Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder

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Abstract

Background—Bipolar disorder is associated with excess cardiovascular mortality. We hypothesized outpatients with bipolar disorder would exhibit excess cardiovascular risk factors, particularly among prevalent users of the second generation antipsychotics associated with weight gain and valproic acid derivatives.

Methods—This chart review of 217 patients with bipolar disorder examined cardiovascular risk factors of the metabolic syndrome. We also evaluated if certain medications were cross-sectionally associated with metabolic syndrome.

Results—Fifty-six patients were not weighed and many did not have available lipid profiles. Over three-quarters of those with available data (N=161) were overweight or obese (body-mass index $\geq$ 25) and nearly half were obese (body-mass index $\geq$ 30). A prevalence exceeding general population estimates was also observed for hypertriglyceridemia, elevated blood pressure/hypertension, and elevated fasting glucose/diabetes. Among those with all requisite data (n = 60), over 50% met criteria for National Cholesterol Education Program defined metabolic syndrome, nearly double the expected prevalence. A trend toward greater prevalence of metabolic syndrome among prevalent users of the second generation antipsychotics associated with weight gain was observed.

Conclusions—Obesity and the metabolic syndrome were common in patients with bipolar disorder. These patients may be under-evaluated for cardiovascular risk and warrant screening and early intervention.

Keywords

bipolar disorder; obesity; hyperlipidemia; hypertension; diabetes mellitus; metabolic syndrome

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INTRODUCTION

Excess cardiovascular mortality has been demonstrated for patients with bipolar disorder (1–3). There further appears to be an excess burden of cardiovascular risk factors with bipolar disorder compared with the general population (4). Associations between bipolar disorder and hyperglycemia have been suggested for nearly a century (5) and clinical samples have indeed suggested an increased prevalence of diabetes mellitus (6,7). Those with bipolar disorder may be at greater risk of hypertension compared to schizophrenia and the general population (8). Bipolar disorder has been associated with obesity (9), independent of self-reported premorbid weight (10). Among 644 outpatients with bipolar disorder from the United States (U.S.) and Europe, McElroy et al. found 58% to be overweight and 26% obese (11), correlated with previous exposure to medications associated with weight-gain. Thirty-two percent of the U.S. participants were obese (11). In a sample of 171 patients with bipolar disorder and a mean age of 47 years, Fagiolini et al. reported a 45% point prevalence of obesity with an additional 29% of participants overweight (12). They further found a higher than expected prevalence of hypertriglyceridemia and a lower than expected prevalence of patients with low high density lipoprotein (HDL) (23%). This latter finding may have attenuated their estimate of metabolic syndrome prevalence, which was 30% (12). A cross-sectional study of 125 bipolar patients with a mean age of 35 years by Yumru et al. found a 32% prevalence of metabolic syndrome, with metabolic syndrome cross-sectionally associated with use of second generation antipsychotics (SGAs) without mood stabilizers (13). A U.S. sample of 98 veterans with bipolar disorder and a mean age of 50 years revealed a 49% prevalence of metabolic syndrome (14). These findings of elevated cardiovascular risk in bipolar disorder are concerning given that patients may be less likely to receive appropriate monitoring (15) and adequate treatment for cardiovascular risk factors (16).

Medications used in the treatment of bipolar disorder may hasten the development of the metabolic syndrome and obesity. Divalproex, a valproic acid derivative, has long-been associated with insulin resistance and weight gain (17,18). Second generation antipsychotics (SGAs) have been increasingly associated with significant metabolic complications including hyperlipidemia (19–23), insulin resistance/diabetes mellitus (20,24–30), and obesity (20,31–33). SGAs are further becoming more popular for use in bipolar disorder. Frequency estimates of antipsychotic use by diagnosis from Veterans Affairs registries suggest contemporary use of first generation antipsychotics in 3.9% and second generation antipsychotics in 42.2% of patients with bipolar disorder (34). Nearly half of physicians surveyed reported using second generation antipsychotics for at least half of their patients with bipolar disorder (35).

We sought to confirm the previously suggested increased risk of obesity, metabolic syndrome, and other cardiovascular risk factors utilizing medical records data from a clinical sample of outpatients with bipolar disorder. We sought to further contribute an estimate of the frequency of monitoring for cardiovascular risk factors. Our primary hypothesis was that outpatients with bipolar disorder would have a prevalence of obesity and other categorical cardiovascular risk factors in excess of general population estimates. Our secondary hypothesis was that patients on second-generation antipsychotics associated with weight gain (clozapine, risperidone, olanzapine, or quetiapine) or valproic acid derivatives would demonstrate a greater burden of cardiovascular risk factors than those not on these medications.

METHODS

The Institutional Review Board at the University of Iowa reviewed and approved the procedures in this retrospective chart review study. Billing data was utilized to identify 217 outpatients seen between January 1, 2006 and June 30, 2006 for a primary diagnosis bipolar disorder from an adult, outpatient psychiatry clinic at a tertiary care hospital. The first visit

within the specified time frame served as the index clinic visit. Primary diagnoses of Bipolar I, Bipolar II, and Bipolar NOS were identified based on billing codes and verified from psychiatric records. Records were reviewed from January 1, 2002 to the earlier of one year after index visit or April 20, 2007.

Age at index visit was obtained from the billing data and verified on chart review. Race and ethnicity were obtained from electronic hospital records when reported. The following diagnoses were systematically abstracted from chart records: hypertension, hyperlipidemia, diabetes mellitus, and thyroid disease. These diagnoses were recorded if identified from electronic record problem lists or physician records indicating diagnosis of and treatment for the condition. These diagnoses were not inferred from vital signs or laboratory values. Psychotropic medications and dosages from index visit were consistently reported and recorded. Non-psychiatric medications were not individually recorded though were considered to assess treatment for the aforementioned diagnoses.

Metabolic monitoring was not obtained consistently enough to allow distillation of simple point or one year prevalence. Measures of weight, fasting glucose, and fasting lipids were systematically recorded. The index visit was utilized as reference point for the following time periods: prior to index visit or baseline, within six months of following index visit, and six to 12 months following index visit. When multiple measures were present for any of these periods, the closest to index visit was selected for baseline, the closest to three months following index visit for the first six months of follow-up, and the closest to 12 months for the six to twelve month period following index visit. For the primary and secondary hypotheses, the value associated with maximum risk was chosen from among these three time points if recordings were present for multiple time periods.

Statistical analyses were performed using SAS software (36). We utilized the more popular National Cholesterol Education Program (NCEP) definition of metabolic syndrome as published in its third Adult Treatment Protocol (ATP III), which requires at least three of the following: abdominal obesity (waist circumference > 40 inches in males or 35 inches in females), elevated triglycerides ($\geq$ 150 mg/dL), low HDL (< 40 mg/dL in men or < 50 mg/dL in women), elevated blood pressure ($\geq$ 130/85 or on antihypertensive medication), or elevated fasting glucose ($\geq$ 110 mg/dL or on medication for diabetes) (37). Descriptive statistics were compiled for body mass index, triglycerides, low density lipoprotein (LDL), HDL, and fasting glucose. A body mass index $\geq$ 25 and < 30 was defined as overweight with $\geq$30 defined as obese. We further substituted a body-mass index (BMI) $\geq$30 for visceral obesity as measured by waist circumference to estimate the prevalence of metabolic syndrome in this sample. BMI and waist circumference are highly correlated ($r = 0.86$) with a BMI of 30 corresponding to a waist circumference of 37.2 inches (38). The National Health and Nutrition Examination Survey (NHANES) 1999–2000 estimates the correlation between BMI and waist circumference as 0.91–0.94 for men and 0.88–0.94 for women (39). With 96% of those with a BMI $\geq$30 and 43% of those with a BMI between 25 and 30 meeting NCEP waist circumference criteria (39), our use of obesity by BMI $\geq$30 as a surrogate for gender-specific waist circumference would be expected to yield a conservative underestimate of the prevalence of this metabolic syndrome criterion. Consistent with the NCEP guidelines for metabolic syndrome, elevated triglycerides was delineated by values $\geq$150 mg/dL, low HDL by values < 40 mg/dL in men or < 50 mg/dL in women, and elevated fasting glucose by values $\geq$110 mg/dL. Because of missing data compromising estimates of metabolic syndrome, we utilized two sub-samples in a sensitivity analysis: a restricted sample of those with all of these measurements available and an extended sample of any participants with at least three of BMI, fasting glucose, fasting triglycerides, fasting HDL or blood pressure available. A 95% confidence interval for the prevalence estimates of cardiovascular risk factors was calculated from the binomial distribution for gross comparison to national data. Chi-square tests compared

differences by categorical variables between those currently prescribed second-generation antipsychotics associated with weight gain or valproic acid derivatives and those not prescribed these medications, selected by strength of association with weight gain and metabolic complications.

RESULTS

The mean (SD) age of participants was 46.3 (15). Other demographic characteristics and diagnoses for this sample of 217 outpatients with bipolar disorder are outlined in Table 1. The majority of patients were female and Caucasian patients were over-represented in this sample. The diagnoses obtained from billing data suggest a majority with bipolar I and nearly one third with bipolar II. Only 7.4% of patients carried a primary diagnosis of bipolar disorder not otherwise specified. The psychiatric medications prescribed at index visit for patients are highlighted in Table 2. Mood stabilizers and antidepressants were prescribed to a majority of patients with lithium and selective serotonin uptake inhibitors the most popular classes within each respective category.

Height and weight were extracted from the chart record for approximately three quarters of participants (n = 161). To screen for patterns of missing data that may be suggestive of selection bias, qualitative differences in the records of those missing were noted. Missing height and or weight subjectively appeared to be associated with lack of primary care visits at the hospital and a single diagnostic visit without subsequent follow-up. Chart diagnoses of obesity were noted on multiple patients without data to calculate BMI, however, diagnoses of obesity were too rarely encountered even among those known to be obese to allow any systematic evaluation for selection bias. Participants were categorized into the following categories based on body mass index: underweight, normal weight, overweight, and obese. This data is summarized in Table 3. Nearly one half of patients met criteria for obesity and over three quarters were overweight or obese.

Approximately one-third of participants had a lipid profile recorded during the five year window sampled. A substantial proportion, nearly one-third, of those with data available had been diagnosed with and treated for hyperlipidemia. This proportion exceeds the 18.4% frequency of diagnosis of and treatment for hyperlipidemia seen in the entire sample and may reflect selection bias. It may further reflect a surveillance bias with diagnosis more likely to be made among those actually screened. Regardless, a substantial portion of patients had profiles condoning cardiovascular risk as illustrated in Table 4.

The frequencies and percentages of specific cardiovascular risk factor components of the metabolic syndrome with substitution of obesity by BMI for visceral obesity by waist circumference were calculated by gender. These values were then compared to published NHANES data for adults greater than 20 years of age and accounting for gender proportions of current sample (40,41). These results are detailed in Table 5. The proportion of patients with diagnosis/treatment for hypertension among those with blood pressure measurements (Table 5) was comparable to that for the entire sample (Table 1). Additionally, the proportion of patients with diagnosis/treatment for diabetes among those with blood glucose assessments (Table 5) was generally comparable to the sample as a whole (Table 1). This lessens the concern for a selection bias among those surveyed for metabolic syndrome criteria 4 and 5. The prevalence of obesity, hypertriglyceridemia, elevated fasting glucose or diabetes, and elevated blood pressure or treatment for hypertension was significantly higher than expected from gender-proportioned, age-appropriate, national general population estimates. A smaller proportion of patients than expected from our sample had a low HDL. The estimated prevalence of metabolic syndrome using the aforementioned restricted and extended samples exceeds population estimates. Using the restricted sample, the prevalence of metabolic syndrome was

approximately double general population estimates. Current medication use was not significantly associated with any specific components of the metabolic syndrome or the metabolic syndrome itself though a trend toward higher cardiovascular risk factor burden among users of the SGAs associated with weight gain (clozapine, risperidone, olanzapine, or quetiapine) was observed. Of patients taking the second generation antipsychotics associated with weight gain, 18/27 or 67% had metabolic syndrome by the restricted definition compared with 14/33 or 42% of those not currently taking these medications ($\chi^2 = 3.5$, df=1, $p < 0.062$).

DISCUSSION

We found evidence for an elevated risk for cardiovascular disease in this chart review of outpatients with bipolar disorder. Our estimates (restricted and extended sample) of metabolic syndrome exceed general population estimates and suggest metabolic syndrome may be up to twice as common in patients with bipolar disorder as illustrated in Figure 1. A trend toward greater prevalence of metabolic syndrome among users of the SGAs associated with weight gain was observed. Lipid profiles were not commonly obtained, consistent with previous monitoring estimates (15,42). Our results bolster concerns that patients with bipolar disorder bear an excess burden of cardiovascular risk and are sub-optimally monitored for this.

Our study has several important limitations, arising largely from the chart review methodology. These limitations are related to impaired ascertainment of data, reliability of acquired data, selection bias among those screened, lack of an internal comparison group, and misclassification. A selection bias for higher risk of metabolic syndrome may have been present in the restricted sample. As blood pressure data was readily available, our higher observed frequencies of elevated blood pressure may reflect repeated measurement. Higher frequencies of elevated glucose values may result from misclassification of fasting status. The utilization of an external comparison group is impeded by an inevitable differential intensity of surveillance. The use of national comparison data for metabolic risk factors subsequently forces our conclusions to be tentative. Nonetheless, the marked differences of several components of metabolic syndrome to published data from NHANES and the consistency of our findings to previous studies are highly suggestive of an elevated risk. The reliability of chart diagnoses represents another important limitation of the chart review methodology. To mitigate this risk, we utilized billing codes only for primary diagnoses to identify cases. Current medications may reflect confounding by indication in that those with metabolic syndrome or other cardiovascular risk factors may be preferentially prescribed medications less associated with weight gain. Analysis of previous medication use was not possible. Despite the aforementioned disadvantages of chart review data, the naturalistic nature of this data allows for a general estimate of frequency of monitoring for metabolic complications of medications and screening for cardiovascular risk. This sample is a fully naturalistic reflection of practice in an outpatient department of a tertiary care hospital.

The NCEP recommends the screening of all adults over age twenty with a fasting lipoprotein profile every five years (37). For patients treated with SGAs, more frequent metabolic monitoring has been proposed. Published recommendations for monitoring patients on SGAs vary with the more widely cited recommendation for fasting lipids at a minimum of baseline, 12 weeks, and every five years in addition to fasting glucose, blood pressure and waist circumference obtained at a minimum of baseline, 12 weeks, and annually thereafter (43,44). Even more frequent monitoring of weight has been recommended (45). While an exact estimate of monitoring cannot be inferred from our data, our clinical sample appears sub-optimally monitored. In response to previous reports of under-monitoring, some suggest that psychiatrists assume responsibility for patients not monitored in a primary care setting and when prescribing medications with potential for metabolic complications (44,46).

Our results support previous findings of elevated cardiovascular risk in patients with bipolar disorder. Close monitoring of cardiovascular risk factors is of critical importance, whether by primary care physicians or psychiatrists.

Acknowledgments

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Metabolic Syndrome Prevalence:
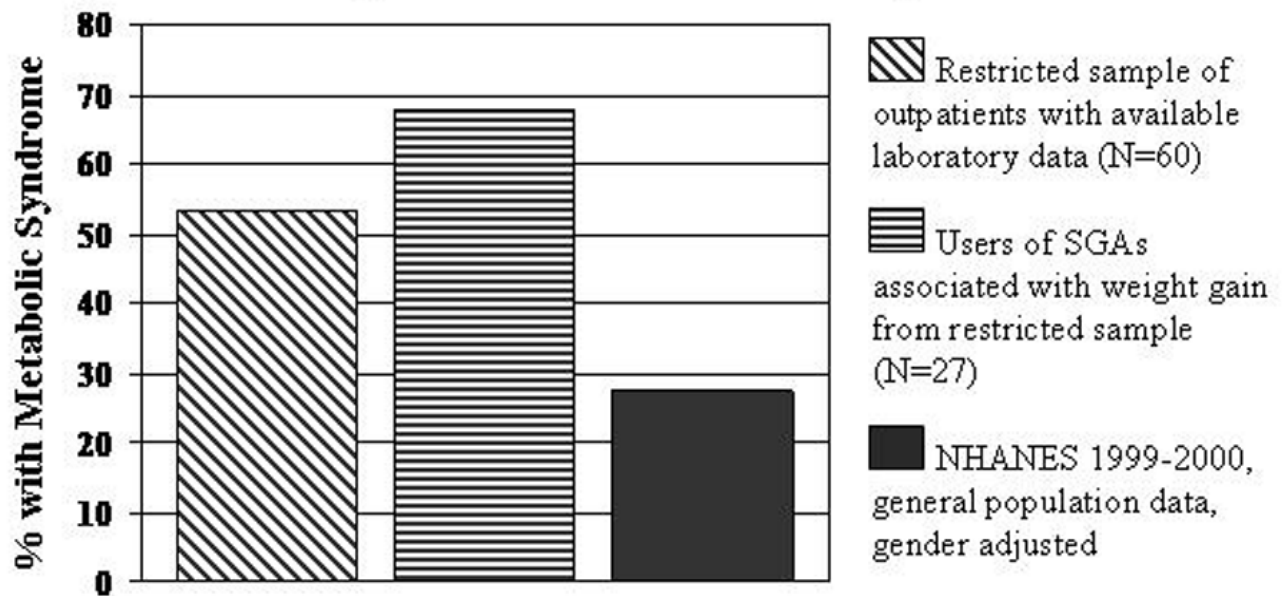## Outpatients with Bipolar Disorder vs. General Population Estimates

Figure 1.
Graphical illustration of metabolic syndrome estimates from current study (restricted sample) contrasted with published general population data. General population data from NHANES 1999–2000 was utilized to provide an expected estimate for our sample based on observed gender proportions. The age distribution of our sample was comparable to the NHANES sample of adults at least 20 years of age. Nearly double the expected prevalence of metabolic syndrome was observed. Prevalent users of the second generation antipsychotics (SGAs) most strongly associated with weight gain (clozapine, risperidone, olanzapine, and quetiapine) had a higher observed metabolic syndrome prevalence though this trend did not reach significance.

Table 1

Demographic characteristics of 217 consecutive outpatients with bipolar disorder

Variable	N (%)
Gender	
Male	80 (37%)
Female	137 (63%)
Race/Ethnicity	
White	185 (85%)
Black	1 (1%)
Asian	1 (1%)
American Indian	1 (1%)
Hispanic	2 (1%)
Other	6 (3%)
Unknown	21 (10%)
Primary Psychiatric Diagnosis	
Bipolar I	127 (59%)
Bipolar II	74 (34%)
Bipolar NOS	16 (7%)
Medical Diagnoses and Treatment	
Diabetes Mellitus	20 (9%)
Hyperlipidemia	40 (18%)
Hypertension	51 (24%)
Thyroid disorders	54 (25%)

Table 2

Mood stabilizer and Antipsychotic regimens at index visit

Medication	N (%) of Patients
Mood Stabilizers	
Lithium	66 (30%)
Divalproex	45 (21%)
Lamotrigine	42 (19%)
Carbamazepine	8 (5%)
Combination [a]	21 (10%)
Antipsychotics	
Atypical Antipsychotics	
Quetiapine	28 (13%)
Olanzapine	24 (11%)
Risperidone	15 (7%)
Aripiprazole	15 (7%)
Ziprasidone	12 (6%)
Clozapine	2 (1%)
Typical Antipsychotics	
Haloperidol	5 (2%)
Chlorpromazine	5 (2%)
Fluphenazine	2 (1%)
Other	2 (1%)
Combination [a]	12 (6%)

[a] When agents used in combination, each agent is also reflected in totals for individual medications.

Table 3

Body Mass Index (BMI) based weight classification in Bipolar Outpatients (N=161)[a]

Variable	N (%)
BMI, mean (median; SD)	30.8 (29.9; 7.6)
Weight Category	
Underweight (BMI < 18.5)	1 (1%)
Normal Weight	39 (24%)
Overweight ($25 \leq$ BMI < 30)	44 (27%)
Obese (BMI ≥ 30)	77 (48%)

[a] Height or weight not available to calculate BMI for 56 (26%) of participants.

Table 4

Fasting Lipid Profiles in Bipolar Outpatients (N = 73–77)[a]

Variable	Mean (Median; SD)
Triglycerides, mean (median; SD)	169.9 (129.5; 130.0)
# Elevated triglycerides (≥ 150 mg/dL)	35 (48%)
Low Density Lipoprotein	112.9 (107; 37.6)
# Elevated LDL (≥ 130 mg/dL)	22 (29%)
High Density Lipoprotein	54.4 (51; 17.9)
# Low HDL (< 40 (men) of < 50 (women) mg/dL)	21 (29%)

[a] Fasting triglycerides and cholesterol values were not available for 144 (66%) and 140 (65%) participants respectively over five year period sampled. Twenty-three (32%) to twenty-five (33%) patients from this sample were being treated for hyperlipidemia compared with 18% of the total sample.

Table 5

Prevalence of specific cardiovascular risk factors from the NCEP-defined metabolic syndrome construct by gender.

Criterion	Description	N	Women	Men	Total	NHANES
1	Obesity[a]	161	48 (46%)	29 (51%)	77 (48%)[b]	32.4%
2	Presence of 2a or 2b	73	16 (40%)	26 (79%)	42 (58%)	32.0%
2a	Triglycerides > 150 mg/dL		11 (28%)	24 (73%)	35 (48%)[c]	
2b	On Lipid-lowering Medication		11 (28%)	12 (36%)	23 (32%)	
3	HDL < 40 (Male) or < 50 (Female) mg/dL	77	12 (29%)	9 (26%)	21 (27%)[c]	40.8%
4	Presence of 4a or 4b	166	63 (61%)	49 (79%)	112 (68%)	38.6%
4a	SBP ≥ 130 or DBP ≥ 85		59 (57%)	46 (74%)	105 (63%)	
4b	Antihypertensive treatment		22 (21%)	21 (34%)	43 (26%)	
5	Presence of 5a or 5b	142	25 (28%)	18 (33%)	43 (30%)[c]	12.5%
5a	Fasting glucose ≥ 110 mg/dL		22 (25%)	17 (32%)	39 (28%)	
5b	On medication for diabetes		7 (8%)	8 (15%)	15 (11%)	
Metabolic Syndrome ≥ 3 criteria, extended sample		125	21 (27%)	24 (52%)	45 (36%)[c]	27.3%
Metabolic Syndrome ≥ 3 criteria, restricted sample		60	16 (46%)	16 (64%)	32 (53%)[c]	

[a] Obesity was employed as a surrogate for the waist circumference criterion given the limitations of chart review data. Criterion estimates are based on a restricted sample of those with the requisite laboratory or vital sign data. The extended sample metabolic syndrome estimate utilized patients with at least three of the following measures available: body mass index, blood pressure, fasting triglycerides, fasting HDL or fasting glucose. The restricted sample utilized only those patients for whom all of these measures were available.

[b] Obesity rate 95% C.I. (40.2–55.5%) significantly exceeds NHANES 2005–2006 general population estimate, accounting for sample gender proportions.

[c] Hypertriglyceridemia rate 95% C.I. (36.9–59.3%) significantly exceeds and low HDL rate (18.6–31.2%) is significantly lower than NHANES 1999–2000 general population estimates. Metabolic syndrome 95% C.I. from extended sample rate (28.1–44.7%) and restricted sample (40.8–65.4%) also exceed general population estimates.