in impulsive and autoaggressive female borderline patients. Biol Psychiatry 2000;47:548–556
110. Sheehan TJ, DuBrava S, DeChello LM, et al. Rates of weight change for black and white Americans over a twenty year period. Int J Obes Relat Metab Disord 2003;27:498–504
111. Wardle J, Waller J, Jarvis M. Sex differences in the association of socioeconomic status with obesity. Am J Public Health 2002;92: 1299–1304
112. Hedley AA, Ogden CL, Johnson CL, et al. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA 2004;291:2847–2850
113. Burke GL, Bild DE. Differences in weight gain in relation to race, gender, age and education in young adults: the CARDIA study. Ethn Health 1996;1:327–335
114. Sobal J, Stunkard AJ. Socioeconomic status and obesity: a review of the literature. Psychol Bull 1989;105:260–275
115. Zhang Q, Wang Y. Socioeconomic inequality of obesity in the United States: do gender, age, and ethnicity matter? Soc Sci Med 2004;58: 1171–1180
116. Angst J, Gamma A, Sellaro R, et al. Toward validation of atypical depression in the community: results of the Zurich cohort study. J Affect Disord 2002;72:125–138
117. Matza LS, Revicki DA, Davidson JR, et al. Depression with atypical features in the National Comorbidity Survey. Arch Gen Psychiatry 2003;60:817–826
118. Langer LM, Warheit GJ, Zimmerman RS. Epidemiological study of problem eating behaviors and related attitudes in the general population. Addict Behav 1991;16:167–173
119. Linde JA, Jeffery RW, Levy RL, et al. Binge eating disorder, weight control self-efficacy, and depression in overweight men and women. Int J Obes Relat Metab Disord 2004;28:418–425
120. Rand CSW, Kuldau JM. Epidemiology of bulimia and symptoms in a general population: sex, age, race, and socioeconomic status. Int J Eat Disord 1992;11:37–44
121. Wilson GT, Nonas CA, Rosenblum GD. Assessment of binge eating in obese patients. Int J Eat Disord 1993;13:25–33
122. Abood Z, Sharkey A, Webb M, et al. Are patients with bipolar affective disorder socially disadvantaged? a comparison with a control group. Bipolar Disord 2002;4:243–248
123. Jones PB, Bebbington P, Foerster A, et al. Premorbid social underachievement in schizophrenia: results from the Camberwell Collaborative Psychosis Study. Br J Psychiatry 1993;162:65–71
124. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002;288:1723–1727
125. Andersen RE, Franckowiak S, Christmas C, et al. Obesity and reports of no leisure time activity among older Americans: results from the third National Health and Nutrition Examination Survey. Educ Gerontology 2001;27:297–306
126. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001;286:1195–1200