Prevalence and Clinical Correlates of Medical Comorbidities in Patients With Bipolar I Disorder: Analysis of Acute-Phase Data From a Randomized Controlled Trial

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Objective: We studied the relationship between number of medical comorbidities in patients with bipolar I disorder and their demographic and clinical characteristics.

Method: Data were from 174 patients in the acute phase of the Pittsburgh Maintenance Therapies in Bipolar Disorder (MTBD) study, a randomized controlled trial comparing Interpersonal and Social Rhythm Therapy to an intensive clinical management approach for individuals with a lifetime diagnosis of bipolar I disorder or schizoaffective disorder, manic type, according to Research Diagnostic Criteria, who were receiving adjunctive protocol-driven pharmacotherapy. Patients entered the MTBD study from 1991 to 2000. We examined the acute-phase Hamilton Rating Scale for Depression (HAM-D) and Bech-Rafaelsen Mania Scale scores, demographics, clinical history, and medical comorbidities.

Results: Patients with a high number of medical comorbidities had longer duration of both lifetime depression ($p = .02$) and lifetime inpatient depression treatment ($p = .04$), had higher baseline HAM-D score ($p = .01$), and were more likely to be treated for a depressed clinical state during the acute phase of the MTBD study ($p = .05$). Moreover, higher severity of baseline medical comorbidities predicted slower decreases in HAM-D score among depressed ($p = .004$) and mixed/cycling ($p = .003$) patients even after controlling for baseline HAM-D score.

Conclusions: Medical illness is correlated with several indicators of poorer prognosis and outcome in bipolar I disorder. Not only do preventing and treating medical comorbidities in bipolar patients decrease the morbidity and mortality related to physical illness, but they could also enhance psychological well-being and possibly improve the course of bipolar illness. Identification of characteristics in bipolar I patients that are correlated to increased risk for medical comorbidities is a fundamental step in understanding the nature of the relationship between bipolar disorder and medical illness.

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A growing body of evidence indicates that medical illness is common in individuals with serious mental illness and increases the morbidity and mortality in this population. Many medical problems have been cited in the few reports focused on patients with bipolar disorder. For instance, several investigations with retrospective follow-up have pointed to a greater mortality from cardiovascular and respiratory causes in individuals with bipolar disorder compared with the general population.[1,2] In a prospective follow-up of patients followed for at least 22 years, Angst et al.[3] confirmed an increased risk of death from cardiovascular and cerebrovascular disorders as well as from accidents and intoxication as compared with nonbipolar depressed patients. Cassidy et al.[4] found the prevalence of diabetes among individuals with bipolar disorder was 3 times higher than in the general population. Furthermore, those bipolar patients with comorbid diabetes had a greater number of lifetime psychiatric hospitalizations than did the nondiabetic subjects.

We[5,6] recently evaluated the presence of obesity in a population of 175 patients with bipolar I disorder and found significant differences between obese and nonobese patients for numbers of previous depressive and manic episodes, baseline depression scores, and duration of the acute episode prior to study entry. Additionally, Kaplan-

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Meier survival analysis indicated significantly shorter time to recurrence among obese patients.

This report evaluates the full spectrum of comorbid medical conditions present at baseline (entry into the acute phase of the study) among a group of 174 patients with bipolar I disorder who were treated in the Maintenance Therapies in Bipolar Disorder (MTBD) study. We examined the relationship between medical comorbidities and demographic characteristics and clinical features of the psychiatric disorder, such as lifetime history of bipolar episodes and type of index episode.

METHOD

Maintenance Therapies in Bipolar Disorder Study

The data for this report were taken from the Maintenance Therapies in Bipolar Disorder (MTBD) study, a randomized controlled trial comparing Interpersonal and Social Rhythm Therapy to an intensive clinical management approach. The MTBD protocol is described in detail elsewhere.[5–8] The MTBD study was divided into an acute treatment phase and a maintenance treatment phase; the data included in the present report are from the acute phase. Study participants were individuals between 18 and 60 years of age with a lifetime diagnosis of bipolar I disorder or schizoaffective disorder, manic type, according to Research Diagnostic Criteria,[9] and in their third or greater lifetime affective episode. The index episode was required to meet minimum severity criteria: 17-item Hamilton Rating Scale for Depression (HAM-D)[10] score ≥ 15, if depressed, or Bech-Rafaelsen Mania Scale (BRMS)[11] score ≥ 15, if manic or mixed. Exclusion criteria included current rapid cycling (> 4 episodes per year); chronic drug or alcohol abuse; pregnancy; active life-threatening medical illness (e.g., late-stage cancer, current acute myocardial infarction); active and severe neurologic disorders (e.g., grand mal seizures); absolute contraindications to the use of lithium, divalproex, and carbamazepine; or meeting full criteria for borderline or antisocial personality, active bulimia, or anorexia. No other Axis I or II disorder constituted an exclusion.

The MTBD study attempted to stabilize the maximum number of patients possible with lithium monotherapy. Patients who could not tolerate lithium received valproic acid or carbamazepine. Patients with major depression whose illness did not stabilize with lithium alone received adjunctive tranylcypromine, or, if they were unwilling to take a monoamine oxidase inhibitor (MAOI), they received paroxetine or another antidepressant. Patients with manic or psychotic symptoms whose condition did not stabilize with lithium alone received an adjunctive neuroleptic. Table 1 presents detailed psychotropic medication data for 174 patients who entered the MTBD study from 1991 to 2000.

Table 1. Medication Data for 174 Patients in the Acute Phase of the MTBD Study Who Entered the MTBD Protocol Between 1991 and 2000

			Days Taking Medication at Study Entry	
Medication	N	%	Mean	SD
Lithium	165	94.9	209	132
SSRIs	46	26.4	122	96
Typical neuroleptics	77	44.3	115	110
Atypical neuroleptics	34	19.5	100	92
Valproic acid	44	25.3	134	97
Carbamazepine	11	6.3	136	112
Benzodiazepines or other hypnotics	71	40.8	105	119
MAOIs	35	20.1	104	93
Tricyclic antidepressants	22	12.6	107	83
Bupropion	13	7.5	97	92
Stimulants	2	1.1	44	25
Lamotrigine	1	0.6	122	
Topiramate	1	0.6	117	

Abbreviations: MAOI = monoamine oxidase inhibitor, MTBD = Maintenance Therapies in Bipolar Disorder, SSRI = selective serotonin reuptake inhibitor.

At each visit, an independent evaluator assessed patient clinical state via the BRMS and the 25-item HAM-D. The 25-item HAM-D is an adaptation of the 17-item HAM-D containing the original 17 items plus 8 additional items intended to assess reverse vegetative symptoms.[12] All MTBD participants also underwent baseline and annual complete medical histories, electrocardiograms (ECGs), and thorough physical examinations, performed at the University of Pittsburgh Division of Internal Medicine (Pittsburgh, Pa.) by a physician assistant supervised by an internist. Baseline and annual laboratory evaluations included complete blood count, differential and platelets, plasma electrolytes panel (sodium, potassium, chloride, total carbon dioxide, calcium), blood urea nitrogen, creatinine, creatinine clearance, alanine aminotransferase (ALT), aspartate aminotransferase (AST), thyroxine (T_4), triiodothyronine (T_3) uptake, free thyroxine index (FTI), thyroid-stimulating hormone (TSH), thyroid binding ratio, and serum pregnancy tests for women of childbearing age. When necessary, additional tests (e.g., ECG stress test, thyroid antibodies, etc.) were ordered by the physician assistant, the internist, or the patient's assigned psychiatrist.

For the purpose of this study, the medical comorbidities were established by the review of the ECG, laboratory history, and physical examination reports for each of the study subjects. Comorbidity severity was evaluated by a chart review using the Duke Severity of Illness checklist (DUSOI).[13] The DUSOI rating (from 0–100) reflects the patient burden caused by the medical condition on the day of the patient visit and during the preceding week. Although we excluded at intake those patients with active life-threatening disorders, active and severe neurologic

disorders (e.g., grand mal seizures), and disorders that contraindicated the use of lithium, divalproex, and carbamazepine (e.g., significant renal impairment concomitant to significant liver disease and/or to a history of severe adverse reactions to divalproex and carbamazepine), patients accepted into the study nevertheless had on average a substantive burden of comorbid medical conditions. In total, 10 subjects were excluded from the study due to severe comorbid medical conditions.

The University of Pittsburgh's biomedical institutional review board approved all recruitment, assessment, and treatment procedures. Individuals who met all inclusion and exclusion criteria provided written informed consent after receiving a complete description of the study and having an opportunity to ask questions.

Specific Methods of the Present Analysis

Of 175 patients who entered the MTBD study from 1991 to 2000, 174 had DUSOI comorbidity information available. This report focuses on the relationship between patient clinical characteristics and baseline medical comorbidities in these 174 patients. To lessen any impact from reporting bias, the analyses below employ only those conditions with a DUSOI score greater than zero; a score of zero indicates the condition is currently of negligible importance. For this report, conditions with DUSOI score greater than zero are called "active" comorbidities.

In the first set of analyses, patient characteristics were compared between 2 subgroups formed by dichotomizing the number of active baseline comorbidities into an indicator of low to moderate medical burden (0–3 comorbidities) or high medical burden (> 3 comorbidities). This dichotomization corresponds to a cutoff point at the 75th percentile of the number of active baseline comorbidities per patient. These initial comparisons were done through t tests and Wilcoxon tests on continuous data and χ^2 tests on contingency data. All p values reported are for 2-tailed tests of significance.

Second, a generalized linear regression model[14] was used to examine the relationship between patient demographic and clinical characteristics and number of active baseline comorbidities (dependent measure). Since number of active baseline comorbidities is a count variable, a Poisson regression was performed. In this Poisson regression model, a coefficient of 0.4 for a variable such as age results in a multiplicative factor of exp (0.4) = 1.50, or an increase of 50% in number of comorbidities per unit increase (in this case, a year) in age. This Poisson regression was limited to the 145 of the 174 patients who had information on total duration of lifetime bipolar episodes available. Variables were selected via a stepwise procedure using the Akaike information criterion.

Finally, linear mixed-effects models were fitted with the longitudinal 17-item HAM-D and BRMS in the acute phase as outcome measures. Baseline DUSOI score was included in the model as an explanatory variable and interacted with the time variable. Baseline HAM-D and BRMS scores were also included as explanatory variables to control for the effect of baseline severity of bipolar episode on longitudinal outcome measures. Separate models were fitted to patients diagnosed with depression, mixed/cycling, or mania in their index episode.

The R statistical computing language (version 1.9.0; Debian: http://packages.debian.org/stable/math/rbase) was used for all analyses.

Table 2. Comorbidities at Baseline (overall) and Comorbidities at Baseline With DUSOI Index Greater Than Zero (active), by Category, for 174 Patients With Bipolar I Disorder Who Entered the MTBD Study Between 1991 and 2000

Category	No. of Overall Comorbidities	No. of Active Comorbidities
Asthma/respiratory	75	41
Bones/joints/muscles	131	56
Cardiovascular	41	32
Diabetes	4	2
Gastrointestinal	97	59
Genitourinary	98	43
Head injury	22	0
Headache/migraine	46	42
Obesity[a]	58	58
Skin	35	23
Thyroid dysfunction	28	22
Other	93	43
Total	728	421

[a]The number 58 differs from a prior report[6] of 62 obese patients at baseline due to an increase of 4 patients with BMI > 30 from initial physical examination to first study visit.
Abbreviations: BMI = body mass index, DUSOI = Duke Severity of Illness checklist, MTBD = Maintenance Therapies in Bipolar Disorder.

RESULTS

Of the 174 patients in the sample, 43% were male, 36% were married, and 90% were white. Their mean age was 35.2 years. A total of 160 (92%) of the patients reported some type of comorbid medical condition at baseline. The mean number of overall baseline medical comorbidities reported per patient was 4.2 (median 4.0) with a maximum of 13. Of the 728 comorbidities reported at baseline, 421 (58%) were "active" in the sense that they had a DUSOI score greater than zero. A total of 141 (81%) of the patients had at least 1 active comorbidity at baseline. The mean number of active comorbidities per patient at baseline was 2.4 (median 2.0) with a maximum of 11. Table 2 presents a breakdown of the baseline comorbidities and active comorbidities, grouping them into 12 categories. Note that obesity was defined as body mass index (BMI) over 30.

Table 3 presents a summary of patient demographic and clinical characteristics by number of active baseline comorbidities dichotomized into low to moderate medical

Table 3. Baseline Differences in Patient Characteristics Between Those Patients With Few to a Moderate Number of Active Comorbidities at Baseline (0–3) and Those Patients With a High Number (> 3) for 174 Patients Entering the MTBD Protocol Between 1991 and 2000

	Few to Moderate			High					
Variable	Mean	SD	Median	Mean	SD	Median	t	df	p
Age, y	34.6	10.2	34.0	37.0	11.6	37.0	1.24	172	.22
Education, y	15.0	1.9	14.0	14.3	1.9	14.0	–2.06	172	.04
Duration of index episode, wk[a]	34.7	60.3	23.0	39.0	50.4	22.3	1.28	172	.20
Age at first manic episode, y	25.8	8.9	23.0	26.7	9.8	25.5	0.57	170	.57
No. of lifetime manic episodes[b]			3.0			3.0			.19[c]
Total duration of lifetime manic episodes, mo[a,d]	12.4	18.0	7.7	14.1	12.1	12.5	1.37	143	.17
No. of inpatient hospitalizations for manic episodes[a,b]	1.3	1.8	1.0	1.4	2.2	1.0	0.11	143	.91
Total lifetime duration of treatment for inpatient manic episodes, mo[a,d]	1.4	2.0	0.5	1.7	3.1	0.5	–0.13	143	.90
Age at first depressive episode, y	22.6	7.9	20.0	21.0	7.4	19.0	–1.16	161	.25
No. of lifetime depressive episodes[b]			4.0			5.0			.06[e]
Total duration of lifetime depressive episodes, mo[a,d]	28.0	29.2	16.5	34.2	23.3	26.5	2.37	143	.02
No. of inpatient hospitalizations for depressive episodes[a,d]	0.8	1.4	0.0	0.9	1.1	1.0	1.17	143	.24
Total lifetime duration of treatment for inpatient depressive episodes, mo[a,d]	0.8	1.4	0.0	1.5	2.6	0.4	2.07	143	.04
17-Item HAM-D score	14.7	7.8	16.0	18.2	5.8	17.0	2.63	172	.01
25-Item HAM-D score	18.6	10.2	21.0	23.2	7.7	23.2	2.70	172	.01
BRMS score[a]	11.8	12.9	5.0	7.2	10.3	2.0	–1.65	172	.10
GAF score	47.5	9.1	50.0	50.3	7.8	51.0	1.76	171	.08
Weeks to remission of acute episode	32.0	20.7	26.0	37.2	22.6	34.0	1.38	172	.17
	N	%		N	%		χ^2	df	p
Men	64	48.1		11	26.9		4.96	1	.03
Married	45	33.8		18	43.9		0.97	1	.32
White	120	90.2		37	90.2		0.08	1	.77
Predominant state during acute phase							5.97	2	.05
Manic	36	27.1		3	8.3				
Mixed or cycling	33	24.8		8	22.2				
Depressed	64	48.1		25	69.4				

[a]Natural log transformation performed before statistical comparison.
[b]Only median shown because some patients report "too many episodes to count."
[c]Nonparametric Wilcoxon test used instead of t test, U = 3071.
[d]Data on number of lifetime bipolar episodes limited to the 145 of the 174 patients with this information available.
[e]Nonparametric Wilcoxon test used instead of t test, U = 3213.
Abbreviations: BRMS = Bech-Rafaelsen Mania Scale, GAF = Global Assessment of Functioning scale, HAM-D = Hamilton Rating Scale for Depression, MTBD = Maintenance Therapies in Bipolar Disorder.

burden (0–3) and high medical burden (> 3). The group with a high number of active baseline comorbidities had significantly less education (t = –2.06, df = 172, p = .04), longer total duration of lifetime depressive episodes (t = 2.37, df = 143, p = .02), longer total duration of lifetime inpatient depressive episodes (t = 2.07, df = 143, p = .04), higher baseline score on the 17-item HAM-D (t = 2.63, df = 172, p = .01), higher baseline score on the 25-item HAM-D (t = 2.70, df = 172, p = .01), a larger proportion in a predominantly depressive state during acute phase (χ^2 = 5.97, df = 2, p = .05), and a higher proportion of females (χ^2 = 4.96, df = 1, p = .03). Additionally, the association between higher active comorbidities and number of lifetime depressive episodes (Wilcoxon test, U = 3213, p = .056) approached statistical significance.

Next, we report results of the Poisson regression on number of active baseline comorbidities. Estimates of parameters given here are for variables that remained in the model after the stepwise selection procedure. For this regression analysis, the sample was limited to the 145 of the 174 patients with information available on total duration of lifetime bipolar episodes. A regression analysis on the full sample of 174 patients, not detailed here, gave substantially similar results. Sex (reference value female) was a significant predictor, with men having on average only 76% as many active baseline comorbidities as women (p = .02). Age at which patients first experienced a depressive episode was a significant predictor; for each year of later onset of depression we observed a 2% decrease in number of active baseline comorbidities (p = .03). Conversely, for each year of later onset of mania we observed a 2% increase in number of active baseline comorbidities (p < .01). Thus, patients who experienced their first depressive episode earlier in life had more baseline comorbidities, whereas patients who experienced their first manic episode earlier in life had fewer baseline comorbidities on average. Additionally, each month of total duration of lifetime depressive episodes increased the number of active baseline comorbidities by 19% (p < .01), and

each month of total duration of lifetime inpatient depressive episodes resulted in an increase of 7% (p = .02) in the number of active baseline comorbidities. Though the information in these last 2 variables overlapped somewhat, both remain significant when included in the model. Note that patient age at entry to study was considered as a candidate variable but was not significant in this sample after inclusion of the other variables.

Finally, we report the results of the linear mixed-effects models. The dependent measures are 17-item HAM-D scores over the acute phase of treatment for the 3 patient groups (patients with index episode of depression, mixed/cycling, or mania), resulting in fitting 3 separate models. Hamilton Rating Scale for Depression scores decreased significantly over the course of the acute phase in depressed patients (–0.40 per week, p < .001), in mixed/cycling patients (–0.21 per week, p < .001), and in mania patients (–0.11 per week, p = .01). More interestingly, baseline DUSOI score had a significant positive interaction with longitudinal HAM-D scores in depressed (0.003, p = .004) and in mixed/cycling (0.002, p = .003) patients but not in mania patients (–0.001, p = .31). Thus, HAM-D scores decreased more slowly for depressed and mixed/cycling patients with more severe baseline comorbidities, even after controlling for baseline severity of depression. For example, HAM-D scores decreased by a mean of –0.21 per week for depressed patients with DUSOI score of 63 (75th percentile of baseline DUSOI scores) versus decreasing –0.4 per week for depressed patients with DUSOI score of zero. Similar analyses with BRMS scores as outcomes (not shown here) showed no significant interactions between baseline DUSOI and time, so that severity of baseline comorbidities had no appreciable effect on decreases in BRMS scores after controlling for baseline severity of mania.

DISCUSSION

The analyses presented in this report demonstrate that the number of medical comorbidities differs significantly between identifiable subgroups of bipolar I patients. For example, we found that patients with a high number (> 3) of active baseline comorbidities had a longer total duration of lifetime depressive episodes, longer total duration of lifetime inpatient depressive episodes, and higher baseline HAM-D scores and were more likely to be treated for depressed clinical state during the acute phase of the MTBD study. Moreover, even after controlling for baseline severity of depression, baseline severity of medical comorbidities (as measured by the patient DUSOI score) was predictive of slower decrease in HAM-D scores over the acute phase of treatment. These findings strongly suggest that depression and severity of medical comorbidities are closely linked in bipolar I patients and that bipolar I patients with more severe medical comorbidities in a depressed or mixed/cycling acute episode have worse prognoses, even after controlling for initial episode severity of depression.

These findings are in agreement with the results of our previous studies. For instance, we[5] have reported that the number of previous depressive episodes significantly contributed to the likelihood of being overweight or obese at study entry. We have also described a positive correlation between the baseline scores on the HAM-D and the amount of weight gain during the acute treatment phase, as well as a negative correlation with baseline scores on the BRMS and the amount of weight gain.

Medical illness could be influencing the outcome of bipolar disorder through several factors including its negative impact on quality of life, functioning, and psychological well-being. Medical comorbidities may also disrupt sleep and other circadian rhythms, thus causing or contributing to mood destabilization. Conversely, bipolar disorder, especially bipolar depression, may increase the risk of medical illness. The side effects associated with the use of mood stabilizers and antipsychotic medications may contribute to intensification of the medical burden in these patients. Also, during acute episodes, bipolar disorder may be accompanied by denial or misinterpretation of the signs of medical illness. Previous studies[15] have established the clear relationship between depression and a host of negative health behaviors including smoking, poor diet, overeating, and sedentary lifestyle. Moreover, it is important to note that social withdrawal is relatively common during the depressive phases of the illness and may contribute to a reluctance to use health care services.

We note possible limitations of the present report. First is the lack of data on adverse health habits, e.g., smoking, use of drugs and alcohol, and sedentary lifestyle. Second, the MTBD study entry exclusion criteria may have resulted in a sample different from the bipolar I population as a whole. For example, as noted in the Method section, 10 patients with truly severe medical burdens were excluded from entry. It seems plausible, however, that inclusion of these 10 patients would have provided even stronger evidence of a relationship between medical comorbidities and bipolar disorder outcomes. Third, some medical illnesses may disproportionately affect women in this age group, e.g., genitourinary complaints, hyperthyroidism, and migraines. Overall, men had fewer baseline comorbidities (76% of number reported by women). Fourth, in comparing subjects with differing levels of medical illness, it should be noted that some of the symptoms in the HAM-D may be capturing aspects of these medical illnesses (e.g., fatigue, somatic anxiety); thus, their depression scores may be elevated independently of actual depression. Fifth, we did not evaluate the relationships (and the directions of causality) between medical illnesses, severity of bipolar disorder, and use of medications such as the atypical antipsychotics that may contrib-

ute to several of the comorbidities measured in this study, i.e., obesity and type 1 diabetes. Sixth, that we did not find any statistically significant relationship between medical burden and mania does not necessarily mean such a relationship does not exist. In fact, the lack of statistical significance may be simply due to the fact that our sample did not include a large enough number of patients with illnesses that may be associated with mania, such as hyperthyroidism or Cushing syndrome.[16,17] Finally, and perhaps most important, the data presented here do not permit the unraveling of the cause and effect relationship questions that our data raise. Clearly, a prospective study on these aspects of the illness is warranted.

In summary, medical illness is correlated with several indicators of a poorer prognosis and outcome in bipolar I disorder. We have been singularly impressed with how medical burden influences the psychiatric outcomes in patients with bipolar disorder (as expressed in levels of functioning, extent of symptomatic remission, and degree of suicidality). Not only do preventing and treating medical comorbidities in bipolar patients decrease the morbidity and mortality related to physical illness, but they could also enhance psychological well-being and possibly improve the course of bipolar illness. We strongly support the development and testing of a model of care that includes interventions specifically designed for patients with bipolar disorder and that integrates medical treatment with the psychiatric treatment of individuals suffering from bipolar I disorder.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), paroxetine (Paxil, Pexeva, and others), topiramate (Topamax), tranylcypromine (Parnate), valproic acid (Depakene and others).

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