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General Medical Burden in Bipolar Disorder: Findings from the LiTMUS Comparative Effectiveness Trial

David E. Kemp, MD, MS[1], **Louisa G. Sylvia, PhD**[2], **Joseph R. Calabrese, MD**[1], **Andrew A. Nierenberg, MD**[2], **Michael E. Thase, MD**[3], **Noreen A. Reilly-Harrington, PhD**[2], **Michael J. Ostacher, MD, MPH, MMSc**[4], **Andrew C. Leon, PhD**[5,*], **Terence A. Ketter, MD**[4], **Edward S. Friedman, MD**[6], **Charles L. Bowden, MD**[7], **Michael Pencina, PhD**[8], **Dan V. Iosifescu, MD**[9], and **The LiTMUS Study Group**

[1]Case Western Reserve University, University Hospitals Case Medical Center, Cleveland, OH USA

[2]Massachusetts General Hospital, Boston, MA USA

[3]University of Pennsylvania, Philadelphia, PA USA

[4]Stanford University School of Medicine, Stanford, CA USA

[5]Weill Cornell Medical College, New York, NY USA

[6]University of Pittsburgh Medical Center, Pittsburgh, PA USA

[7]University of Texas Health Science Center, San Antonio, TX USA

[8]Harvard Clinical Research Institute, Boston, MA USA

[9]Mount Sinai School of Medicine, New York, NY USA

Abstract

Objective—This study examined general medical illnesses and their association with clinical features of bipolar disorder.

Methods—Data were cross-sectional and derived from the Lithium Treatment – Moderate Dose Use Study (LiTMUS), which randomized symptomatic adults (n=264 with available medical comorbidity scores) with bipolar disorder to moderate doses of lithium plus optimized treatment (OPT) or to OPT alone. Clinically significant high and low medical comorbidity burden were defined as a Cumulative Illness Rating Scale (CIRS) score ≥ 4 and < 4, respectively.

Results—The baseline prevalence of significant medical comorbidity was 53% (n=139). Patients with high medical burden were more likely to present in a major depressive episode (P=.04), meet criteria for obsessive-compulsive disorder (P=.02), and experience a greater number of lifetime mood episodes (P=0.02). They were also more likely to be prescribed a greater number of psychotropic medications (P=.002). Sixty-nine percent of the sample was overweight or obese as defined by body mass index (BMI), with African-Americans representing the racial group with the highest proportion of stage II obesity (BMI ≥ 35; 31%, n=14).

Author Correspondence: David E. Kemp, MD, MS, 10524 Euclid Ave., 12th Floor, Cleveland, OH 44106, P: 216-844-2865, F: 216-844-2875, kemp.david@gmail.com.

*posthumous

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Dedication: This work is dedicated to the memory of Andrew C. Leon, Ph.D.

Conclusions—The burden of comorbid medical illnesses was high in this generalizable sample of treatment-seeking patients and appears associated with worsened course of illness and psychotropic medication patterns. (Funded by NIMH Contract N01MH80001; ClinicalTrials.gov number NCT00667745).

Keywords

Bipolar disorder; medical comorbidity; obesity; lithium; effectiveness

INTRODUCTION

Bipolar disorder is a common and severe psychiatric illness, estimated to affect between 2–3% of the general population (1). In addition to experiencing an elevated rate of psychiatric comorbidity (1, 2), individuals with bipolar disorder are at increased risk for several general medical conditions including cardiovascular disease (3), respiratory disorders (4, 5), thyroid disease (6), hepatitis C (7), type-2 diabetes (8), and obesity (9, 10). Such comorbid medical illnesses can lead to elevated economic costs from medical expenditures and lost productivity (11), poorer psychiatric treatment outcomes (12), and changes in physical health-related quality of life (13). Moreover, these general medical conditions contribute to an earlier mortality, leaving bipolar disorder patients with a life expectancy that is up to 30% shorter when compared to individuals in the general population (14).

For certain illnesses, such as cardiometabolic disorders, the relationship with bipolar disorder appears bi-directional. Individuals with bipolar disorder often display poor self-care behaviors characterized by limited exercise and high-calorie diets that can increase the propensity for developing obesity and type-2 diabetes (15). Conversely, specific cardiometabolic conditions have been shown to predispose to the development of depressive symptoms and have been associated with longer and more severe mood episodes and shorter times to illness recurrence (16–18).

Studies reporting on medical conditions that co-occur with bipolar disorder have predominantly focused on single chronic illnesses (7, 19) or on discrete patient populations such as the elderly (20), those with the bipolar I subtype (21), or individuals participating in clinical trials with strict inclusion and exclusion criteria (5, 16). In contrast, the primary aim of this analysis was to evaluate the relationship between general medical conditions and bipolar disorder in a generalizable group of treatment-seeking patients entering the Lithium Treatment - Moderate Dose Use Study (LiTMUS). LiTMUS is an NIMH-sponsored trial designed to test whether the strategy of using tolerable doses of lithium in combination with other medications for bipolar disorder is superior to optimized treatment (OPT; guideline-informed, evidence-based, and personalized treatment based on current symptoms, prior treatment history, and course of disorder) without lithium.

Aims of the study

The current report estimates the prevalence and burden of general medical illnesses and their association with clinical features associated with bipolar I or II disorder. We hypothesized that greater frequency of bipolar episodes and more severe depressive and manic symptomatology would occur in those with high medical burden. We specifically analyzed the rates of overweight and obesity in this sample, as well as the association between baseline psychotropic medication use and high medical burden.

METHOD

The methods of the LiTMUS clinical trial have been described in more detail elsewhere(22). The key elements of the methods are described below.

Study Overview

LiTMUS is a randomized parallel-group, single (rater)-blinded trial of adjunctive moderate dose lithium (i.e., 600 mg initially for 8 weeks) for the treatment of outpatients with bipolar I or II disorder. At study entry, participants were required to have mood symptoms of at least mild severity to warrant a change in treatment and that, in the investigator's judgment, lithium would be a feasible therapeutic option. A total of 283 participants were enrolled over eighteen months and received six months of follow-up treatment. This study examines data collected only at baseline (Week 0), not the randomized phase.

Study Population

To achieve the goal of recruiting a representative group of patients with bipolar disorder, LiTMUS utilized broad inclusion criteria and limited exclusion criteria to produce a cohort of highly generalizable subjects. This methodology stands in contrast to typical industry-sponsored efficacy trials that may lack external validity due to the use of double-blind, placebo-controlled methodology and strict exclusion criteria. The study was conducted at bipolar or mood disorder specialty clinics in diverse geographic regions, with much effort taken to recruit participants who were racially and ethnically representative of the general population. In order to limit participant study burden, rating scales not critical to the primary aims of the study were excluded, trial duration was limited to 6 months, and laboratory monitoring was performed at only four time points (23).

Patients eligible for enrollment into LiTMUS included those with bipolar I or II disorder who were 18 years of age or older. Participants must have been currently symptomatic as defined by a Clinical Global Impression Scale-Bipolar Version (CGI-BP) (24) score ≥ 3 and not have been taking lithium for at least 30 days prior to enrollment. Women of child bearing potential were permitted to enroll so long as they agreed to use adequate contraception and inform their study clinician at the earliest possible time of their plans to conceive. Individuals with concurrent medical illnesses were permitted to enroll, with the exception of renal impairment (serum creatinine > 1.5 mg/dL), dehydration, severe cardiovascular disease that would preclude treatment with lithium, or the presence of thyroid stimulating hormone >20% above the upper normal limit, given the potential safety risks associated with lithium treatment.

The LiTMUS infrastructure included a national coordinating center in Boston, Massachusetts and six regional centers across the United States. The affiliated institutional review board approved all recruitment, assessment, and treatment procedures.

Baseline Assessments

Participants were interviewed using the Extended Mini-International Neuropsychiatric Interview, an extended version of a validated structured diagnostic interview to determine current and lifetime Diagnostic and Statistical Manual-Version IV (DSM-IV) diagnoses (25). The only exception is that the Structured Clinical Interview for DSM-IV Substance Use Disorder Module (26), rather than the Extended Mini- International Neuropsychiatric Interview Substance Use Disorder Module, was used to assess substance use disorders, as it provides additional detail regarding use course specifiers. At baseline, trained study staff completed the CGI-BP, Montgomery-Asberg Depression Rating Scale (MADRS) (27), and Young Mania Rating Scale (YMRS) (28) to assess participants' severity of illness and

bipolar symptoms. Participants completed the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16), a self-administered measure of depressive symptoms (29). Validated measures of function and quality of life were also administered, including the Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q) (30) and the LIFE- Range of Impaired Functioning Tool (LIFE-RIFT) (31).

General medical conditions were assessed by the 14-item Cumulative Illness Rating Scale (CIRS), a valid and reliable tool for measuring medical comorbidity (32). The CIRS was completed by the treating clinician who was trained on using a manual to guide scoring (33). In brief, a score was generated ranging from 0 to 4 for each of 14 organ systems. A score of 0 represents 'no problem', a score of 1 represents a 'current mild or past significant problem', a score of 2 represents 'moderate disability requiring first line treatment', a score of 3 represents 'uncontrollable chronic problems or significant disability' and a score of 4 represents 'end organ failure requiring immediate treatment'. Since the CIRS includes a category for psychiatric illness, this section was modified to capture comorbid psychiatric disorders other than bipolar disorder, since every subject would have met criteria for bipolar disorder as a requirement of study entry.

Clinically significant or "high" medical comorbidity burden was defined as a score ≥ 4 on the CIRS, while "low" medical comorbidity was defined as a score < 4 on the CIRS. A CIRS score ≥4 would include those patients with at least two moderately disabling medical problems requiring first-line treatment. This cutoff was based on previously conducted analyses in major depressive disorder (34) and bipolar disorder (5).

Statistical Analyses

Subjects with and without significant medical comorbidity were descriptively compared using a one-way ANOVA. For categorical variables, group percentages were calculatedand χ^2 tests performed. Multiple linear regression was then used to test the association between medical comorbidity burden and selected clinical variables identified as significant in the bivariate analysis, controlling for the covariates age, gender, bipolar subtype, and comorbid substance use. Gender differences in BMI in relationship to bipolar subtype were analyzed by a polytomous regression model. Given the exploratory nature of the statistical results, no multiple comparison adjustments were applied. Statistical analyses were performed using SAS. All tests employed a two-tailed, uncorrected alpha = .05.

RESULTS

A total of 283 participants were enrolled into LiTMUS. Of this group, 19 were excluded because of missing CIRS data, leaving 264 subjects available for analysis. Compared to the analyzed sample, there were no significant differences in age, gender, psychiatric symptom severity, or BMI among individuals without available CIRS scores. The mean age of study participants was 39.2 (range 18 to 68, SD = 12.4) and was 56% (n=149) female and 17% (n=46) African-American. The mean total score of the CIRS was 4.2 (SD=3.2); excluding psychiatric burden the mean was 2.6 (SD=2.7).

Sociodemographic and clinical summary

Table 1 presents the association of general medical comorbidity with baseline sociodemographic characteristics and clinical variables. No significant differences were observed by race, marital status, educational background, household income, age, or gender, with the exception of a trend for females to show a greater burden of general medical comorbidity than males (P=.06). Participants with significant medical comorbidity were more likely to be experiencing a current major depressive episode (P=.04), to meet criteria

for obsessive-compulsive disorder (P=.02), and to have a lifetime history of psychotic symptoms (P=.02). Patients with high medical comorbidity burden experienced an average of 10 additional depressive episodes and 15 additional manic or hypomanic episodes over their lifetime than individuals with lower medical burden (P=.02).

Psychotropic prescribing patterns

At baseline, patients were prescribed a mean 2.6 (SD=1.6) psychotropic medications. Patients with significant medical comorbidity burden were prescribed a greater number of psychotropic medications (P=0.002). However, they were no more likely to be prescribed SGAs (47.1%) than were participants without significant medical problems (46.0%).

After performing the bivariate analyses, associations between the clinical variables of interest and relevant covariates were further explored in a multiple linear regression model. The number of past mood episodes, lifetime manic/hypomanic episodes, number of psychotropic medications and number of classes of psychotropic medications remained significant in the multivariate analysis (P<.05). Past depressive episodes remained marginally significant (P=.06). Other clinical outcomes were not associated with an increased burden of medical problems, including baseline symptom severity and quality of life as measured by YMRS, MADRS, Q-LES-Q and LIFE-RIFT scores, even when adjusted for age, gender, and race (all P's > .05).

Table 2 outlines the prevalence rates for the type of medical comorbidity by organ system as measured by the CIRS. A summary of individual medical conditions of participants at baseline is reported in Table 3. The most common chronic conditions affecting patients were obesity (38%), migraines (25%), hypertension (17%), hyperlipidemia (16%), and asthma (14%). Cigarette smoking was reported by 45% of individuals with bipolar disorder.

Cardiometabolic features

Fasting laboratory parameters were obtained 8 or more hours after the last meal. Abnormalities among the individual components of metabolic syndrome are highlighted in Table 1. Metabolic syndrome occurred in 30% of participants and was more often present in patients with high medical comorbidity (36% vs. 23%; P=.03). An enlarged waist circumference was more often identified in females (52.4%, n=76) as compared with males (33.0%, n=37; χ^2=9.63, P=.002).

At baseline, the mean weight of participants was 84.3 kg (SD = 20.9) and the mean BMI was 29.2 (SD = 7.2). Among 279 participants with available BMI data, a total of 31%(n=87) were overweight and 38% (n=105) were obese. Stage II obesity, defined as a BMI ≥ 35 was met by 19% (n=53) of the study population. As shown in Table 4, the proportion of subjects with bipolar I disorder meeting criteria for overweight or obesity (68%; n=145) was similar to those with bipolar II disorder (70%; n=47). Likewise, males were as likely as females to meet criteria for overweight or obesity (74%, n=89 vs. 65%, n=103). When stratified by bipolar subtype, men with bipolar II disorder were predominantly overweight or obese, while women with bipolar II disorder had similar distributions across BMI categories. In addition, a significant gender by diagnosis interaction was identified for baseline BMI. Male patients with bipolar I disorder were more likely to be overweight, whereas female patients with bipolar I disorder were more likely to be obese (χ^2=7.44, df=2, P=0.02).

Using criteria established by the National Cholesterol Education Program's Adult Treatment Panel III for the identification of metabolic syndrome (35), raised blood pressure (systolic ≥ 130 or diastolic ≥ 85) was present among 44% (114/259) of the overall sample, 49% (67/137) with high medical comorbidity and 39% (47/122) of those with low medical burden. Hypertriglyceridemia (≥150 mg/dl) was present among 31% (81/264) of the overall

sample, 34% (47/139) of those with high medical comorbidity and 27% (34/125) with low medical burden. Among the 114 (44%) patients with raised blood pressure, 61% (n=69) did not report it at baseline. Among the 81 patients (31%) with dyslipidemia, 48% (n=39) did not report a previous diagnosis of dyslipidemia.

DISCUSSION

The objective of this report was to characterize the type and severity of comorbid general medical conditions affecting a representative group of patients with bipolar disorder and to examine whether medical burden was associated with specific clinical characteristics. All patients were participants within LiTMUS, a randomized effectiveness study that, in contrast to traditional efficacy trials, did not exclude patients on the basis of general medical conditions, with the exception of illnesses that may have precluded safe treatment with lithium. Therefore, the results are widely generalizable to patients with bipolar disorder seen in outpatient settings.

In this sample, multiple comorbid medical conditions were commonly observed, with the most frequent being obesity, migraines, hypertension, hyperlipidemia, and asthma. The high prevalence of respiratory and cardiometabolic disorders is consistent with findings from both clinical and nationally representative epidemiological studies (4, 5, 21). Migraines affected one-fourth of the sample, in line with previous reports suggesting that migraines occur nearly twice as often in patients with bipolar disorder as compared with the general population (19). Although the metabolic syndrome affected 30% of participants, the rate of type-1 and type-2 diabetes combined was lower, affecting 6% of participants. The prevalence of both conditions resembles rates internationally, where metabolic syndrome ranges from 17–55% (36) and the rate of type-2 diabetes is approximately 7% in those with bipolar disorder (8). Current smokers comprised 45% of the cohort, much higher than the 13% prevalence of nicotine dependence in the general population (37).

Although rates of renal, thyroid, and parathyroid disorders did not disproportionally affect the current sample, each are known adverse effects of lithium. Thyroid and parathyroid abnormalities occur in about 25% of patients receiving lithium therapy, whereas the incidence of end-stage renal failure is low, occurring in approximately 0.5% of patients with long-term use (38, 39). Subclinical hypothyroidism can also contribute to weight gain and be accompanied by alterations in lipid metabolism and cardiac contractility. Albeit weight gain is a known adverse effect of lithium, the risk is less than with many other agents used to stabilize mood, particularly the atypical antipsychotics.

Despite the common occurrence of several general medical conditions in this sample, compared with prior reports of medical comorbidity in bipolar disorder, the overall severity of medical burden appears lower. For instance, 53% of participants in the present sample demonstrated a high burden of medical comorbidity (CIRS score ≥ 4). This is lower than the 64% rate of significant medical comorbidity observed among bipolar I and II patients with rapid-cycling features and co-occurring substance use disorders (5). Likewise, when evaluating overall CIRS scores after exclusion of the psychiatric item, participants in the present sample had a mean score of 2.6, compared with a mean score of 4.7 among treatment-seeking outpatients with bipolar disorder or schizoaffective disorder (40) and more than three times lower than a mean CIRS score of 9.6 reported in a geriatric population with bipolar disorder aged 60 years and older (20). The lower burden of medical comorbidity is likely reflective of the younger age of the current sample (mean 39.2 years vs. 59.5 years in the geriatric cohort) and the relatively low rate of concurrent alcohol or substance use disorders, which were identified in only 12% of participants.

A major focus of this study centered on the relationship between medical comorbidity burden and psychiatric illness characteristics. At study entry, patients with high medical burden more often presented in a major depressive episode and with comorbid obsessive-compulsive disorder. They also experienced a greater number of lifetime mood episodes, despite a similar age at study entry and age of illness onset. The number of additional lifetime mood episodes was substantial, averaging 15 additional manic/hypomanic episodes and 10 additional major depressive episodes. Such findings are in agreement with previous studies that have found an association between the number of medical problems and a longer duration and frequency of depressive episodes, both in populations with bipolar disorder (16) and unipolar major depression (41). Moreover, chronicity of depression may lead to negative effects on medical burden, as recurrent depression is associated with decrements in physical health that is greater than in first-episode depression(42).

In contrast to our initial hypothesis, the severity of current mood symptoms did not differ significantly between the two medical comorbidity cohorts. This may reflect, in part, the lower overall baseline symptom severity scores among LiTMUS participants. On average, patients had mean MADRS scores of 22.5 and YMRS scores of 12.6 at study entry, whereas the baseline MADRS and YMRS scores from traditional efficacy trials of bipolar depression and mania are typically >30 and >25, respectively. The lower baseline severity scores in LiTMUS reflect the intent to enroll a more representative sample, including subsyndromal subjects.

Our findings suggest that significant medical comorbidity is associated with more complex psychotropic prescribing patterns, perhaps reflective of the greater depressive morbidity in this sample. At baseline, patients were receiving a mean of 2.6 different psychotropic medications, with greater overall use of psychotropic medications as well as different classes of psychotropic medications in those with high medical burden. However, we did not observe an increased use of SGA's in those with greater medical burden as originally hypothesized. Whether more targeted treatment of co-occurring medical illnesses can decrease the need for psychotropic polypharmacy is unclear.

When assessing for specific medical disorders, it is noteworthy that a history of hypertension and hyperlipidemia was self-reported by only 17% and 16% of participants, respectively. However, cardiometabolic abnormalities occurred more frequently when using objective laboratory data to estimate prevalence. Raised blood pressure was present in 44% of participants and dyslipidemia occurred in 31%. Thus, participants were unaware of having clinically meaningful abnormalities in blood pressure and lipids in 61% and 48% of cases, respectively. This discrepancy between the rate of reported and observed cardiometabolic risk factors is meaningful, as it may indicate that many patients with bipolar disorder are often undiagnosed or unaware of having elevations in blood pressure or lipids and suggests that potential treatment opportunities may be missed.

Any intervention to improve general medical health in bipolar disorder should focus on the consequences of excess adiposity, as nearly 70% of our sample met criteria for overweight or obesity as defined by BMI. The prevalence of obesity paralleled the high rates found in the United States, which exceeds 30% in most age groups (43). Consistent with prior observations in both bipolar disorder and schizophrenia, the rates of abdominal obesity in the present cohort were higher in women than in men (44, 45). Meaningful variations in the rates of obesity also occurred by ethnicity and bipolar subtype. Among those with bipolar I disorder, women were more likely to be obese than men. Grade 2 obesity (BMI ≥ 35) was highest among African-Americans, affecting 31% of this population, followed by a 26% prevalence among Hispanics. However, it should be noted that BMI may not directly reflect

differences in adiposity, as relative to white men and women at the same BMI, African-Americans have a higher lean mass and lower fat mass (43, 46).

Taken together, current evidence supports a bidirectional relationship between depression and medical disorders. For instance, social withdraw and the inability to begin or sustain activities are characteristic of negative symptoms that can interfere with the ability to maintain a healthy diet, engage in regular exercise, or pursue medical follow-up. Such deficit symptoms may secondarily lead to obesity or cardiometabolic disease.

Alternatively, depression may result from the biochemical changes directly caused by medical disorders or from the stresses associated with living with these comorbid illnesses. Functional impairment may also ensue as a result of comorbid medical conditions. Even when in symptomatic remission, nearly half of patients with bipolar disorder continue to experience functional impairment, with neurocognitive dysfunction being one of the most common clinical factors leading to disability (47). Obesity and vascular disease are known risk factors for the development of cognitive impairment in the general population. Among psychiatric patients, the metabolic syndrome has been specifically associated with impaired attention, processing speed, and working memory (48). Cognitive deficits may also lead to an inability to effectively communicate medical problems to health care providers or maintain adherence to treatment recommendations (49).

Although the rate of metabolic syndrome was higher among patients with significant medical comorbidity, it was not explained by differences in SGA use, as SGAs were taken by approximately 47% of those with or without significant medical comorbidity. Given the cross-sectional nature of this report, however, the role of psychotropic medication on body weight cannot be determined.

Several strengths characterize the current study. The use of structured diagnostic interviews and standardized measurements provide an advance over prior reports of medical comorbidity in bipolar disorder that were based upon epidemiologic reports, billing claims data, or were restricted to discrete patient populations (i.e. veterans). The CIRS as a measure of medical comorbidity was selected in part for its ability to estimate burden for a range of illnesses, rather than focusing on single diseases or in isolation of the complex comorbidity patterns that typify patients with bipolar disorder.

However, several limitations should be noted. The analysis used a CIRS total score of 4 or greater as the cutoff to represent a significant burden of medical comorbidity, consistent with previous publications in bipolar disorder and major depressive disorder (5, 34). Although this allowed for consistency between reports, a higher cutoff might have generated a greater number of associations between medical burden and measures of current and lifetime illness severity. The decision to enroll patients only at academic clinical sites could have produced a selection bias that resulted in a sample of bipolar individuals less representative of the general population, such as those with greater treatment resistance. However, the care taken to broaden the inclusion criteria, minimize the exclusion criteria, and include patients with only minimal symptom severity make this assumption less plausible. Participants in a research study are treatment seeking thus, may be more likely to pursue treatment for their medical comorbidities. Reliance upon patient report as opposed to a comprehensive physical exam and review of a full medical record may underestimate the true burden of illness in patients with limited access to medical care, as medical conditions may be present that are undiagnosed. This is likely to have occurred, as reflected by the low rate of reported cardiometabolic risk factors in comparison with the objective values. Because the study is cross-sectional and solely utilized baseline data, we cannot determine

causality of the associations between medical burden and various clinical characteristics of bipolar disorder.

Conclusion

This highly generalizable study provides evidence of an association between elevated medical comorbidity burden and several clinical features of bipolar disorder, including a higher rate of lifetime mood episodes and greater use of psychotropic medications. Furthermore, overweight and obesity was highly prevalent, affecting more than two-thirds of patients with bipolar disorder, particularly African-Americans. Given the influence of medical burden on both psychiatric symptom presentations and mortality, future studies are needed to improve our understanding of how medical comorbidity impacts treatment response and how clinicians can more effectively identify and address the myriad health risks that occur in bipolar disorder. We advocate for a multidisciplinary approach to the management of bipolar disorder that integrates pharmacotherapy, psychosocial interventions, and general medical care in an effort to enhance long-term patient outcomes.

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Significant outcomes

- The Cumulative Illness Rating Scale (CIRS) was used to assess medical comorbidity burden. High medical burden was defined as a CIRS total score ≥ 4 and affected 53% (n=139) of patients with bipolar disorder. The most common medical conditions included obesity, migraines, hypertension, hyperlipidemia, and asthma.
- Patients with significant medical comorbidity experienced a greater number of lifetime depressive and manic/hypomanic episodes and were prescribed a greater number of psychotropic medications than patients with low medical comorbidity burden.
- Despite the high rate of overweight and obesity in this sample, patients were often unaware of having clinically relevant abnormalities in blood pressure and lipids, suggesting that potential treatment opportunities for individuals with bipolar disorder may frequently be missed.

Limitations

- Lack of a control group without bipolar disorder.
- Given the exploratory nature of the statistical results, no multiple comparison adjustments were applied.
- Cross-sectional collection of data does not allow determination of causality between medical burden and clinical characteristics of bipolar disorder.

Table 1

Comparison of Medical Comorbidity Groups on Sociodemographic Characteristics and Clinical Variables

Baseline Characteristic	High Medical Comorbidity (CIRS ≥ 4) (N=139)	Low Medical Comorbidity (CIRS <4) (N=125)	Overall Sample (N=264)	Test Statistic (df)	P-value
Age					
Mean±SD (N)	40.0±12.6 (139)	38.2±12.2 (125)	39.2±12.4 (264)	1.41 (1)	0.24
Gender				3.52 (1)	0.06
Male	38.1% (53/139)	49.6% (62/125)	43.6% (115/264)		
Female	61.9% (86/139)	50.4% (63/125)	56.4% (149/264)		
Race				0.18 (1)	0.68
White	72.7% (101/139)	76.0% (95/125)	74.2% (196/264)		
African American/Black	20.9% (29/139)	13.6% (17/125)	17.4% (46/264)		
Asian/Asian American	2.2% (3/139)	7.2% (9/125)	4.5% (12/264)		
Other*	4.3% (6/139)	3.2% (4/125)	3.8% (10/264)		
BIPOLAR SUBTYPE				0.07 (1)	0.88
Type I	76.3% (106/139)	77.6% (97/125)	76.9% (203/264)		
Type II	23.7% (33/139)	22.4% (28/125)	23.1% (61/264)		
CURRENT EPISODE					
Major Depressive Episode	71.3% (92/129)	57.8% (63/109)	65.1% (155/238)	4.75 (1)	0.04
Manic Episode	29.3% (27/92)	41.1% (39/95)	35.3% (66/187)	2.80 (1)	0.13
Hypomanic Episode	29.3% (27/92)	29.1% (23/79)	29.2% (50/171)	0.00 (1)	1.0
Panic Disorder	14.4% (20/139)	24.0% (30/125)	18.9% (50/264)	3.96 (1)	0.07
General Anxiety Disorder	0.0% (0/139)	0.8% (1/125)	0.4% (1/264)	1.12 (1)	0.47
Social Phobia	18.7% (26/139)	12.0% (15/125)	15.5% (41/264)	2.26 (1)	0.17
Obsessive-Compulsive Disorder	14.4% (20/139)	5.6% (7/125)	10.2% (27/264)	5.54 (1)	0.02
Posttraumatic Stress Disorder	12.9% (18/139)	12.0% (15/125)	12.5% (33/264)	0.05 (1)	0.85
Alcohol Abuse/Dependence	8.6% (12/139)	5.6% (7/124)	7.2% (19/263)	0.87 (1)	0.48
Drug Abuse/Dependence	8.6% (12/139)	10.4% (13/125)	9.5% (25/264)	0.24 (1)	0.68
CLINICAL FEATURES					
Previously Hospitalized for Psychiatric Reasons	44.4% (60/135)	43.0% (52/121)	43.8% (112/256)	0.06 (1)	0.90
Prior Attempted Suicide	38.7% (53/137)	43.5% (54/124)	41.0% (107/261)	0.64 (1)	0.45

Baseline Characteristic	High Medical Comorbidity (CIRS ≥ 4) (N=139)	Low Medical Comorbidity (CIRS <4) (N=125)	Overall Sample (N=264)	Test Statistic (df)	P-value
Age of Depression Onset	16.9±8.8 (133)	16.7±8.0 (124)	16.8±8.4 (257)	0.06 (1)	0.81
Age of Manic or Hypomanic Onset	19.4±9.0 (126)	18.5±7.7 (116)	19.0±8.4 (242)	0.60 (1)	0.44
Previous Mood Episodes, Lifetime	66.5±84.4 (60)	37.7±34.3 (51)	53.3±67.6 (111)	5.20 (1)	0.02
Previous Depressive Episodes, Lifetime	29.5±38.5 (65)	19.7±19.3 (63)	24.7±30.8 (128)	3.34 (1)	0.07
Previous Manic/hypomanic Episodes, Lifetime	34.9±44.9 (74)	18.3±20.5 (54)	27.9±37.5 (128)	6.40 (1)	0.01
Previous Depressive Episodes, Past Year	3.6±3.3 (118)	3.0±3.6 (100)	3.4±3.5 (218)	1.60 (1)	0.21
Previous Manic/hypomanic Episodes, Past Year	4.5±7.7 (116)	4.1±6.3 (101)	4.3±7.1 (217)	0.14 (1)	0.71
Number of Psychotropic Medications	2.9±1.7 (138)	2.3±1.5 (124)	2.6±1.6 (262)	140.24 (1)	0.002
Number of Different Classes of Psychotropic Medications	2.3±1.2 (138)	1.9±1.1 (124)	2.1±1.2 (262)	8.25 (1)	0.004
Receiving a Second Generation Atypical Antipsychotic	47.1% (65/138)	46.0% (57/124)	46.6% (122/262)	0.03 (1)	0.90
METABOLIC SYNDROME					
Overall Metabolic Syndrome**	36.0% (50/139)	23.2% (29/125)	29.9% (79/264)	5.12 (1)	0.03
Abnormal Abdominal Circumference				2.53 (2)	0.29
>35 (in) in Females	33.8% (46/136)	24.8% (30/121)	29.6% (76/257)		
>40 (in) in Males	13.2% (18/136)	15.7% (19/121)	14.4% (37/257)		
Abnormal HDL Cholesterol				0.33 (2)	0.88
<40 (mg/dL) in Males	14.4% (20/139)	16.1% (20/124)	15.2% (40/263)		
<50 (mg/dL) in Females	20.1% (28/139)	17.7% (22/124)	19.0% (50/263)		
Abnormal Blood Glucose (>=100 mg/dl)	22.5% (31/138)	15.7% (19/121)	19.3% (50/259)	1.89 (1)	0.21
Abnormal Triglycerides (>=150 mg/dl)	33.8% (47/139)	27.2% (34/125)	30.7% (81/264)	1.35 (1)	0.29
Abnormal Blood Pressure (>=130 mmHg Systolic, >=85 mmHg Diastolic)	48.9% (67/137)	38.5% (47/122)	44.0% (114/259)	2.82 (1)	0.10
Obesity (BMI ≥ 30)	39.4% (54/137)	34.2% (42/123)	36.9% (96/260)	0.77 (1)	0.38
Stage II Obesity (BMI ≥ 35)	19.7% (27/137)	15.5% (19/123)	17.7% (46/260)	0.81 (1)	0.37
Body Weight (kg)	85.0±20.6 (137)	83.6±21.2 (123)	84.3±20.9 (260)	0.28 (1)	0.60
Body mass index (kg/m^2)	29.6±7.1 (137)	28.8±7.3 (123)	29.4±7.4 (260)	0.86 (1)	0.36

*Other includes Native American, Native Hawaiian, and subjects who checked ‘other’ or more than one race category

**P-value is calculated using Mann-Whitney Test.

CIRS=Cumulative Illness Rating Scale

Table 2

Multivariate Analysis of Baseline Medical Comorbidity

	Adjusted Mean Difference (StdErr): High vs. Low Comorbidity	Test Statistic (df)	P-value
Past Mood Episodes: Lifetime	35.61 (13.00)	7.50 (1)	0.007
Past Manic/Hypomanic Episodes: Lifetime	20.46 (6.80)	9.06 (1)	0.003
Past Depressive Episodes: Lifetime	10.70 (5.51)	3.77 (1)	0.055
Number of Psychotropic Medications	0.42 (0.17)	5.89 (1)	0.016
Number of Classes of Psychotropic Medications	0.27 (0.14)	4.01 (1)	0.046

* Mean difference adjusted for age, gender, bipolar subtype (I or II), alcohol abuse/dependence, and drug abuse/dependence

Table 3

Summary of Baseline Medical Comorbidity According to CIRS Scores

		Level of Severity					
		Absent		Mild		Moderate or more	
Baseline Comorbidity	**Total N**	**N**	**%**	**N**	**%**	**N**	**%**
Heart	264	234	88.6	17	6.4	13	4.9
Vascular	261	217	83.1	19	7.3	25	9.6
Haematopoietic	219	205	93.6	10	4.6	4	1.8
Respiratory (lungs, bronchi, trachea below the larynx)	264	193	73.1	53	20.1	18	6.8
Head and neck (eyes, ear, nose, throat, larynx)	264	226	85.6	31	11.7	7	2.7
Upper GI (esophagus, stomach, duodenum, biliary and pancreas)	264	206	78.0	36	13.6	22	8.3
Lower GI (intestines, hernias)	264	235	89.0	23	8.7	6	2.3
Liver	263	253	96.2	9	3.4	1	0.4
Renal (kidneys only)	264	258	97.8	5	1.9	1	0.4
Genitourinary	264	219	83.0	32	12.1	13	4.9
Musculoskeletal/Integument	264	177	67.0	44	16.7	43	16.3
Neurological (brain, spinal cord, nerves)	264	201	76.1	39	14.8	24	9.1
Psychiatric illness (mental)	264	78	29.5	32	12.1	154	58.3
Endocrine/metabolic and breast (includes diffuse infections, poisoning)	264	198	75.0	41	15.5	25	9.5

Table 4

Summary of Medical History

Patient Characteristics	Overall Sample* (N=264)
Obesity	36.9% (96/260)
Migraines	24.5% (64/261)
Head Trauma with Loss of Consciousness	18.5% (48/260)
Hypertension	17.0% (45/264)
Hyperlipidemia	16.0% (42/262)
Asthma	14.4% (38/263)
Polycystic Ovarian Syndrome*	9.4% (14/149)
Thyroid Disease	6.5% (17/261)
Diabetes	5.7% (15/264)
Insulin Dependent	1.5% (4/264)
Oral Hypoglycemics	3.4% (9/264)
Diet Controlled	0.08% (2/264)
Hepatitis	4.2% (11/262)
Seizures	3.1% (8/258)
Cancer	2.7% (7/261)
Previous Myocardial Infarction	1.9% (5/264)
Coronary Artery Disease	1.1% (3/263)
Kidney Disease	1.1% (3/263)
Smoking cigarettes	
Never	46.6% (122/262)
Former Smoker	8.8% (23/262)
Current Smoker	44.7% (117/262)

*denominator includes women only

Table 5

Body Mass Index (BMI) by Gender and Bipolar Subtype

A. Bipolar I (N=212)

Gender	Underweight/Normal (BMI <25) N (%)	Overw eight BMI 25–29.9 N (%)	Obese BMI ≥ 30 N (%)
Male	27 (13)	42 (20)	27 (13)
Female	40 (19)	21 (10)	55 (26)

B. Bipolar II (N=67)

Gender	Underweight/Normal BMI <25 N (%)	Overweight BMI 25–29.9 N (%)	Obese BMI ≥30 N (%)
Male	5 (7)	9 (13)	11 (16)
Female	15 (22)	15 (22)	12 (18)