Published in final edited form as:

J Affect Disord. 2009 July ; 116(1-2): 64–69. doi:10.1016/j.jad.2008.11.011.

Medical and Substance Use Comorbidity in Bipolar Disorder

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Abstract

Objective—National Comorbidity Survey data indicate that bipolar disorder is characterized by high lifetime rates of co-occurring anxiety and substance use disorders (SUDs). Although compelling evidence suggests SUD comorbidity predicts non-response to treatment, the relationship between medical comorbidity and treatment response has not been studied adequately. In an attempt to understand the impact of medical comorbidity on treatment outcome, an analysis was conducted to inform the relationship between co-occurring medical illness, the phenomenology of bipolar disorder, and response to treatment with mood stabilizers.

Method—A total of 98 adult outpatients with rapid-cycling bipolar I or II disorder and co-occurring SUDs were prospectively treated with the combination of lithium and valproate for up to 24 weeks. A logistic regression analysis was conducted to explore the relationship between phenomenology, response to mood stabilizers, and medical comorbidity as assessed by the Cumulative Illness Rating Scale (CIRS). High and low medical comorbidity burden were defined as a CIRS total score ≥ 4 and ≤ 3 , respectively.

Results—Every patient enrolled into this study had at least 1 medical illness (most commonly respiratory, 72%) and on average had 4.9 different medical conditions. Over half of patients (52%) exhibited illnesses across four or more different organ systems, 24% had uncontrollable medical illnesses, and the mean overall total CIRS score was 5.56. The average body mass index (BMI) was 28.1 with 38% being overweight and 29% being obese. High medical burden was observed in 64% and was most strongly predicted by a diagnosis of bipolar I disorder (OR=34.9, $p=0.002$, 95%CI=3.9–316.1). A history of attempted suicide (OR=10.3, $p=0.01$, 95%CI=1.7–62.0), a history of physical abuse (OR=7.6, $p=0.03$, 95%CI=1.3–45.7) and advancing age (OR=1.2, $p<0.001$, 95%CI=1.1–1.3) also independently predicted a high burden of general medical problems. Only 21% (N=21) of subjects enrolled into this study showed a bimodal response to treatment with lithium plus valproate, and neither BMI nor any summary CIRS measure predicted response.

Conclusion—Rapid cycling with co-occurring substance use is not only associated with poor response to mood stabilizers, but is also a harbinger of serious medical problems. A high burden of medical comorbidity was associated with the bipolar I subtype, a history of attempted suicide, a history of physical abuse, and advancing age.

National Comorbidity Survey Replication data indicate that bipolar disorder is characterized by high lifetime rates of co-occurring anxiety and substance use disorders (SUDs) (Merikangas

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et al., 2007). Increasing evidence suggests that medical illnesses also frequently co-occur in bipolar disorder (Beyer et al., 2005; Kilbourne et al., 2004; Krishnan, 2005; McIntyre et al., 2006) and may contribute to an increase in premature mortality from natural causes of death (Osby et al., 2001). Although an increased prevalence of medical comorbidity affects nearly every organ system, the high rate of cardiometabolic conditions such as diabetes, cardiovascular disease, and dyslipidemia is particularly alarming (Angst et al., 2002; Kilbourne et al., 2007).

While several studies have assessed the impact of medical comorbidity on treatment response in unipolar depression (Iosifescu et al., 2003; Papakostas et al., 2003), a paucity of related investigations exist in bipolar disorder. Black and colleagues (1988) retrospectively identified that medically-ill hospitalized patients with bipolar disorder were more likely to be older, have an earlier age of onset, and experience a lower rate of recovery. Others have found the number of comorbid medical problems to predict baseline illness severity (Beyer et al., 2005) and for greater medical burden to predict slower improvement in depression (Thompson et al., 2006). During maintenance phase treatment, obese patients with bipolar disorder experience an earlier recurrence of new mood episodes, primarily toward the depressive pole (Fagioli et al., 2003).

To date, studies evaluating treatment response in relationship to general medical comorbidity in bipolar disorder have either excluded co-occurring drug or alcohol use disorders or did not report their presence. Yet, patients who abuse substances are at greater risk of developing medical complications (Adrian and Barry, 2003; Fan et al., in press; Salloum et al., 2004). When alcohol and drug use disorders co-occur, the odds of having multiple physical disorders increase by 3- to 8-fold (Salloum et al., 2004). Rapid cycling, a prognostic indicator of mood instability and treatment non-response (Calabrese et al., 2001), has also been associated with increased rates of diabetes and elevations in body mass index (BMI) (Hajek et al., 2008).

Given these observations, a post hoc exploratory analysis was undertaken to examine the interplay between co-occurring medical illness and treatment response in patients with rapid-cycling bipolar disorder and co-occurring SUDs. We specifically examined whether any clinical characteristics could differentiate those patients with a low versus high burden of medical comorbidity and assessed whether medical burden decreased the likelihood of response to treatment with lithium and valproate.

METHOD

Subjects and Procedures

A total of 98 evaluable patients between the ages of 17 and 62 were treated during the open phase of a clinical study in which they received combination therapy with lithium and valproate for up to 6 months (Kemp et al., in press). The study was divided into an acute stabilization phase and a maintenance treatment phase; the data included in the present report are solely from the acute phase. The primary objective of the acute stabilization phase was to prospectively establish bimodal response to combination treatment with lithium and valproate. This study was conducted at the Mood Disorders Program of University Hospitals Case Medical Center from 1997–2006. The affiliated institutional review board approved all recruitment, assessment, and treatment procedures. All subjects provided written informed consent prior to participation.

Patients were recruited from advertisements, private and public mental health centers, and from community-based medical practices. Subjects met *DSM-IV* criteria for rapid-cycling bipolar disorder type I or II as ascertained by Extensive Clinical Interview (ECI) and the Mini-International Neuropsychiatric Interview (MINI) performed by a research psychiatrist and

research assistant (Sheehan et al., 1998). For the diagnosis of SUDs, the Structured Clinical Interview for the DSM-IV, Patient Edition (SCID-P; First et al., 1997) was used instead of the MINI. The ECI consists of questions and criteria for the diagnosis of DSM-IV Axis I disorders, which is similar to the SCID-P, but also contains items to assess mental status, severity of suicidality, demographics, and other variables of interest. In addition, all subjects met *DSM-IV* criteria for abuse or dependence on alcohol, cannabis, and/or cocaine. Patients with substance dependence must have continued to meet abuse or dependence criteria for a substance(s) in the past 6 months of the initial assessment; those with a diagnosis of substance abuse had to demonstrate abuse of the substance(s) within the last 3 months.

Patients were required to have experienced a manic, hypomanic, or mixed episode within 3 months of study entry. Patients were excluded from study participation if they had previous intolerance to lithium or valproate, had alcohol-related liver disease, were pregnant or planning to become pregnant, were taking exogenous steroids, required anticoagulant drug therapy, or were actively suicidal.

At the screening visit, each subject underwent a physical examination. Baseline laboratory assessments included complete blood count, plasma electrolytes panel, alanine aminotransferase (ALT), aspartate aminotransferase, thyroxine, triiodothyronine uptake, thyroid-stimulating hormone, and urine pregnancy tests for women of childbearing age.

A study physician (D.E.K.) and psychiatric research assistant (E.C.) reviewed the blinded charts of each patient enrolled in the trial and independently generated a score on the Cumulative Illness Rating Scale (CIRS). Any differences in CIRS ratings were discussed amongst the authors in order to reach a consensus. The CIRS is a valid and reliable tool for measuring medical comorbidity (Linn et al., 1968). Criterion validity for the instrument is established by high correlation coefficients when comparing CIRS scores generated from retrospective chart reviews with those based on autopsy findings (Conwell et al., 1993). A standardized algorithm for scoring the CIRS was utilized in this report (Hudon et al., 2007). In brief, a score was generated ranging from 0 to 4 for each of 13 organ systems. Since the CIRS includes a category for psychiatric illness, this section was excluded for the purposes of the present analysis. 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'. In accordance with guidelines for using this instrument, the following four summary measures were calculated for each subject: number of categories endorsed, total score, severity index (total score ÷ number of categories endorsed), and the number of categories scored as 3.

At each study visit, an independent evaluator assessed patient clinical status via the HAMD-17, Young Mania Rating Scale (YMRS), and Global Assessment of Functioning Scale (GAF). Bimodal response was achieved upon simultaneously meeting the following a priori criteria for four consecutive weeks: (1) HAMD-17 score ≤ 20 ; (2) YMRS score ≤ 12.5 ; (3) GAF score ≥ 51 ; (4) lithium level ≥ 0.8 meq/L; and (5) valproate level ≥ 50 $\mu\text{g/ml}$. Antidepressant response was defined as experiencing a $\geq 50\%$ decrease from baseline to endpoint in the overall HAMD-17 score, while remission of depression was defined as a HAMD-17 total score ≤ 7 at conclusion of the stabilization phase.

Statistical Analysis

Comparisons with respect to demographic and historical variables were performed using t-tests for continuous variables and χ^2 or Fisher exact test for categorical variables, as appropriate. All reported p-values are for 2-tailed tests of significance.

A logistic regression model was fitted to examine the relationship between low (CIRS score 0–3) and high (CIRS score ≥ 4) medical comorbidity burden and a variety of demographic and clinical characteristics (Papakostas et al., 2003). Variables were selected via a stepwise procedure. Separate multiple logistic regression analyses were also conducted to test whether any of the four CIRS summary measures could predict bimodal response, antidepressant response, or remission from depression, after adjustment for patient age, gender, and baseline HAMD-17 total score. A generalized linear regression model was used to determine whether the CIRS total score could predict the percentage change in HAMD-17 total score at study endpoint.

RESULTS

Of 98 evaluable outpatients with rapid-cycling bipolar I or II disorder and concurrent SUDs, 62.2% (N=61) were male. The mean age of the sample was 39.4 (SD=7.6) years old. Twenty-one percent (N=21) of subjects receiving open-label lithium and valproate met criteria for bimodal response. Every patient enrolled into the study had at least 1 comorbid medical illness; the average number of medical illnesses per patient was 4.90 (SD=3.33). The mean number of organ systems affected was 3.82 (SD=1.75), with over half of patients (52% [N=51]) exhibiting illnesses across four or more different organ systems. Nearly one-fourth (24% [N=24]) of patients had illnesses scored as 3, indicating the presence of an uncontrollable chronic problem or a problem causing significant disability. No subject in this study received a score of 4. The mean total CIRS score for this population was 5.56 (SD=3.14). Participant characteristics and their distribution by burden of medical illness are presented in Table 1. Figure 1 shows the number of comorbid medical conditions to increase in proportion with advancing age. The prevalence of affected organ systems by category is presented in Table 2. Medical comorbidities affected the respiratory system most commonly (71.8% of clinical sample), followed by the musculoskeletal (55.5%) and neurologic (37.3%) systems.

The mean BMI of subjects was 28.13 (SD=6.08). The mean BMI of male patients (29.2 [SD=5.9]) was significantly higher than the BMI of females (26.6 [SD=5.5], $t=2.17$, $df=95$, $p=0.04$). BMI was abnormal in more than two-thirds of patients, with 38% (N=37) meeting criteria for being overweight (BMI ≥ 25) and 29% (N=28) meeting criteria for obesity (BMI ≥ 30). No significant difference in BMI was observed among responders or non-responders to the combination of lithium and valproate. The demographic and clinical characteristics of bipolar patients stratified by the magnitude of medical burden are displayed in Table 3. The majority of bipolar I, but not bipolar II, subjects suffered from a high medical burden (CIRS score ≥ 4).

Results of the logistic regression analysis identified five routinely collected clinical characteristics to differentiate low from high medical burden (Model $\chi^2=41.58$, $df=5$, $p<0.001$). A diagnosis of bipolar I disorder was the strongest predictor, increasing the likelihood of high medical burden by more than 34-fold (OR=34.9, $p=0.002$, 95% CI=3.9–316.1) compared to individuals with bipolar II disorder. Other predictors of a high burden of general medical conditions included a history of attempted suicide (OR=10.3, $p=0.01$, 95% CI 1.7–62.0), a history of physical abuse (OR= 7.6, $p=0.03$, 95% CI=1.3–45.7), and advancing age (OR=1.2, $p<0.001$, 95% CI 1.1–1.3). In contrast, a history of prior psychiatric hospitalization (odds ratio 0.68, $p=0.005$, 95% CI 0.52–0.89) was associated with a low burden of medical comorbidity. All independent predictors were fully adjusted for the other significant variables in the model. Age of first illness onset, the number of manic or depressive episodes in the past 12 months, a history of an anxiety disorder, and a history of sexual abuse showed no statistically significant relationship with the magnitude of medical burden.

None of the four summary CIRS measures were significant predictors of bimodal response. Likewise, the CIRS total score did not significantly predict the percentage change observed in HAMD-17 total score.

DISCUSSION

To our knowledge, this is the first report to associate greater medical comorbidity burden with bipolar I as compared with bipolar II disorder. Consistent with prior reports showing general medical illnesses to be highly prevalent in bipolar disorder, we found patients to have on average 4.9 medical conditions affecting 3.8 different organ systems. In fact, nearly two-thirds (64.3%) of patients exhibited a high burden of medical comorbidity (CIRS total score ≥ 4), suggesting that medical problems may be even more common in the setting of substance abuse and rapid cycling.

The most frequently affected organ category was the respiratory system, likely reflective of the large number of smokers in our sample (67% [N=66]). Consistent with guidelines for scoring the CIRS, individuals with a smoking history of up to 20-pack years are given a category 1 rating on the respiratory component item (Hudon et al., 2007). Abnormalities in body weight were also prevalent, with more than two-thirds satisfying criteria for overweight and obesity.

Severity of Medical Burden and Relationship to Treatment Response

In a clinical trial of fluoxetine for unipolar major depressive disorder, the mean CIRS score was 1.90 (SD=1.86) (Iosifescu et al., 2003). A similar CIRS score of 2.31 (SD=1.90) was found in a population with treatment resistant major depression (Papakostas et al., 2003). These values contrast with a mean CIRS score of 5.56 found in our sample (SD=3.14), suggesting that patients with bipolar disorder suffer from a substantial magnitude of general medical burden. This value is also higher than a CIRS total score of 4.7 (SD=2.9) found in geriatric patients with remitted depression (Alexopoulos et al., 2000), despite the mean age of our sample being almost 35 years younger (*ie.* mean age 39.4 vs. 73.6 years old). Soreca and colleagues (2008) have shown the CIRS total score to be 4.7 (SD=2.9) among bipolar patients without an active SUD. The exclusion of patients with active SUDs from that study may account for the lower overall CIRS scores compared with the present findings.

To our knowledge, no study has investigated the relationship between medical comorbidity and treatment response in a population with rapid-cycling accompanied by co-occurring alcohol and drug use disorders. Our results do not suggest that bimodal response to lithium and valproate are significantly related to the severity of baseline medical conditions, the number of organ systems affected by medical illness, or the percentage improvement on HAMD-17 scores. These findings differ from some (Evans et al., 1997; Keitner et al., 1991) but not all (Papakostas et al., 2003) studies of major depressive disorder, where medical illness has been linked to greater mood disorder chronicity, lower recovery rates, and higher relapse rates (Gilmer et al., 2005; Iosifescu et al., 2004; Iosifescu et al., 2003; Rudisch and Nemeroff, 2003). Although medical comorbidity was not found to be related to treatment response, it is notable that none of the 11 patients who exhibited a CIRS score ≥ 10 , (indicative of a severe degree of medical comorbidity) responded to treatment with lithium and valproate [Table 1].

Overlapping Pathophysiology between Bipolar Disorder, Substance Use, and General Medical Conditions

General medical conditions (*eg.* obesity) and SUDs appear subserved by related behavioral aberrations and pathophysiological abnormalities. Individuals with depression and substance dependence often neglect their general health, resulting in disrupted eating habits, nutrient absorption, and metabolism (McIntyre et al., 2007). Obesity is associated with the production

of pro-inflammatory cytokines that may induce sickness behaviors resembling depression (Dantzer, 2004). Another common pathophysiological mechanism linking bipolar disorder and medical comorbidity includes allostatic load, which represents the cumulative physiological adaptations to environmental stressors (Kapczinski et al., 2008). Lastly, it is known that chronic corticosteroid elevation leads to insulin resistance and increased body fat, potentially accounting for the high rates of obesity and metabolic syndrome among individuals with bipolar disorder (Fagiolini et al., 2005). Hyperreactivity of the HPA-axis and autonomic nervous system may explain the association between bipolar disorder, abuse history, and increased medical comorbidity in this report (Akiskal, 1983; Daban et al., 2005; Merola et al., 1994).

Strengths and Limitations

Our results offer improved generalizability over prior reports by focusing on patients with rapid-cycling and comorbid SUDs, a population often excluded from clinical trial participation due to unpredictable response patterns. Additional strengths include the use of a validated instrument to quantify medical comorbidity burden and assessment of outcomes among patients taking lithium and valproate, two first-line treatments for bipolar disorder.

Limitations include the moderate sample size and high prevalence of medical comorbidity across multiple organ systems, potentially narrowing our ability to detect the effects of subtle differences in comorbid medical conditions between responders and non-responders to lithium and valproate. The lack of a comparator group precludes evaluation of differences in the burden and severity of medical comorbidity among non-rapid cycling patients or those without comorbid SUDs. In addition, the rate of comorbid disorders may be elevated due to Berkson's bias (Berkson, 1946).

Conclusion

Rapid cycling with co-occurring substance use is accompanied by poor bimodal response to combined treatment with lithium and valproate. However, the low response rate cannot be directly attributed to the frequency or severity of medical burden. A high burden of medical comorbidity is preliminarily associated with the bipolar I subtype, a history of attempted suicide, a history of physical abuse, and advancing age.

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FIGURE 1.
Number of Medical Comorbidities Stratified by Age Among Patients with Rapid-Cycling Bipolar I or II Disorder and Co-Occurring Substance Use Disorders (N=98)

TABLE 1

Clinical Characteristics and Cumulative Illness Rating Scale Scores of Patients with Rapid-Cycling Bipolar I or II Disorder and Co-Occurring Substance Use Disorders.

Cumulative Illness Rating Score	Patients with Score		Age (years)		Female Gender		17-item Hamilton Depression Rating Scale Score				Bimodal Response ^a	
	N	%	Mean	SD	N	%	Initial		Final		N	%
							Mean	SD	Mean	SD		
1	6	6.1	29.0	7.9	4	66.7	17.2	8.7	10.5	10.4	0	0
2	6	6.1	28.5	6.4	1	16.7	13.6	6.7	10.3	6.5	1	17
3	18	18.4	31.5	9.8	8	44.4	17.3	6.2	11.3	6.9	7	39
4	13	13.3	37.4	9.2	1	7.7	14.8	7.9	12.1	7.5	4	31
5	9	9.2	37.4	15.1	2	22.2	14.7	7.9	17.4	6.69	2	22
6	11	11.2	37.5	7.3	7	63.6	17.2	5.3	13.2	6.4	3	27
7	9	9.2	36.1	6.6	1	11.1	14.9	7.8	12.8	5.5	1	11
8	9	9.2	36.2	11.9	6	66.7	17.4	8.9	12.5	9.5	1	11
9	6	6.1	44.8	8.8	3	50	19.0	5.5	15.0	9.9	2	33
10	4	4.1	40.5	4.7	1	25	15.3	5.9	11.7	9.1	0	0
11	2	2	45.5	23.9	1	50	12.0	12.7	10	--	0	0
12	1	1	49.8	--	1	100	13.0	--	4.0	--	0	0
13	2	2	40.3	5.3	0	0	14.0	4.24	22.0	--	0	0
14	1	1	39.2	--	0	0	24.0	--	--	--	0	0
15	1	1	57.2	--	1	100	22.0	--	2.0	--	0	0
Group Total	98	100	39.4	7.6	37	37.8	16.4	3.3	11.8	4.9	21	21

^aBimodal response is defined as meeting all of the following criteria: Hamilton Depression Rating Scale 17-item score ≤ 20 ; Young Mania Rating Scale score ≤ 12.5 ; Global Assessment Scale score ≥ 51 ; lithium level ≥ 0.8 meq/L; and valproate level ≥ 50 μ g/ml.

TABLE 2

Prevalence of Affected Organ Systems Among Outpatients with Rapid-Cycling Bipolar I or II Disorder and Co-Occurring Substance Use Disorders.

	Number of subjects	Percentage (%)
Respiratory	79	71.82
Musculoskeletal/Integument	61	55.5
Neurologic	41	37.3
Endocrine/Metabolic/Breast	40	36.4
Genitourinary	29	26.4
Head & Neck	27	24.6
Vascular	24	21.8
Lower GI	23	20.9
Hepatic	17	15.5
Upper GI	17	15.5
Cardiac	10	9.1
Renal	7	6.7

TABLE 3

Demographic and Clinical Characteristics of Patients with Rapid-Cycling Bipolar Disorder and Co-Occurring Substance Use Disorders Classified by Medical Comorbidity Burden.

Characteristic	Medical Comorbidity Burden						Significance
	High CIRS score ≥ 4			Low CIRS score ≤ 3			
(N=98)	Mean	SD	Mean	SD	Mean Difference	95% CI	P
Age	38.7	10.1	30.4	8.7	4.1 to 12.6		<0.001
Age at First Diagnosis	35.6	10.2	28.5	8.8	2.9 to 11.4		0.001
Age of Mania Onset	16.2	8.1	14.7	4.0	-1.6 to 4.6		0.341
Age of Depression Onset	14.0	7.4	12.9	4.6	-1.8 to 4.0		0.462
Age of SUD Onset	18.0	7.4	15.3	4.6	-1.3 to 6.8		0.179
Manic Episodes Past 12 Mo	5.5	3.4	6.3	4.0	-2.4 to 0.9		0.380
Depressive Episodes Past 12 Mo	5.4	3.5	6.4	4.3	-2.7 to 0.7		0.252
Past Suicide Attempts	1.4	2.3	0.9	1.8	-0.5 to 1.4		0.302
Past Hospitalizations	1.6	2.1	2.5	4.5	-2.2 to 0.4		0.182
Body Mass Index	28.8	6.3	27.0	4.4	-0.8 to 4.4		0.172
	N	%	N	%	OR	95% CI	P
Gender (N=98)							
Male	44	64.7	19	63.3	1.06	0.43, 2.59	
Female	24	35.3	11	36.7	0.94	0.39, 2.30	0.896
History of Suicide Attempt (N=98)	35	51.5	12	40.0	1.59	0.67, 3.80	0.295
Bipolar Subtype (N=98)							
Bipolar I	59	86.8	20	66.7	3.28	1.17, 9.21	
Bipolar II	9	13.2	10	33.3	0.31	0.11, 0.86	0.020
Comorbid Anxiety Disorder (N=98)	39	57.4	18	60.0	0.90	0.37, 2.15	0.807
Sexual Abuse (N=87)	15	24.6	3	11.5	2.50	0.66, 9.52	0.169
Physical Abuse (N=87)	21	34.4	2	7.7	6.30	1.36, 29.27	0.010
Psychotic Episode (N=98)	38	55.9	17	56.7	0.97	0.41, 2.30	0.943
Tobacco Use (N=76)	43	79.6	12	54.5	3.26	1.12, 9.49	0.027
Alcohol (N=98)							

Characteristic	Medical Comorbidity Burden				Mean Difference	Significance
	High CIRS score ≥ 4	Low CIRS score ≤ 3				
Abuse	12	17.6	11	36.7	0.37	0.14, 0.98
Dependence	48	70.6	16	53.3	2.10	0.87, 5.10
Cannabis (N=94)						
Abuse	21	31.8	11	39.3	0.72	0.29, 1.80
Dependence	19	28.8	6	21.4	1.42	0.50, 4.05
Cocaine (N=95)						
Abuse	8	11.8	8	29.6	0.32	0.09, 1.13
Dependence	27	39.7	12	44.4	0.82	0.33, 2.03

CI=Confidence Interval; CIRS=Cumulative Illness Rating Scale; Mo=Months; OR=Odds Ratio; SD=Standard Deviation; SUD=Substance Use Disorder p-value derived from χ^2 statistics for dichotomous variables and student's t-tests for continuous variables