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Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome

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Abstract

Objective—The present study examined the relationship between medical burden in bipolar disorder and several indicators of illness severity and outcome. It was hypothesized that illnesses of the endocrine/metabolic system would be associated with greater psychiatric symptom burden and would impact the response to treatment with lithium and valproate.

Method—Data were analyzed from two studies evaluating lithium and valproate for rapid-cycling presentations of bipolar I and II disorder. General medical comorbidity was assessed by the Cumulative Illness Rating Scale (CIRS). Descriptive statistics and logistic regression analyses were conducted to explore the relationships between medical burden, body mass index (BMI), substance use disorder status, and depressive symptom severity.

Results—Of 225 patients enrolled, 41.8% had a recent substance use disorder, 50.7% were male, and 69.8% had bipolar I disorder. The mean age of the sample was 36.8 (SD = 10.8) years old. The mean number of comorbid medical disorders per patient was 2.5 (SD = 2.5), and the mean CIRS total score was 4.3 (SD = 3.1). A significant positive correlation was observed between baseline depression severity and the number of organ systems affected by medical illness ($p = 0.04$). Illnesses of the endocrine/metabolic system were inversely correlated with remission from depressive symptoms ($p = 0.02$), and obesity was specifically associated with poorer treatment outcome. For every 1-unit increase in BMI, the likelihood of response decreased by 7.5% [odds ratio (OR) = 0.93, 95% confidence interval (CI): 0.87–0.99; $p = 0.02$] and the likelihood of remission decreased by 7.3% (OR = 0.93, 95% CI: 0.87–0.99; $p = 0.03$). The effect of comorbid substance use on the likelihood of response differed significantly according to baseline BMI. The presence of a comorbid substance use disorder resulted in a lower odds of response, but only among patients with a BMI ≥ 23 ($p = 0.02$).

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Conclusion—Among patients with rapid-cycling bipolar disorder receiving lithium and valproate, endocrine/metabolic illnesses, including overweight and obesity, appear to be associated with greater depressive symptom severity and poorer treatment outcomes.

Keywords

endocrine; inflammation; insulin resistance; lithium; medical comorbidity; obesity; substance use disorders; treatment response; valproate

Psychiatric comorbidity is a prevailing hallmark of bipolar disorder. Over 97% of patients with bipolar I disorder meet criteria for a concurrent psychiatric illness, and the co-occurrence of three or more disorders is dramatically higher than comorbidity with only one disorder across the bipolar spectrum (1). General medical conditions also cluster heavily within bipolar populations (2-4) and result in an earlier and increased mortality from cardiovascular, respiratory, and endocrine causes (5). Of increasing concern, clinical and epidemiologic studies reveal more than half of bipolar disorder patients are either overweight or obese (6,7), a finding that appears independent of treatment with weight-promoting psychotropic medications (8).

A full one-third of patients with bipolar disorder also meet criteria for metabolic syndrome, a group of risk factors prominently associated with the development of heart disease, stroke, and type II diabetes (9). Among patients receiving atypical antipsychotics, metabolic syndrome is now recognized to occur at an equivalent rate in bipolar disorder as in schizophrenia (10). These cardiometabolic risk factors also appear to herald the presence of greater psychiatric symptom severity. For instance, attempted suicides are more common among patients with concurrent metabolic syndrome (9). Similarly, poorer treatment outcomes are more likely in the setting of generalized obesity (11). Not only do obese patients experience an increased lifetime number of depressive and manic episodes, but they also relapse more quickly following stabilization, primarily into depressive episodes (12).

Although metabolic-related illnesses may be associated with more complex illness presentations and greater severity of mood symptoms, there is incongruity as to the role comorbid medical conditions play in moderating or predicting treatment response. Some authors have found significant associations between the absolute number of comorbid medical illnesses and worsened bipolar outcomes (13,14), whereas others have identified no such relationships (15). Thompson and colleagues (16), studying patients with bipolar I or schizoaffective disorder, found the presence of a high number of baseline medical comorbidities to be associated with depressive episodes of greater severity and longer duration. Moreover, patients with greater baseline medical burden in that study improved more slowly throughout the course of treatment.

The most common medical illnesses afflicting patients with bipolar disorder include those of cardiovascular (e.g., hypertension) and endocrine/metabolic origin (e.g., obesity, hyperlipidemia, and type II diabetes) (2,3,17). Rather than simply representing a pharmacological side effect or the sequelae of a complex and unpredictable disorder, it is highly probable that the pathophysiology underlying bipolar disorder fosters the development of a variety of medical disorders (18). For instance, women with bipolar disorder store a greater proportion of fat in visceral or abdominal regions than obese controls (19). Visceral fat is metabolically active, secreting proinflammatory cytokines and other acute phase reactants that have been correlated with increased severity of depressive symptoms (20). Abnormalities in other metabolic-inflammatory networks suggest that biological mechanisms common to bipolar disorder and metabolic syndrome include abnormal glucocorticoid signaling, oxidative stress, autonomic dysregulation, and altered

energy biosynthesis (21). Thus, medical comorbidity may represent a core feature of bipolar disorder, rather than an incidental event or side effect of treatment (18).

The primary objective of this report was to evaluate the multifaceted relationship between medical comorbidity, indicators of mood disorder severity, and response to treatment with lithium and valproate. We hypothesized that illnesses of the endocrine/metabolic system would be associated with greater psychiatric symptom burden and would negatively influence acute treatment response. Our hypothesis was based on clinical experiences with bipolar patients and published literature relating obesity to an increased risk for bipolar disorder, attempted suicide, and earlier relapses. Given that prior studies of medical comorbidity in bipolar populations have generally excluded (2,16) or focused entirely on patients with substance use disorders (SUDs) (17), a secondary objective was to compare the burden of medical comorbidity among two cohorts with rapid-cycling bipolar disorder differing only in a recent history of an alcohol or drug use disorder.

Methods

The data for this report were taken from two studies evaluating the open-label use of lithium and valproate for rapid-cycling presentations of bipolar disorder (www.clinicaltrials.gov; NCT00221975 and NCT00063362). Patients 16 to 65 years of age were eligible for participation. The studies were divided into an acute stabilization phase lasting up to 24 weeks and a randomized, double-blind treatment phase lasting up to 12 weeks. The primary objective during the acute stabilization phase was to prospectively establish response to the combination of lithium and valproate at minimum therapeutic levels of ≥ 0.5 mEq/L and ≥ 50 μ g/mL, respectively. Nonresponders were subsequently randomized to receive double-blind lamotrigine or placebo in combination with lithium and valproate. The data for the present analysis were derived solely from the open-label stabilization phase. These studies were conducted at the Mood Disorders Program of the University Hospitals Case Medical Center from 2001 to 2007. The affiliated institutional review board approved all recruitment, assessment, and treatment procedures. All subjects provided written informed consent prior to participation.

Subjects met DSM-IV criteria for rapid-cycling bipolar disorder type I or II as ascertained by extensive clinical interview and the Mini-International Neuropsychiatric Interview (MINI) (22), performed by a research psychiatrist and research assistant, respectively. For the diagnosis of SUD, the Structured Clinical Interview for the DSM-IV, Patient Edition (23) was used instead of the MINI. A recent comorbid SUD diagnosis was made if patients met criteria for substance dependence and continued to meet abuse or dependence criteria for a substance(s) in the six months preceding the initial assessment or if they met criteria for substance abuse and continued to abuse a substance(s) in the last three months. During the initial assessment, a significant other was required to be present in order to collect collateral information to either support or refute the psychiatric diagnoses. Subjects were required to be experiencing an episode of major depression at the screening or baseline visit. Patients were excluded if they met criteria for a clinically significant neurological disorder (e.g., structural brain damage from trauma, demyelinating, or progressive degenerative disorder), had had previous treatment with an adequate trial of lamotrigine, currently used exogenous steroids, required anticoagulant drug therapy, were pregnant or planning to become pregnant, or were actively suicidal. At each study visit, an independent evaluator assessed patient clinical status via the Montgomery-Åsberg Rating Scale (MADRS) (24), Young Mania Rating Scale (YMRS) (25), and Global Assessment of Functioning (GAF) Scale (26). Bimodal response was achieved upon simultaneously meeting the following *a priori* criteria for four consecutive weeks: (i) MADRS score ≤ 19 ; (ii) YMRS score ≤ 13 ; (iii) GAF ≥ 51 ; (iv) lithium level ≥ 0.5 mEq/L; and (v) valproate level ≥ 50 μ g/mL.

Antidepressant response was defined as experiencing a 50% decrease from baseline to endpoint in the overall MADRS score, while remission of depression was defined as a MADRS total score ≤ 10 at conclusion of the stabilization phase.

Prior to study entry, all patients underwent baseline medical histories and thorough physical examinations by a physician. Baseline laboratory evaluations included complete blood count, electrolytes, thyroid indices, and liver function tests. A study psychiatrist (DEK) and psychiatric research assistant reviewed the blinded charts of each patient enrolled in the trial and independently generated a score on the Cumulative Illness Rating Scale (CIRS) (27). Any differences in CIRS ratings were discussed among the authors in order to reach a consensus.

Prior studies have confirmed criterion validity (28), inter-rater reliability (29), and construct validity (30) for the CIRS, which served as the primary instrument to evaluate medical comorbidity burden (27). A standardized algorithm for scoring the CIRS was utilized in this report (31). In summary, the severity of medical illnesses on 13 different organ systems was rated from 0 to 4, with a higher score indicating a higher level of physical comorbidity. 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'. CIRS-derived summary measures are not only useful for summarizing illness burden, but also appear capable of predicting mortality and rehospitalization rates (32,33)

Statistical analysis

Comparisons between the patients with and without recent SUDs were examined with respect to socio-demographic and illness characteristics using *t*-tests for continuous variables and χ^2 tests for categorical variables. The strength and direction between medical comorbidity and depression severity were examined utilizing the Spearman rank correlation coefficient. All reported *p*-values are for two-tailed tests of significance. Given the exploratory nature of the analysis, no adjustments were made for multiple comparisons.

A logistic regression model was fitted to examine the relationship between body mass index (BMI) and response or remission status. The statistical interaction of BMI and SUD status was assessed by including a cross-product term in our models and assessing significance using the Wald test. A stepwise logistic regression model was also fitted to examine the relationship between a low (CIRS ≤ 3) or high (CIRS ≥ 4) burden of general medical comorbidity and a variety of demographic and clinical characteristics.

Results

Medical comorbidity in relation to symptom severity and treatment response

Of the combined sample of 225 patients with and without a recent SUD, 50.7% were male, 69.8% had bipolar I disorder, and 75.1% had a lifetime comorbid anxiety disorder. Their mean age was 36.8 (SD = 10.8) years. The mean number of baseline medical comorbidities per patient was 2.5 (SD = 2.5). The mean CIRS total score was 4.3 (SD = 3.1), and the mean number of organ systems affected was 3.1 (SD = 2.0). The rates of bimodal response to the combination of lithium and valproate by CIRS total score among subjects with and without a comorbid SUD are reported in Table 1. A total of 47% of patients had a moderate burden of medical comorbidity (CIRS total score 4-8), whereas 8% of patients had a severe burden (CIRS score ≥ 9).

A correlation matrix was used to examine the relationship between medical comorbidity and depression severity. A significant positive correlation was observed between baseline depression severity and the number of organ systems affected by medical illness. The Spearman correlation coefficient for the baseline MADRS score and number of affected organ systems was $r = 0.14$ ($p = 0.04$). Increasing medical burden was significantly correlated with higher MADRS scores after treatment with lithium and valproate ($r = 0.15$; $p = 0.03$). Of all organ systems, only the Spearman correlation coefficient for the endocrine/metabolic system was significantly correlated with remission status ($r = -0.16$, $p = 0.02$).

BMI and response or remission status

Concerning the relationship between body weight and depression, BMI was found to be a significant predictor of nonresponse and nonremission to combined treatment with lithium and valproate. For every 1-unit increase in BMI, the likelihood of responding decreased by 7.5% [odds ratio (OR) = 0.93, 95% confidence interval (CI): 0.87–0.99; $p = 0.02$] and the likelihood of remitting decreased by 7.3% (OR = 0.93, 95% CI: 0.87–0.99; $p = 0.03$). Obesity, but not overweight, was a significant negative predictor of remission as measured by the MADRS total score ($p = 0.03$). The likelihood of attaining remission was 64.8% less likely for an obese individual compared to those in all other weight categories (OR = 0.35, 95% CI: 0.14–0.89).

The effect of SUD status on the likelihood of achieving response differed significantly according to baseline BMI. Patients with an SUD and BMI < 23 had a greater probability of response than subjects without an SUD. However, subjects with an SUD and BMI ≥ 23 had a lower probability of response than subjects without an SUD (p for interaction = 0.02).

Clinical predictors of high medical comorbidity burden

Next, we report results of the logistic regression for predicting a high burden of general medical comorbidity. Estimates of the parameters given here are for variables that remained in the model after a stepwise selection procedure. For this regression analysis, the sample was limited to 174 of the 225 patients who had no missing information available on all of the candidate variables. Age at study entry (OR = 1.04, 95% CI: 1.01–1.07, $p = 0.01$), BMI (OR = 1.05, 95% CI: 1.01–1.10, $p = 0.03$), and a diagnosis of substance dependence (OR = 2.06, 95% CI: 1.07–3.97, $p = 0.03$) were significant predictors of high medical comorbidity burden. A diagnosis of substance abuse, number of psychiatric hospitalizations, bipolar subtype, anxiety disorder comorbidity, and a history of sexual abuse were considered as candidate variables but were not significant in this sample after inclusion of the other variables.

Relationship between medical comorbidity and SUD status

Table 2 presents a summary of patient demographic, clinical, and medical comorbidity measures stratified by SUD status. Patients with co-occurring recent SUDs were more likely to be male ($\chi^2 = 5.13$, $df = 1$, $p = 0.02$), diagnosed with bipolar I disorder ($\chi^2 = 11.3$, $df = 1$, $p < 0.001$), have a history of psychosis ($\chi^2 = 3.9$, $df = 1$, $p = 0.05$), have experienced a manic/hypomanic/mixed episode over the 12 months prior to study entry (t -value = -2.31, $p = 0.02$), and to lack health care coverage ($\chi^2 = 22.9$, $df = 5$, $p < 0.001$). There was no significant difference in the mean CIRS total score, number of organ systems affected by medical illness, or overall number of baseline medical illnesses between the cohorts with and without co-occurring SUDs.

Although BMI was lower among patients with a co-occurring SUD [mean = 27.1 (SD = 6.9)] compared to those without [mean = 30.2 (SD = 7.2)], the proportion of patients with a moderate or severe burden of medical comorbidity was found to be similar between the

cohorts with and without an SUD ($p = \text{NS}$). Similarly, patients with a low CIRS score were as likely to achieve bimodal response as those with a moderate or high CIRS score, regardless of SUD status ($p = \text{NS}$).

Discussion

Patients with bipolar disorder have a higher prevalence of obesity (7), metabolic syndrome (9), and diabetes (34) than individuals in the general population. Likewise, the rate of comorbid lifetime drug or alcohol use disorders is higher in bipolar disorder than in any other psychiatric illness (35). Despite the commonality of these co-occurring conditions, little is known about their ability to impact treatment outcomes. This study therefore examined whether medical comorbidity burden was associated with baseline symptom severity and treatment outcome among a diverse group of patients with bipolar disorder who were receiving combination treatment with lithium and valproate.

One of the key findings from this report is evidence for a significant association between medical burden and the severity of mood symptoms in bipolar disorder. Not only were the number of affected organ systems and baseline depression severity significantly correlated, but over a period of up to 24 weeks higher medical burden was associated with less improvement in measures of depression symptom severity.

Contrary to our hypothesis, we did not find lower rates of bimodal response among patients with a moderate or severe burden of comorbid medical problems. The NS finding may reflect limited power to detect differences across various thresholds of medical comorbidity, as only 36.4% ($n = 82$) demonstrated a bimodal response to lithium and valproate. The low rate of treatment responders may be secondary to the definition of bimodal response used in this study, where patients were required to maintain a MADRS score ≤ 19 and YMRS score ≤ 13 in addition to therapeutic blood levels of lithium and valproate over four consecutive weeks.

Although the burden of comorbid medical problems and number of organ systems affected by medical illnesses was similar across the two cohorts, the average BMI was lower among patients with a comorbid SUD. This finding is consistent with the results of large epidemiologic studies of psychiatric disorders in general (36) and bipolar disorder in particular (37), in which overweight or obesity was found to be associated with a significantly lower risk of having an SUD. It has been suggested that the observed inverse relationship between overweight/obesity and SUDs may be attributed to competition for analogous reward-motivation neural networks (37).

The results of the logistic regression model, however, indicated that patients with a recent diagnosis of substance dependence were more than twice as likely as those without an SUD to experience a high burden of comorbid medical problems (i.e., CIRS score ≥ 4). In contrast, a diagnosis of substance abuse was not retained in the model, suggesting that greater severity of alcohol or drug use may be necessary to detect an association with increased medical burden. Given that neurobiological changes occur during the transition from abuse to dependence, it appears warranted that future studies of medical comorbidity in bipolar disorder examine outcomes for substance abuse and dependence independently (38).

In prior studies of patients diagnosed with unipolar major depressive disorder, response and remission status to fluoxetine treatment were significantly related to the burden of comorbid medical illness (39), revealing a significant negative impact of medical comorbidity on acute depression outcomes. Our preliminary findings extend this association to patients with rapid-cycling bipolar disorder, although the magnitude of the association was not as robust as in major depression. The results also complement our previous analysis that found over

half of patients with concurrent SUDs to have medical illnesses affecting four or more different organ systems (17). In that study, which comprised an entirely different group of subjects with comorbid SUDs, high medical burden was strongly predicted by the bipolar I subtype, a history of attempted suicide, a history of physical abuse, and advancing age (17). Unlike the present report, no associations were identified between medical burden and mood disorder severity or response to mood-stabilizer treatment.

Our results suggest that metabolic disorders in general and body weight in particular may negatively affect treatment response during the depressive phase of bipolar illness. An elevated BMI has previously been identified as a risk factor for early relapse and is associated with a chronic course and longer duration of bipolar illness (12,40). Although others have found that patients who achieve complete remission to lithium have lower BMIs than nonremitters (40), to our knowledge this is the first study to show an incremental decrease in the rates of response and remission for every unit increase in BMI among patients receiving combination treatment with lithium and valproate. However, BMI is limited by reflecting only generalized obesity. Because abdominal obesity is one of the most commonly observed parameters of metabolic syndrome in bipolar disorder and is a much stronger predictor of insulin resistance than overall obesity, future studies should also examine the role of adiposity distribution in predicting treatment response.

Careful attention to the effects of medical comorbidity on symptom improvement can be a pathway toward developing more personalized treatments for bipolar disorder. By assessing individual patterns of response in subgroups with obesity or other metabolic disorders, a large (or small) treatment effect might be discovered that becomes obscured when only examining overall group means (41). Future research examining the role of medical comorbidity as a moderator of treatment outcome will require prospective, longitudinal studies that stratify patients by severity of medical illness burden or by the presence or absence of a metabolic disorder. The information from such a study would be valuable to not only identify predictors of treatment response/nonresponse, but would improve our understanding of the medical needs that remain unaddressed in this population. This will bring us closer to the ultimate goal of tailoring clinical practice to meet the needs of each individual.

Overlapping pathophysiology of bipolar disorder and medical illnesses

Several overlapping mechanisms may act to sustain the relationships between medical burden and worsened outcomes in bipolar disorder. Alterations in the sleep cycles and circadian rhythms of bipolar patients have been repeatedly identified and are markers for mood fluctuations (42). In addition, a circadian phase delay may be one of several factors contributing to the high rate of obesity and obesity-related diseases in bipolar disorder, as patients with an evening chronotype have been found to have a higher percentage of body fat than patients with a morning chronotype (43). Another complication associated with obesity is obstructive sleep apnea, which is commonly diagnosed in patients with mood disorders and other psychiatric illnesses (44). Major depressive episodes and sleep apnea share common symptoms, including sleep disturbance, generalized fatigue, decreased volition, and impaired cognitive abilities. Upon receiving successful treatment for sleep apnea, comorbid depressive symptoms have been shown to improve (45).

To partially explain the higher rate of medical comorbidity and earlier mortality in bipolar disorder, the concept of allostatic load has been purported (46). Allostatic load represents the cumulative physiologic toll that is required when adapting to recurrent and chronic stress. These adaptations lead to several physiologic abnormalities, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, altered immunity, activation of pro-

inflammatory pathways, and a rise in oxidative stress. These alterations in allostatic load may leave patients with bipolar disorder more vulnerable to a variety of illnesses.

To more effectively manage medical and psychiatric illnesses in patients with bipolar disorder, the establishment of integrated care programs may be necessary. Such programs typically make use of certified nurse practitioners who provide first-line medical care within the psychiatric outpatient setting and help coordinate care between psychiatrists, primary care physicians, and other medical specialists. A recently completed pilot study evaluating the integrated care model found that over the course of one year, the rate of both psychiatric and medical hospitalizations was reduced in the integrated care sample as compared with patients receiving routine psychiatric care (47). Other studies have shown that in comparison with usual care, patients receiving integrated or collaborative care for major depressive episodes are about twice as likely to experience an antidepressant response (48,49). By emphasizing self-management skills and the coordination of care across different providers and healthcare systems, integrated care models may represent an important means of enhancing care for individuals with comorbid medical and psychiatric disorders and slow the decline in their health-related quality of life (50).

The results of this study also raise interesting theories about whether medications directed at aberrant metabolic and insulin signaling pathways may represent novel treatment opportunities for relieving depression. Animal models indicate that insulin plays an important role in regulating dopamine systems, including dopamine clearance and the function of dopamine transporters (51,52). Several plausible biological mechanisms support the rationale for studying metabolic treatments in mood disorders. Glucose-lowering agents have the potential to reduce insulin resistance and relieve stress on the HPA axis, reduce the release of immunoinflammatory cytokines, combat oxidative stress, and mitigate autonomic nervous system dysfunction. Clinical trials of an intranasal formulation of insulin to improve cognition in bipolar disorder (53) and of the insulin-sensitizer pioglitazone to treat depressive symptoms are currently ongoing (54). Insulin signaling pathways, through its unique regulation of brain dopamine, may be a future target for the treatment of mood symptoms in patients with co-occurring obesity and related cardiometabolic disorders.

Limitations and strengths

We recognize that there are several limitations to the present report. First, the analysis was performed *post hoc* on two clinical trials that were neither originally designed nor powered to detect differences in the rates of medical comorbidity. Adjustments were not made for multiple comparisons; thus, the results should be viewed as preliminary in the spirit of hypothesis generation. Second, this study examined outcomes in patients with rapid-cycling bipolar disorder who were treated solely with the combination of lithium and valproate. The homogeneity of treatments does not permit extrapolation to patients taking other medications, including atypical antipsychotic drugs that are known to contribute to weight gain and metabolic dysregulation. Third, patients demonstrated insufficient manic/hypomanic symptom severity, precluding determination of whether these relationships are similar during states of depression and mania. Fourth, the direction of the association between medical burden and illness severity is uncertain. It is unclear whether depression led to the development of metabolic illnesses because of negative health behaviors or whether the metabolic milieu facilitated the development and maintenance of mood symptoms, although these relationships are most likely reciprocal. Fifth, data were not available regarding exercise, dietary, or nutritional habits that may have mediated the observed outcomes. Finally, inflammatory markers were not collected during this study, which have previously been shown to explain the increased rate of depressive symptoms in patients with metabolic syndrome (55).

This report is also characterized by several strengths, including a number of design features that make the results more generalizable to real-world populations with bipolar disorder. The sample enrolled subjects with bipolar I and II disorder, classified subjects into separate cohorts by SUD status, and did not exclude patients with comorbid medical illnesses or those taking concomitant medications, with the exception of excluding subjects with a serious neurological disorder or those taking steroids or anticoagulants. The duration of acute treatment was longer than most clinical trials of bipolar disorder, lasting up to 24 weeks. The extended duration of observation ensured that patients met a stable definition of bimodal response and allowed collection of data at multiple time points using a prospective, longitudinal design. In addition, the MADRS was employed as the primary outcome measure instead of the Hamilton Depression Rating Scale, to avoid capturing aspects of medical illnesses (i.e., fatigue or somatic anxiety) as symptoms of depression, which could have falsely elevated the actual depression score.

Conclusion

In conclusion, in this large group of individuals with bipolar disorder taking lithium and valproate, several aspects of medical burden were positively correlated with increased severity of depressive symptoms and negatively correlated with measures of illness improvement. Additionally, a diagnosis of substance dependence significantly predicted a high burden of underlying medical problems. Clinicians should be mindful of the potential moderating effect of comorbid medical illnesses on treatment outcomes, particularly those disorders affecting the endocrine/metabolic system. Future clinical trials should analyze outcomes separately for obese and medically burdened patients in order to provide insight into the factors that may contribute to pharmacological nonresponse.

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Table 1

Rates of bimodal response by Cumulative Illness Rating Scale (CIRS) total score and substance use disorder (SUD) status

CIRS total score	Patients with score		Patients meeting bimodal response criteria	
	SUD absent (n = 131)	SUD present (n = 94)	SUD absent (n = 46)	SUD present (n = 36)
0	12 (9.2)	3 (3.2)	2 (4.3)	1 (2.8)
1	14 (10.7)	10 (10.6)	5 (10.9)	5 (13.9)
2	19 (14.5)	15 (16.0)	4 (8.7)	5 (13.9)
3	16 (12.2)	11 (11.7)	6 (13.0)	4 (11.1)
4	13 (9.9)	20 (21.3)	5 (10.9)	6 (16.7)
5	16 (12.2)	11 (11.7)	4 (8.7)	4 (11.1)
6	16 (12.2)	8 (8.5)	10 (21.7)	2 (5.6)
7	4 (3.1)	3 (3.2)	2 (4.3)	1 (2.8)
8	10 (7.6)	5 (5.3)	3 (6.5)	2 (5.6)
9	3 (2.3)	5 (5.3)	1 (2.2)	3 (8.3)
10	0 (0)	2 (2.1)	0 (0)	2 (5.6)
11	2 (1.5)	0 (0)	1 (2.2)	0 (0)
13	2 (1.5)	1 (1.1)	0 (0)	1 (2.8)
14	2 (1.5)	0 (0)	1 (2.2)	0 (0)
15	1 (0.8)	0 (0)	1 (2.2)	0 (0)
19	1 (0.8)	0 (0)	1 (2.2)	0 (0)

Values are indicated as n (%).

Table 2

Illness characteristics of subjects with rapid-cycling bipolar disorder by substance use disorder (SUD) status

Characteristic	Comorbid SUD absent (n = 131) n (%)	Comorbid SUD present (n = 94) n (%)	Statistic (χ^2)	p-value
Gender, male	58 (44.3)	56 (59.6)	5.13	0.02
Bipolar subtype I	80 (61.1)	77 (81.9)	11.28	< 0.001
History of physical abuse	37 (28.2)	34 (36.2)	0.88	0.35
History of sexual abuse	28 (21.4)	22 (23.4)	0.01	0.92
History of verbal abuse	55 (42.0)	42 (44.7)	0.47	0.49
History of psychosis	48 (36.6)	47 (50.0)	3.92	0.05
History of GAD	90 (68.7)	55 (58.5)	2.48	0.12
History of panic disorder	55 (42.0)	45 (47.9)	0.77	0.38
History of OCD	16 (12.2)	11 (11.7)	0.91	0.91
Lack of health care coverage	42 (32.1)	56 (59.6)	22.85	< 0.001
	Mean (SD)	Mean (SD)	Statistic (t-value)	p-value
Age	38.0 (11.3)	35.2 (9.9)	1.92	0.06
Age of first depression	13.4 (6.5)	12.3 (5.4)	1.26	0.20
Age of first mania	17.1 (8.1)	15.3 (7.4)	1.72	0.09
Mood episodes over past 12 months	13.1 (9.5)	15.9 (12.0)	-1.79	0.08
Manic episodes over past 12 months	6.2 (3.7)	7.8 (5.7)	-2.31	0.02
Depressive episodes over past 12 months	6.9 (7.2)	8.1 (7.0)	-1.18	0.24
Body mass index	30.2 (7.2)	27.1 (6.9)	3.17	0.002
CIRS total score	4.4 (3.5)	4.2 (2.6)	0.43	0.67
No. organ systems affected on CIRS	3.0 (2.1)	3.3 (1.8)	-1.12	0.26
No. active medical illnesses	2.6 (2.8)	2.5 (2.0)	0.47	0.66

GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder.