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Original Article

Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians

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Objective: This study sought to evaluate the presence of the metabolic syndrome in a group of 171 patients with bipolar disorder who were consecutively recruited in the Bipolar Disorder Center for Pennsylvanians.

Methods: Data were collected from participants entering the Bipolar Disorder Center for Pennsylvanians protocol between 2003 and 2004. The study focused on the presence of the metabolic syndrome, as defined by the National Cholesterol Education Program Expert Panel on Detection, Evaluation And Treatment of High Blood Cholesterol in Adults (NCEP ATP III).

Results: Thirty percent of the sample met the NCEP ATP III criterion for the metabolic syndrome, 49% met the criterion for abdominal obesity, 41% met the criterion for hypertriglyceridemia, 48% met the criterion for hypertriglyceridemia or were on a cholesterol-lowering medication, 23% met the criterion for low high-density lipoprotein cholesterol, 39% met the criterion for hypertension and 8% met the criterion for high fasting glucose or antidiabetic medication use. Patients with the metabolic syndrome and patients endorsing the obesity criterion were more likely ($p = 0.05$ and $p = 0.004$, respectively) to report a lifetime history of suicide attempt/s.

Conclusions: The prevalence of the metabolic syndrome in patients with bipolar disorder is alarmingly high, as it is for the general population. The prevalence of obesity is even higher than the already very high prevalence that has been estimated for the US general population. Our findings are a reason for concern, considering the difficulty in implementing prevention and treatment programs in the bipolar population. We strongly support the development and testing of interventions specifically designed for preventing and treating the metabolic syndrome and its components in patients with bipolar disorder.

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In the past several years, a great deal of attention has been devoted to the medical burden suffered by patients with schizophrenia (1). More recently, similar concerns have arisen for patients with bipolar disorder. Studies evaluating obesity (2–8), diabetes (9–14), dyslipidemia (9, 15–17) and hypertension (18) have been conducted in patients with bipolar disorder. However no study to date has evaluated the clustering of the illnesses described above, with the exception of a pilot study on

patients with schizoaffective disorder bipolar type (19).

The clustering of risk factors for cardiovascular disease, including abdominal obesity, dyslipidemia, insulin resistance, and hypertension has been described as 'metabolic syndrome' (20). In 2001, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) suggested a working definition of this syndrome based on the presence of three or more of the following characteristics: abdominal obesity (waist circumference), hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), high blood pressure and fasting hyperglycemia (21).

The presence of the metabolic syndrome appears to identify substantial additional risk above and beyond the individual risk factors (22). In fact, the syndrome has very highly significant health implications, including a three- to five-fold increased risk of mortality due to coronary heart disease (22–24), and a sixfold risk of developing type 2 diabetes (25). According to the National Health and Nutrition Examination Survey conducted in the years 1999 and 2000 (NHANES 1999–2000) the metabolic syndrome is alarmingly prevalent in the United States, with estimates as high as 28% when patients taking cholesterol-lowering medications are included in the group of patients endorsing hypercholesterolemia (26).

This study evaluates the prevalence of the metabolic syndrome and each of its criterion items in a group of 171 patients with bipolar disorder participating in the 'Bipolar Disorder Center for Pennsylvanians' study. We hypothesized that there would be a high prevalence of the metabolic syndrome and its criterion items in this group, and that the metabolic syndrome would correlate with indices of illness severity such as lifetime history of suicide attempts, current (past week) Clinical Global Impression-Severity-Bipolar Version score (CGI-S-BP) (27), and current (past week) Global Assessment of Functioning (GAF) score. Our hypotheses were based on the results of previous studies of the medical burden observed in patients with bipolar or schizoaffective-bipolar type disorder, on our previous observations about the high prevalence of obesity in patients with bipolar disorder (2, 3) and about the influence of obesity on severity indices such as suicidality (28) and scores on the Hamilton Rating Scale for Depression (3), as well as on our clinical observations about the high prevalence in these patients of symptoms such as increased appetite and reduced energy expenditure, unhealthy eating habits, and weight gain, often correlated with current or previous treatment with psychotropic medications. However, given its cross-sectional design, this study was not intended to evaluate the relationship between potential risk factors such as the use of certain psychotropic medications, and the metabolic syndrome.

Methods

The Institutional Review Board at the University of Pittsburgh reviewed and approved all the procedures described in this protocol and all subjects gave written informed consent prior to participating in the study.

The Bipolar Disorder Center for Pennsylvanians Study is a multicenter randomized controlled study involving subjects with bipolar I, bipolar II, bipolar not otherwise specified (NOS), or schizoaffective bipolar subtype. The study compares the clinical outcomes of subjects who receive enhanced clinical intervention (ECI) with the clinical outcomes of subjects who do not receive ECI on a background of standardized but accepted drug regimens. Patients participated in a research diagnostic interview using the Structured Clinical Interview for DSM-IV (SCID).

The present study includes 171 adult (age ≥18 years) patients with bipolar I, bipolar II, and bipolar NOS disorder, consecutively recruited into the Pittsburgh site of the Bipolar Disorder Center for Pennsylvanians study from November 2003 to August 2004.

The diagnostic and demographic characteristics of the study sample are reported in Table 1.

Blood studies evaluated as part of the present study included pregnancy test, fasting glucose, and fasting lipoprotein profile. Serum triglycerides, HDL-C, and serum glucose were measured by the University of Pittsburgh Presbyterian University Hospital's General Laboratory using a colorimetric technique on a Vitros 950 (Ortho Clinical Diagnostic, Rochester, NY, USA) orthodiagnostic machine. Patients were reminded to fast for the 12 h prior to the collection of the blood specimen when the appointment for the blood specimen collection was scheduled and they received a reminder call the day prior to their appointment. At the time when blood was drawn, patients were asked if they had fasted for the previous 12 h. Those patients who had not (or could not remember if they had) fasted for at least the previous 10 h were re-scheduled for another day.

Subjects underwent baseline measurements of blood pressure, anthropometrics and body fat

Table 1. Demographic characteristics of 171 patients consecutively enrolled in the Bipolar Disorder Center for Pennsylvanians Study in the years 2003 and 2004

Variable	n (%)
Age, mean (SD)	46.9 (16.5)
Age at first manic episode (first hypomanic episode for bipolar II patients), mean (SD)	29.1 (14.0)
Age at first depressive episode, mean (SD)	22.1 (11.7)
Gender	
Male	67 (39)
Female	104 (61)
Race	
White	150 (88)
Black	17 (10)
Asian	2 (1)
Other/unknown	2 (1)
Education	
High school diploma or less	35 (20)
Some college or Associates degree	60 (35)
College diploma	46 (27)
Graduate degree	30 (18)
Employment status	
Full-time	34 (20)
Part-time	19 (11)
Homemaker	13 (8)
Disabled	46 (27)
Retired	22 (13)
Unemployed	29 (17)
Other	8 (5)
Marital status	
Married or living as married	59 (34)
Widowed	10 (6)
Separated or divorced	37 (22)
Never married	65 (38)
Diagnosis (DSM-IV)	
Bipolar I	121 (71)
Bipolar II	45 (26)
Bipolar NOS	5 (3)

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; NOS = not otherwise specified.

distribution. Waist circumference, which is considered an accurate estimate of visceral adiposity, was measured from patients at minimal respiration at the smallest circumference of the waist, the 'natural' waistline.

Height and body weight were measured in light clothing, without jackets or shoes.

The NCEP ATP III report (21) has defined the metabolic syndrome as the presence of three or more of the following criteria:

1 Abdominal obesity: waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women;
2 Hypertriglyceridemia: ≥150 mg/dL (1.69 mmol/L);
3 Low HDL-C: <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women;
4 High blood pressure: ≥130/85 mmHg;
5 High fasting glucose: ≥110 mg/dL (≥6.1 mmol/L).

In this study, as in the NHANES 1999–2000 study: (i) patients who were receiving treatment with a blood pressure-lowering medication, because of a previously diagnosed hypertension, were considered to have met the fourth criterion even when their blood pressure was not ≥130/85 mmHg; (ii) patients who were receiving treatment with a glucose-lowering medication, because of a previously diagnosed high fasting glucose, were considered to have met the fifth criterion even when their fasting glucose was not ≥110 mg/dL; (iii) because cholesterol-lowering medications can affect triglyceride levels, the prevalence of hypertriglyceridemia was calculated once based on serum triglyceride concentrations and again based on serum triglyceride concentration and/or the use of cholesterol-lowering medications; (iv) patients taking cholesterol-lowering medications were considered to have met the 'low HDL-C' criterion only if their HDL-C was <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women.

Two blood pressure measurements were obtained at two different visits. The first measurement was obtained at the time of the history and physical examination during screening, using a mercury sphygmomanometer [first and fifth phases of Koroktoff sounds taken as systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively], with the subject in a lying position. The second measurement was obtained using an electronic arm sphygmomanometer, at the time of the first study visit, with the subject in a seated position for at least 5 min. For the three patients whose lying blood pressure was missing, the first measurement was obtained at the first study visit and the second was obtained at the following visit. The high blood pressure criterion was considered as endorsed if patients had an average SBP ≥130 and an average DBP ≥85 between the two consecutive measurements described above. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Individuals were considered underweight if their BMI was <18.50, of normal weight if their BMI was 18.50–24.99, overweight if their body mass index was 25.00–29.99, and obese if their BMI was ≥30.00. The patients' medication regimens at entry in the study are reported in Table 2.

Results

Forty-nine percent of the sample met the NCEP ATP III criterion for abdominal obesity. Forty-one

Table 2. Patients' medication regimens at entry in the study

Type of psychiatric medication	% of patients	Mean (SD) blood level
Lithium	44	0.72 (0.28)
Divalproex	9	50.1 (24.1)
Carbamazepine	4	6.82 (1.77)
Atypical antipsychotics	34	
Aripiprazole	5	
Olanzapine	12	
Quetiapine	8	
Risperidone	9	
Ziprasidone	3	
Typical antipsychotics	1	
Antidepressants	54	
Lamotrigine	20	
Benzodiazapine/hypontic/antianxiety	35	
Stimulants/ADHD medications	6	
Other psychotropics	14	
Glucose-lowering medications	5	
Cholesterol-lowering medications	13	
Antihypertensives	25	
Antihistamines	8	

ADHD = Attention Deficit Hyperactivity Disorder.

percent of the sample met the criterion for hypertriglyceridemia and 48% met the criterion for 'hypertriglyceridemia or being on a cholesterol lowering medication.' Twenty-three percent met the criterion for abnormal HDL-C, 39% met the criterion for hypertension and 8% met the criterion for diabetes mellitus (Table 3).

The prevalence of the metabolic syndrome in our group of patients was 30% (27% if the hypertriglyceridemia criterion did not include patients on cholesterol-lowering medication). Similar results were found when the evaluations were limited to the 147 adult patients who were younger than 65 years. The prevalence of the metabolic syndrome in this group was 29%, and the prevalence of abdominal obesity was 49%.

Table 4 reports the weight class and BMI observed in our sample. Seventy-four percent of our patients were either obese (45%) or overweight (29%).

Table 4. Weight class (BMI) in the study group (n = 171)

Variable	n (%)
BMI, mean (SD)	29.4 (6.5)
Weight category	
Underweight	1 (1)
Normal weight	44 (26)
Overweight	49 (29)
Obese	77 (45)

BMI = body mass index.

No statistically significant difference was found between patients with and without the metabolic syndrome for CGI-S-BP score and GAF score at entry in our study. However, a statistically significant difference was found for lifetime history of suicide attempts. The percentage of patients reporting a history of at least one suicide attempt was 53% in patients with the metabolic syndrome and 36% in patients without the metabolic syndrome ($\chi^2 = 4.02$, $df = 1$, $p = 0.05$). Patients who endorsed the abdominal obesity criterion of the metabolic syndrome were also more like to report a history of suicide attempt(s) (52% versus 30%, $\chi^2 = 8.48$, $df = 1$, $p = 0.004$). No significant differences between patients with and without a history of suicide attempt(s) were found for the endorsement of the other four criteria.

Discussion

This cross-sectional study shows that an alarmingly high number of patients with bipolar disorder met the criteria for the metabolic syndrome. The prevalence of the metabolic syndrome was similar to the prevalence that has been estimated in the general population. However, this observation is all but reassuring. In fact: (i) the high prevalence of the metabolic syndrome in the general population is a cause for concern; (ii) the implementation of preventative and treatment programs is more difficult in patients with bipolar disorder than in the general population; (iii) patients with bipolar disorder very

Table 3. Prevalence of metabolic syndrome in patients with bipolar disorder (n = 171)

Criterion	Description	Women (n = 104)	Men (n = 67)	Total	Missing
MS 1	Waist circ. >40 in (men) or >35 in (women)	55 (53)	28 (42)	83 (49)	1
MS 2	Triglycerides >150 mg/dL or being on cholesterol-lowering medication	40 (39)	41 (62)	81 (48)	3
MS 3	HDL <40 mg/dL (men) or <50 mg/dL (women)	20 (20)	18 (27)	38 (23)	3
MS 4	SBP ≥130 mmHg and DBP ≥85 mmHg or being on blood pressure medication	40 (38)	27 (40)	67 (39)	0
MS 5	Fasting glucose ≥110 mg/dL or being on a glucose-lowering drug	9 (9)	4 (6)	13 (8)	4
MS	At least three of MS1–MS5	30 (29)	21 (31)	51 (30)	2

Values are expressed as n (%). HDL = high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure.

frequently present with considerable additional medical burden (9); (iv) the metabolic syndrome (or at least some of its components, especially obesity) can contribute to a worse prognosis of bipolar disorder through its negative impact on general physical well-being and functioning, quality of life, self-esteem, and psychological well-being (3). For instance, Kinder et al. (29) found that, among the subjects who participated in the Third National Health and Nutrition Examination Survey, women with a history of a major depressive episode were twice as likely to have the metabolic syndrome compared with those with no history of depression. We previously demonstrated that obesity is correlated with worse outcome in patients with bipolar I disorder (3) and, in this present paper, we demonstrated a relationship between the metabolic syndrome in general, and obesity in particular, and a history of suicidal attempts. We believe that this last finding is of particular interest, despite our inability to establish the direction of causality (given that we were unable to determine whether the suicide attempt preceded or followed the development of the metabolic syndrome).

We have been impressed with the degree of medical burden in patients with bipolar disorder. For instance, about half of the patients in our sample had large waist circumference, which is considered an accurate estimate of visceral adiposity. A similar percentage of patients had a BMI $\geq$30 and were therefore classifiable as obese. The prevalence of obesity is dramatically increasing. In the general population, the prevalence has increased from 22.9% in NHANES III (1988–1994) to 30.5% in NHANES 1999–2000 (30). In patients with bipolar disorder, McElroy et al. (7) reported a prevalence of 25% for the American patients recruited between 1995 and 2001, we previously reported a prevalence of 35% for patients recruited in the period 1991–2000 (3), and we are now reporting a prevalence of 45%. The prevalence of obesity in our sample was noticeably greater than the prevalence that has been estimated in the general population, which is itself a cause for concern: 45% in our sample versus 30.5% in the general population (30), based on BMI, and 49% in our sample versus 44% in the general population (26), based on waist measurement. This finding is cause for concern, considering the difficulty in implementing obesity prevention programs and weight loss intervention (e.g., exercise, diet, pharmacological treatment for obesity or surgical treatment) in the bipolar population. Interestingly, the prevalence of low HDL-C was actually lower in our sample than has been estimated for the general population (23% in our sample, 40% in the NHANES 1999–2000 sample). However, the prevalence of hypertriglyceridemia (41% in our sample, 33% in the NHANES 1999–2000 general population sample) was higher. Although this study was not intended to evaluate the relationship between the use of specific medications and the metabolic syndrome in general and obesity in particular, although the prevalence of the metabolic syndrome and the prevalence of obesity is rising in the general population as well, and although we do not believe that the metabolic syndrome and obesity are 'exclusively' due to the use of psychotropic medications, it is our observation that the increased use of second-generation antipsychotics has contributed to the increased prevalence of obese patients in our clinic. However, it is important to note that the elevated rates of obesity and metabolic syndrome observed in our particular group of bipolar patients may not generalize to all persons receiving pharmacotherapy for bipolar disorder, nor to all persons with bipolar disorder in the community.

The underlying pathophysiology of the metabolic syndrome continues to be a subject of controversy, although there have been suggestions of a causal relationship with insulin resistance, obesity and/or visceral adiposity (24). There is no controversy about the fact that, regardless of what the exact underlying pathophysiology is, the overall risk of medical illnesses in those with metabolic syndrome is far greater than the simple arithmetic sum of its individual components (31–33).

Early intervention is the key to preventing the metabolic syndrome. It is our opinion that preventing and treating the metabolic syndrome may favorably influence the prognosis of bipolar disorder. A reduction in the daily caloric intake to promote weight loss is the most important component of the dietary recommendation in those with metabolic syndrome. Weight loss of 20% may reduce cardiovascular risk by 40% (34), but even modest weight loss (5–10%) may have beneficial effects on blood glucose (35), plasma lipids (35–37), and blood pressure (35).

The ideal diet in individuals with metabolic syndrome should be the one with a favorable effect on the components of this disorder (i.e., overweight state or abdominal adiposity, hypertension, hyperglycemia, hypertriglyceridemia, low HDL-C, and increased small, dense LDL-C). Ideally the diet should lower LDL-C, although LDL-C is not typically elevated in this disorder (38).

Among the limitations of this study we would like to acknowledge is its cross-sectional design, which did not permit evaluation of the possible causes and the possible changes over time of each

component of the metabolic syndrome. For instance, we were not able to evaluate the possible liability of the medication treatment. In fact, the information about the treatment that the patients were receiving at the time of onset of the metabolic syndrome and about whether or not those patients were switched to a different medication before starting our study was not available. However, the patients described in the present paper, and the patients who will enter the Bipolar Disorder Center study in the next year, will be followed until the year 2007, at which time we will be able to report the results of our longitudinal observation. Among other things, we will evaluate important factors such as the relationship between the metabolic syndrome and the duration of exposure to medications, including the atypical antipsychotics, and the relationship between the metabolic syndrome effects of disease-specific symptoms such as increases in appetite and reduced energy expenditure. Another limitation is that this present report is restricted to adult patients and that the study sample size limits comparison by age and ethnicity. However, the Bipolar Disorder Center study is actively enrolling adolescents (age 12–18 years), increasing the recruitment of adult, late life patients and of African-American patients. Once the study has achieved its recruitment goals, we expect to be able to achieve a number of patients that will permit an evaluation of the metabolic syndrome by age and ethnicity.

The high prevalence of the metabolic syndrome that we found in our sample of patients with bipolar disorder suggests that the development and testing of specific interventions that target this epidemic are urgently needed. Ideally, diet and exercise counseling should be provided to all bipolar disorder patients before the various components of the metabolic syndrome become evident and definitely once they have occurred. We strongly support the development and testing of interventions specifically designed for preventing and treating the metabolic syndrome in patients with bipolar disorder.

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