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Brief Report

Medical burden in bipolar disorder: findings from the Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE)

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Objectives: Individuals with bipolar disorder have high rates of other medical comorbidity, which is associated with higher mortality rates and worse course of illness. The present study examined common predictors of medical comorbidity.

Methods: The Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE) enrolled 482 participants with bipolar I or bipolar II disorder in a six-month, randomized comparative effectiveness trial. Baseline assessments included current and lifetime DSM-IV-TR diagnoses, demographic information, psychiatric and medical history, severity of psychiatric symptoms, level of functioning, and a fasting blood draw. Medical comorbidities were categorized into two groups: cardiometabolic (e.g., diabetes, hyperlipidemia, and metabolic syndrome) and non-cardiovascular (e.g., seizures, asthma, and cancer). Additionally, we looked at comorbid substance use (e.g., smoking and drug dependence).

Results: We found that 96.3% of participants had at least one other medical comorbidity. Older age predicted a greater likelihood of having a cardiometabolic condition. Early age of onset of bipolar symptoms was associated with a lower chance of having a cardiometabolic condition, but a greater chance of having other types of medical comorbidity. Additional predictors of other medical comorbidities in bipolar disorder included more time spent depressed, less time spent manic/hypomanic, and longer duration of illness. Medications associated with weight gain were associated with low high-density lipoprotein and abnormal triglycerides.

Conclusions: There appears to be a substantial medical burden associated with bipolar disorder, highlighting the need for collaborative care among psychiatric and general medical providers to address both psychiatric and other medical needs concomitantly in this group of patients.

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Individuals with bipolar disorder have high rates of medical comorbidities in addition to chronic, debilitating mood symptoms and impairments in functioning (1–5). Previous studies have found that over 50% of individuals with bipolar disorder have at least one medical comorbidity (6–8); patients are at increased risk for cardiovascular disease (9–13), respiratory disorders (14, 15), thyroid disease (16), hepatitis C (17), type-2 diabetes (18), and obesity (19, 20), as compared to rates in the general population. This medical burden in bipolar disorder is associated with a higher rate of morbidity and mortality (21–23) and a 30% shorter life expectancy (24). It is also associated with increased costs of medical care and loss of productivity (25), worse course of bipolar illness (i.e., more episodes, longer duration of episode, and poor functioning) (6, 26–29), and higher rates of treatment with psychotropic medications (6). Moreover, medications commonly prescribed to treat bipolar disorder can exacerbate risks of metabolic disturbances (30, 31) and cardiovascular disease (32–34).

Given the negative impact of this substantial medical burden in bipolar disorder, it is vital to understand what features of bipolar disorder contribute to this increased risk of comorbidity. Extant research in bipolar disorder has limited generalizability, as it has tended to be focused only on a few possible medical conditions (17, 35) or on specific subgroups, such as elderly people (36, 37), or homogenous samples (15, 27). Thus, the aim of the present study was to assess the rates of different comorbidities in a large, heterogeneous sample of individuals with bipolar disorder, and to assess demographic and clinical predictors of such comorbidity. We expected that rates of comorbid cardiometabolic conditions (e.g., type 2 diabetes) and other medical comorbidities (e.g., asthma and cancer) would not differ by bipolar subtype, but that worse course of illness (i.e., longer duration, more frequent mood episodes, and poor functioning) and earlier age of onset would be associated with an increased likelihood of having medical comorbidities. We also expected that medications known to induce weight gain would be associated with greater metabolic disturbances.

Materials and methods

Procedures

The Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE) (38) was a six-month, multi-site, randomized comparative effectiveness trial comparing a classic mood stabilizer (lithium) to a common antipsychotic used to treat bipolar disorder (quetiapine). Study physicians were able to prescribe additional medications as needed (although antipsychotics were excluded in patients randomized to lithium, and other antipsychotics and lithium were excluded in patients randomized to quetiapine) as long as medications were consistent with the guidelines used to treat bipolar disorder (39) and personalized to the needs of the patient (40). The rationale, design, and methods of Bipolar CHOICE are reported elsewhere (38). The

present study examined data from the baseline visit (see Fig. 1).

Participants

The Institutional Review Boards of the 11 sites approved the study protocol. Bipolar CHOICE enrolled 482 individuals between the ages of 18 and 68 years. Limited inclusion and exclusion criteria were designed to maximize heterogeneity of the sample and hence generalizability of results (38), but participants were required to have a DSM-IV-TR bipolar I or bipolar II diagnosis and be at least mildly symptomatic [Clinical Global Impression Scale for Bipolar Disorder (CGI-BP) $\geq$ 3] at study entry.

Psychiatric and substance use diagnoses were determined using the extended Mini-International Neuropsychiatric Interview, an electronic version of a validated structured diagnostic interview (41). The CGI-BP assessed bipolar illness severity on three separate subscales for mania, depression, and overall bipolar illness, ranging from 1 to 7 (normal to very severely ill) (42). Psychiatric symptom severity and overall functioning and life satisfaction were measured with the Bipolar Inventory of Symptoms Scale (BISS) (43, 44) and LIFE-Range of Impaired Functioning Tool (LIFE-RIFT) (45), respectively. Clinical interviews obtained demographic information, psychiatric/medical history (e.g., asthma, myocardial infarction, and hepatitis) and current medications. A fasting blood draw was also conducted to assess cardiometabolic variables such as levels of triglycerides and cholesterol.

Statistical analyses

Medical comorbidities were divided into two groups to understand specific trends in the conditions associated with bipolar disorder: (*Group 1*) cardiometabolic disturbances (coronary artery disease, myocardial infarction, diabetes, hyperglycemia, hyperlipidemia, hypercholesterolemia, triglyceridemia, and metabolic syndrome); (*Group 2*) non-cardiovascular conditions (kidney disease, seizures, thyroid disease, asthma, migraines, cancer, hepatitis, and head trauma). Comorbid substance use (smoking, alcohol and drug abuse/dependence) was also included in the analyses. The rationale for these groupings was that we expected cardiometabolic disorders and substance use to be particularly associated with the course of bipolar disorder (6).

Predictors of medical comorbidity were tested using chi-square tests for categorical variables and *t*-tests for continuous variables. If an overall chi-square was significant, we used logistic regression to determine specific contrasts of interest. The primary analysis assessed the association of medical disorders with demographic characteristics and clinical features of bipolar disorder. Analyses involving number of lifetime depressive/manic episodes and total number of years depressed/manic were adjusted for age. All predictors were then considered for entry into multivariate models using stepwise logistic regression to evaluate which variables uniquely predicted medical comorbidity. Finally, we assessed whether reported use of medications known to induce weight gain

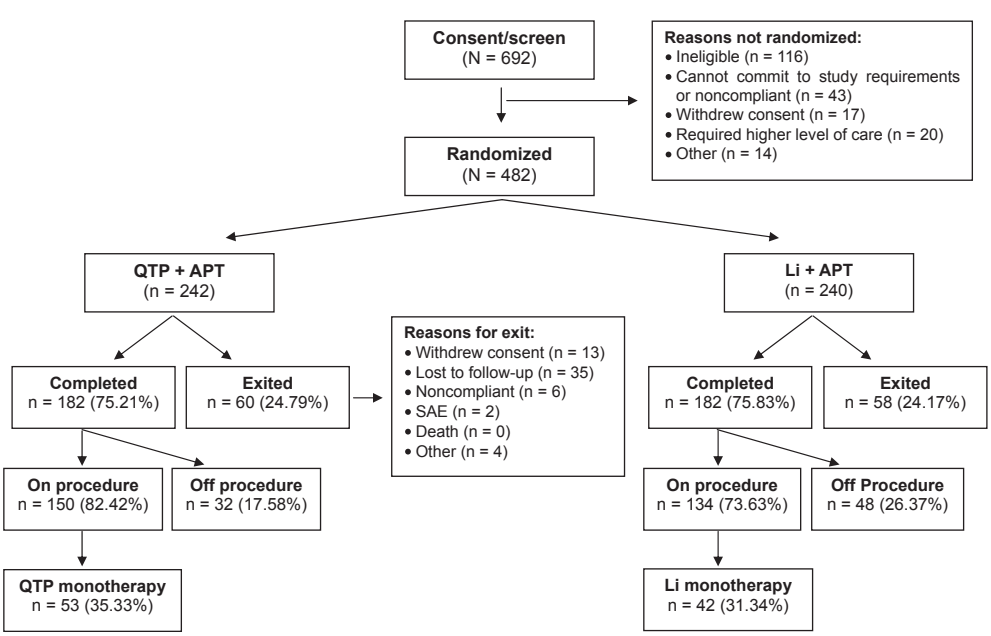

Fig. 1. CONSORT chart. APT = antipsychotic; Li = lithium; QTP = quetiapine; SAE = serious adverse event.

(lithium, valproate, clomipramine, imipramine, amitriptyline, mirtazapine, clozapine, olanzapine, quetiapine, or risperidone) correlated with cardiometabolic disturbances at baseline.

Results

Demographic and clinical features are reported in Table 1. In this sample, we found that 96.3% of participants met criteria for at least one medical

Table 1. Baseline demographic and clinical measures in the Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE)

Characteristic	Overall (n = 482)	Li + APT (n = 240)	QTP + APT (n = 242)	p-value
Female, %	58.7	58.3	59.1	0.87
Age, years, mean ± SD	38.9 ± 12.1	38.6 ± 12.1	39.1 ± 12.2	0.63
Race, %				
White	72.2	72.5	71.9	0.83
Black	19.9	19.2	20.7	
Asian	3.3	3.8	2.9	
Other	4.6	4.6	4.5	
Ethnicity: Hispanic or Latino, %	11.0	13.3	8.7	0.09
Education, %				
Less than high school	5.0	5.0	5.0	0.85
High school or GED	20.3	18.3	22.3	
Some college	30.9	30.0	31.8	
Technical school or associate degree	12.0	12.9	11.2	
College diploma	24.3	25.8	22.7	
Graduate or professional degree	7.5	7.9	7.0	
Employment status, %				
Employed	36.3	39.2	33.5	0.56
Unemployed	35.3	32.9	37.6	
Disability recipient	15.4	15.8	14.9	
Student	9.1	7.5	10.7	
Retired	1.7	2.1	1.2	
Other	2.3	2.5	2.1	
Bipolar I disorder, %	68.3	66.7	69.8	0.46
History of psychiatric hospitalizations, %	46.8	45.6	47.9	0.61
History of suicide attempts, %[a]	36.1	36.3	36.0	0.94
Any substance use disorder (lifetime), %[b]	61.4	62.1	60.7	0.76
Any anxiety disorder (current), %[c]	57.5	55.4	59.5	0.36
Age (years) of first, mean ± SD:				
Depressive episode	16.4 ± 8.0	16.0 ± 8.6	16.7 ± 7.5	0.36
Manic episode	19.8 ± 9.5	19.5 ± 9.8	20.1 ± 9.1	0.47
Mood episode	15.5 ± 7.7	15.1 ± 8.3	16.0 ± 7.1	0.17
Duration (years) of, mean ± SD:				
Depression	22.5 ± 12.3	22.6 ± 12.3	22.4 ± 12.3	0.90
Mania	19.0 ± 12.2	19.1 ± 12.1	18.9 ± 12.3	0.92
Illness	23.3 ± 12.4	23.6 ± 12.5	23.1 ± 12.4	0.70
BISS total score, mean ± SD				
Overall	56.1 ± 18.8	55.7 ± 18.8	56.5 ± 19.0	0.67
Depression	37.6 ± 14.0	38.0 ± 13.4	37.2 ± 14.6	0.53
Mania	18.5 ± 12.1	17.8 ± 12.1	19.3 ± 12.1	0.16
CGI-BP severity score, mean ± SD	4.5 ± 0.9	4.5 ± 0.8	4.5 ± 0.9	0.83
MADRS score, mean ± SD	23.8 ± 10.3	24.2 ± 10.0	23.5 ± 10.6	0.44
YMRS score, mean ± SD	13.4 ± 8.7	13.0 ± 8.9	13.8 ± 8.6	0.33

Statistics reported are % (n/N) for categorical variables and mean ± standard deviation (SD) (N) for continuous variables. p-values reported are based on chi-square test for categorical variables and *t*-test for continuous variables.

APT = antipsychotic; BISS = Bipolar Inventory of Symptoms Scale; CGI-BP = Clinical Global Impressions for Bipolar Disorder; GED = General Educational Development; Li = lithium; MADRS = Montgomery–Åsberg Depression Rating Scale; QTP = quetiapine; YMRS = Young Mania Rating Scale.

[a]Based on the Columbia Suicide Severity Rating Scale, a scale used to assess recent and lifetime suicide-related thoughts and behaviors (59).

[b]Includes patients with any current alcohol/drug abuse/dependence [based on the Mini-International Neuropsychiatric Interview (MINI)].

[c]Includes patients with any one of the following current diagnoses (based on the MINI): panic disorder, agoraphobia, social phobia, and generalized anxiety disorder.

comorbidity, 71.2% for at least one cardiometabolic disturbance (Group 1), 56.2% for at least one other non-cardiometabolic, medical comorbidity (Group 2), and 80.5% for substance use (*Group 3*). Notably, more than 70% of participants reported being current or past smokers. Substance use was more prevalent in bipolar I than bipolar II disorder (Table 2).

Older participants were more likely to have a Group 1 condition. A later age of onset, more depressive symptoms, and fewer manic symptoms at baseline were associated with a higher likelihood of having a Group 1 disorder. Spending more time in the past year manic/hypomanic and current manic/hypomanic symptoms (BISS) corresponded to a decreased likelihood of having a Group 1 disorder, such that a 20% increase in time spent manic/hypomanic decreased the odds of a Group 1 disorder by 23% (Table 3). For each 20% increase in time depressed in the last year (e.g., from 0–20% to 20–40%), the odds of a Group 1 disorder increased by 18%, though the effect was marginally significant ($p = 0.069$).

Female gender, greater percentage of time spent depressed, presence of lifetime substance use disorder, younger age of illness onset, and longer duration of illness (even when controlling for participants' age) predicted Group 2 conditions (Tables 3 and 4). When controlling for age, participants who reported spending a larger percentage of the past year depressed were more likely to have at least one Group 2 condition. Each 20% increase in time depressed elevated the odds of a Group 2 disorder by 23%.

The likelihood of meeting criteria for substance use (Group 3) was significantly associated with race, lower household income, older age, lower education level, comorbid anxiety disorder diagnosis, and worse depression and life functioning (LIFE-RIFT) as well as greater illness severity (CGI-BP overall and depression; percentage of past year spent depressed) (Tables 3 and 4). Follow-up tests showed that Asians had 27% lower odds of substance use than non-Asians. Finally, medications associated with weight gain were associated with low high-density lipoprotein (HDL) cholesterol and abnormal (high) triglycerides (Table 5).

In our multivariate models (i.e., each variable is adjusted for all other covariates in the model), we found that older age and less severe manic symptoms remained associated with the presence of Group 1 conditions [95% confidence interval (CI): 1.03–1.07, $p < 0.001$; 95% CI: 0.91–0.97, $p < 0.001$, respectively]. In Group 2, female gen-

Table 2. Prevalence of individual medical conditions and categories of conditions and differences between bipolar I and bipolar II disorder subtypes

	Overall (n = 482)	Bipolar I (n = 329)	Bipolar II (n = 153)	p-value (χ^2-test)
Group 1				
Hypertension	18.7	19.1	17.8	0.72
Coronary artery disease/ myocardial infarction	1.2	0.9	2.0	0.33
Diabetes	6.2	6.4	5.9	0.83
Hyperglycemia	14.5	14.0	15.7	0.62
Hyperlipidemia	21.4	19.8	24.8	0.21
High total cholesterol	12.7	13.8	10.5	0.32
Low HDL	32.8	33.9	30.3	0.42
High LDL	28.1	28.9	26.5	0.59
Abnormal triglycerides	28.4	27.8	29.6	0.69
Metabolic syndrome	27.3	26.6	28.9	0.61
Any Group 1	71.2	72.3	68.6	0.40
Group 2				
Kidney disease	2.7	3.0	2.0	0.50
Seizures	5.0	6.1	2.6	0.10
Thyroid disease	4.6	4.0	5.9	0.34
Asthma	20.1	20.4	19.6	0.85
Migraines	28.5	26.2	33.3	0.11
Cancer	4.4	3.3	6.5	0.11
Hepatitis	4.0	5.8	0	0.002
Head trauma	16.2	17.0	14.4	0.46
Any Group 2	56.2	55.6	57.5	0.70
Group 3 (substance use)				
Current smoker	51.8	56.7	41.2%	0.001
Ever smoker	72.4	76.6	63.4%	0.003
Alcohol dependence (lifetime)	34.3	39.0	24.2%	0.001
Drug dependence (lifetime)	36.2	42.7	22.2%	<0.001
Any Group 3	80.5	85.4	69.9%	<0.001
Any Group 1, 2, or 3	96.3	96.7	95.4%	0.51

Values are reported as %. Criteria were based on either medical history or laboratory values. Hyperglycemia was defined as being present if fasting blood glucose ≥100 mg/dL; high total cholesterol if total cholesterol ≥240 mg/dL; low high-density lipoprotein cholesterol (HDL-C) if HDL-C <50 mg/dL (female) or <40 mg/dL (male); high low-density lipoprotein cholesterol (LDL-C) if LDL-C ≥130 mg/dL; high triglycerides if triglycerides ≥150 mg/dL; metabolic syndrome if three or more of the following criteria were met: waist circumference >35 inches (female) or >40 inches (male), triglycerides ≥ 150 mg/dL, HDL-C <50 mg/dL (female) or <40 mg/dL (male) or participant on medications for hypercholesterolemia, systolic blood pressure <130 mm Hg or diastolic blood pressure >85 mm Hg or participant on medications for hypertension, or fasting blood glucose ≥100 mg/dL or participant on medications for diabetes.

Table 3. Demographic and clinical variables associated with medical comorbidities

Variables	Overall n (%)	Any Group 1 n (%)			Any Group 2 n (%)			Any Group 3 n (%)		
		Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Gender										
Female	283 (58.7)	199 (58.0)	84 (60.4)	0.626	172 (63.5)	111 (52.6)	0.016	223 (57.5)	60 (63.8)	0.261
Male	199 (41.3)	144 (42.0)	55 (39.6)		99 (36.5)	100 (47.4)		165 (42.5)	34 (36.2)	
Race										
White	348 (72.2)	252 (73.5)	96 (69.1)	0.168	203 (74.9)	145 (68.7)	0.301	286 (73.7)	62 (66.0)	0.011
Black	96 (19.9)	69 (20.1)	27 (19.4)		50 (18.5)	46 (21.8)		79 (20.4)	17 (18.1)	
Asian	16 (3.3)	8 (2.3)	8 (5.8)		6 (2.2)	10 (4.7)		8 (2.1)	8 (8.5)	
Native American	1 (0.2)	0 (0)	1 (0.7)		0 (0)	1 (0.5)		1 (0.3)	0 (0)	
Other	21 (4.4)	14 (4.1)	7 (5.0)		12 (4.4)	9 (4.3)		14 (3.6)	7 (7.4)	
Marital status										
Divorced/separated	100 (20.7)	78 (22.7)	22 (15.8)	<0.001	58 (21.4)	42 (19.9)	0.168	88 (22.7)	12 (12.8)	0.083
Married/living as married	150 (31.1)	118 (34.4)	32 (23.0)		94 (34.7)	56 (26.5)		118 (30.4)	32 (34.0)	
Single/never married	225 (46.7)	140 (40.8)	85 (61.2)		115 (42.4)	110 (52.1)		175 (45.1)	50 (53.2)	
Widowed	7 (1.5)	7 (2.0)	0 (0)		4 (1.5)	3 (1.4)		7 (1.8)	0 (0)	
Household income										
<$25,000	249 (52.1)	178 (52.0)	71 (52.2)	0.968	134 (50.0)	115 (54.8)	0.721	216 (56.3)	33 (35.1)	0.003
$25,000 to <$50,000	90 (18.8)	65 (19.0)	25 (18.4)		52 (19.4)	38 (18.1)		67 (17.4)	23 (24.5)	
$50,000 to <$75,000	60 (12.6)	44 (12.9)	16 (11.8)		34 (12.7)	26 (12.4)		44 (11.5)	16 (17.0)	
≥$75,000	79 (16.5)	55 (16.1)	24 (17.6)		48 (17.9)	31 (14.8)		57 (14.8)	22 (23.4)	
Education										
<High school	24 (5.0)	18 (5.2)	6 (4.3)	0.862	17 (6.3)	7 (3.3)	0.746	21 (5.4)	3 (3.2)	0.012
High school or GED	98 (20.3)	70 (20.4)	28 (20.1)		55 (20.3)	43 (20.4)		87 (22.4)	11 (11.7)	
Some college	149 (30.9)	101 (29.4)	48 (34.5)		82 (30.3)	67 (31.8)		121 (31.2)	28 (29.8)	
Technical school/associate degree	58 (12.0)	41 (12.0)	17 (12.2)		30 (11.1)	28 (13.3)		47 (12.1)	11 (11.7)	
College diploma	117 (24.3)	85 (24.8)	32 (23.0)		67 (24.7)	50 (23.7)		90 (23.2)	27 (28.7)	
Graduate school or professional degree	36 (7.5)	28 (8.2)	8 (5.8)		20 (7.4)	16 (7.6)		22 (5.7)	14 (14.9)	
% of last year depressed										
0–20	52 (10.8)	34 (9.9)	18 (12.9)	0.069	183 (67.5)	146 (69.2)	0.008	281 (72.4)	48 (51.1)	<0.001
21–40	115 (23.9)	82 (23.9)	33 (23.7)		88 (32.5)	65 (30.8)		107 (27.6)	46 (48.9)	
41–60	138 (28.6)	93 (27.1)	45 (32.4)		20 (7.4)	32 (15.2)		40 (10.3)	12 (12.8)	
61–80	127 (26.3)	90 (26.2)	37 (26.6)		67 (24.7)	48 (22.7)		91 (23.5)	24 (25.5)	
81–100	50 (10.4)	44 (12.8)	6 (4.3)		70 (25.8)	68 (32.2)		115 (29.6)	23 (24.5)	
% of last year manic/hypomanic										
0–20	222 (46.3)	174 (50.9)	48 (34.8)	0.012	84 (31.0)	43 (20.4)	0.375	99 (25.5)	28 (29.8)	0.314
21–40	158 (32.9)	103 (30.1)	55 (39.9)		30 (11.1)	20 (9.5)		43 (11.1)	7 (7.4)	
41–60	61 (12.7)	40 (11.7)	21 (15.2)		135 (49.8)	87 (41.6)		174 (45.1)	48 (51.1)	
61–80	28 (5.8)	20 (5.8)	8 (5.8)		83 (30.6)	75 (35.9		124 (32.1)	34 (36.2)	
81–100	11 (2.3)	5 (1.5)	6 (4.3)		30 (11.1)	31 (14.8)		53 (13.7)	8 (8.5)	

Table 3. (Continued)

Variables	Overall n (%)	Any Group 1 n (%)			Any Group 2 n (%)			Any Group 3 n (%)		
		Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Any SUD lifetime										
Yes	296 (61.4)	211 (61.5)	85 (61.2)	0.941	17 (6.3)	11 (5.3)	0.006	25 (6.5)	3 (3.2)	<0.001
No	186 (38.6)	132 (38.5)	54 (38.8)		6 (2.2)	5 (2.4)		10 (2.6)	1 (1.1)	
Any anxiety disorder (current)										
Yes	277 (57.5)	198 (57.7)	79 (56.8)	0.858	181 (66.8)	115 (54.5)	0.086	284 (73.2)	12 (12.8)	0.036
No	205 (42.5)	145 (42.3)	60 (43.2)		90 (33.2)	96 (45.5)		104 (26.8)	82 (87.2)	
ADHD (current)										
Yes	161 (33.7)	113 (33.3)	48 (34.5)	0.801	165 (60.9)	112 (53.1)	0.304	232 (59.8)	45 (47.9)	0.105
No	317 (66.3)	226 (66.7)	91 (65.5)		106 (39.1)	99 (46.9)		156 (40.2)	49 (52.1)	

ADHD = attention-deficit hyperactivity disorder; GED = General Educational Development; SUD = substance use or dependence.

der, presence of a lifetime substance use disorder, younger age of illness onset, and longer illness duration remained as predictors of Group 2 conditions (all $p < 0.05$). Finally, lower household income ($\chi^2 = 15.72$, $p < 0.001$) and higher manic severity (CGI mania) predicted substance use (95% CI: 1.02–1.63, $p < 0.035$), with older age marginally predicting substance use (95% CI: 1.00–1.05, $p = 0.062$).

Discussion

This study is consistent with previous data demonstrating high rates of medical comorbidity in bipolar disorder (11, 13, 46), but extends these data by highlighting specific associations among these conditions with specific demographic and clinical features. For example, a complicated association of age and age of bipolar illness onset with medical comorbidity. Consistent with findings for non-bipolar samples, the likelihood of having a cardiometabolic condition (Group 1) as well as substance use increased with age (47, 48) which remained significant in the multivariate models; however, this finding did not hold for other, non-cardiovascular medical conditions (Group 2). This may suggest that, with age, bipolar patients are susceptible to developing cardiometabolic disease and substance problems, or conditions associated with unhealthy lifestyle choices, but not necessarily other medical conditions. This finding may also be explained by migraines and asthma having early ages of onset as they were the most prevalent Group 2 conditions (49–51).

We found that an earlier age of onset and longer duration of illness, independent of age and other variables, predicted having a Group 2 condition (which remained significant in the multivariate analyses) and later age of onset was associated with a greater likelihood of having a Group 1 condition. Thus, perhaps cardiometabolic conditions that develop with age (as discussed above) could trigger a later onset of bipolar disorder, as these medical conditions are risk factors for depressive symptoms and mood episodes (27, 52, 53). Alternatively, perhaps Group 1, cardiometabolic conditions and substance use, or those most modifiable, become the focus of treatment instead of psychiatric conditions, such as bipolar disorder, resulting in later detection or age of onset. Similarly, low income was associated with substance use, presenting another potential barrier to diagnosis or treatment. Further research is needed to better understand these data.

More severe manic symptoms were unexpectedly associated with a *decreased* likelihood of having a

Table 4. Demographic and clinical variables associated with medical comorbidities (difference of mean and 95% confidence intervals)

	Any Group 1		Any Group 2		Any Group 3	
Variables	Difference of means	95% CI	Difference of means	95% CI	Difference of means	95% CI
Age (years) at:						
Study	7.16[b]	4.85–9.47	1.61	−0.58 to 3.79	3.11[c]	0.39–5.84
Depression onset	1.84[c]	0.26–3.42	−1.98[c]	−3.41 to −0.54	0.18	−1.63 to 1.99
Mania onset	2.65[c]	0.79–4.51	−2.06[c]	−3.76 to −0.35	−0.14	−2.28 to 2.00
Illness onset	1.79[c]	0.26–3.32	−2.14[c]	−3.53 to −0.75	−0.21	−1.97 to 1.55
No. lifetime depressive episodes[a]	1.23	−7.08 to 9.53	3.20	−4.44 to 10.84	8.37	−1.15 to 17.89
No. lifetime manic episodes[a]	−3.14	−12.8 to 6.48	4.28	−4.56 to 13.12	8.50	−2.47 to 19.46
Time spent (years)[a]:						
Depressed	5.35	2.96–7.74	3.46[b]	1.26–5.66	2.95	0.19–5.71
Manic	4.45	2.07–6.83	3.58[c]	1.40–5.77	3.19	0.45–5.93
Ill	5.37	2.96–7.79	3.75[b]	1.52–5.97	3.32	0.52–6.12
CGI-BP score						
Overall	0.01	−0.16 to 0.18	0.07	−0.08 to 0.23	0.28[c]	0.08–0.47
Mania	−0.22	−0.46 to 0.03	0.10	−0.13 to 0.33	0.24	−0.05 to 0.52
Depression	0.23	0.01–0.45	0.10	1.40–5.77	0.30[c]	0.04–0.55
BISS score						
Depression	1.87[c]	0.42–3.31	0.82	−0.51 to 2.14	1.87[c]	0.22-3.52
Mania	−2.43[b]	−3.66 to −1.19	−0.14	−1.29 to 1.01	1.28	−0.15 to 2.71
LIFE-RIFT score	0.64	−0.03 to 1.31	−0.16	−0.78 to 0.45	0.78[c]	0.02–1.54

BISS = Bipolar Inventory of Symptoms Scale; CGI-BP = Clinical Global Impression Scale for Bipolar Disorder; CI = confidence interval; LIFE-RIFT = LIFE–Range of Impaired Functioning Tool.
[a]Analyses of number of lifetime manic and depressive episodes and numbers of years spent depressed, manic, and ill were adjusted for age.
[b]$p \leq 0.001$.
[c]$p \leq 0.05$.

Table 5. Association between history of weight-gain medications and metabolic conditions

			Weight-gain medications[a]				
	Overall		Yes		No		p-value
Meets criteria for:	n (%)	Total N	n (%)	Total N	n (%)	Total N	(χ^2-test)
Hypertension	90 (18.7)	481	20 (19.0)	105	70 (18.6)	376	0.920
Coronary artery disease/myocardial infarction	6 (1.2)	482	1 (1.0)	105	5 (1.3)	377	0.760
Diabetes	30 (6.2)	482	5 (4.8)	105	25 (6.6)	377	0.483
Hyperglycemia	70 (14.5)	482	16 (15.2)	105	54 (14.3)	377	0.814
Hyperlipidemia	103 (21.4)	482	23 (21.9)	105	80 (21.2)	377	0.880
High total cholesterol	61 (12.7)	479	11 (10.7)	103	50 (13.3)	376	0.480
Low HDL cholesterol	157 (32.8)	479	43 (41.7)	103	114 (30.3)	376	0.029
High LDL cholesterol	133 (28.1)	473	27 (26.7)	101	106 (28.5)	372	0.727
Abnormal triglycerides	136 (28.4)	479	45 (43.7)	103	91 (24.2)	376	<0.001

Criteria were based on either medical history or laboratory values. Hyperglycemia was defined as being present if fasting blood glucose ≥100 mg/dL; high total cholesterol if total cholesterol ≥240 mg/dL; low high-density lipoprotein cholesterol (HDL-C) if HDL-C <50 mg/dL (female) or <40 mg/dL (male); high low-density lipoprotein cholesterol (LDL-C) if LDL-C ≥130 mg/dL; high triglycerides if triglycerides ≥150 mg/dL.
[a]Weight-gain medications = amitriptyline, aripiprazole, clomipramine, clozapine, doxepin, imipramine, lithium, mirtazepine, olanzapine, quetiapine, risperidone, and valproate.

cardiometabolic condition, which remained significant in the multivariate models. These data might be explained by depression having a causal link to cardiometabolic health (6, 29); more mania in the last year could reduce the time spent depressed, therefore reducing the exposure to the depressed state and the associated cardiometabolic risk. Furthermore, depressed patients may be more likely to gain weight than manic patients (54). Recent studies have also shown that increased manic symptoms may be correlated with more frequent exercise, which could also account for this finding

(55, 56). Nearly half of our sample experienced less than 20% of the previous year in an elevated mood state; thus, it is also possible that the sample experiencing elevated mood was not large enough for us to detect an association. Yet, Fiedorowicz and colleagues found that manic symptoms were associated with increased cardiovascular mortality, independent of cardiovascular risk factors present at baseline, age, and gender (57).

Finally, medications prescribed for bipolar disorder, such as mood stabilizers and antipsychotics, were associated with low HDL and high triglyceride levels, as expected given that these medications are typically associated with risk factors for cardiovascular disease (30, 31). Yet, other parameters (e.g., hypertension, hyperlipidemia, and diabetes) were not associated with these medications. This may be due to a lack of power given the lower prevalence of these conditions in our sample, although the data did not trend in this direction. Alternatively, providers may be becoming more conservative in prescribing these medications given their known deleterious side effects.

Limitations of the current study include relying on self-report of substance use and Group 2 conditions as well as these data being assessed only at one time-point which does not allow us to draw any causal conclusions. Data were collected through a clinical trial, potentially limiting the generalizability of the findings. There may also be overlap between the groups, as lifetime substance use predicted the presence of a Group 2 condition. Of note, the other medical comorbidity group (Group 2) includes several medical conditions and thus, the heterogeneity of Group 2 is a potential limitation. Finally, the lack of a control group limits our ability to discern if these effects are unique to the bipolar population; however, the findings with mania (negative correlation with cardiometabolic conditions and positive correlation with substance use) do present an important and specific relationship with bipolar disorder.

Despite these potential limitations, these data highlight the substantial medical burden in bipolar disorder, but perhaps more to the point, that medical comorbidities could often reflect the effects of the illness and not the conditions themselves. We hope that, by elucidating the potential interplay between bipolar disorder and its high medical burden, we will improve the treatment of the disease (e.g., highlight the need for greater collaboration between providers, and increase awareness that depression or age of onset is associated with specific medical conditions). This is important as patients with bipolar disorder are frequently unaware of their predisposition for medical comorbidities and most of the illnesses can be prevented (6, 58). Thus, these data highlight the need to adopt strategies to reduce medical burden in bipolar disorder as well as to integrate medical and psychiatric care for these patients with the aim to improve overall outcomes.

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