Impact of Comorbid Anxiety Disorders on Outcome in a Cohort of Patients With Bipolar Disorder

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Background: High rates of comorbid anxiety disorders have been described in individuals with bipolar disorder. Although it is well recognized that anxiety disorders often co-occur with bipolar disorder, few studies have examined the impact of more than 1 anxiety disorder on long-term outcome in patients with bipolar disorder.

Method: The rates of DSM-IV generalized anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, and posttraumatic stress disorder were determined using structured clinical interviews in 138 patients with bipolar disorder who presented consecutively between 1994 and 1999. Patients were then followed for up to 3 years with longitudinal clinical surveillance. The impact of 1 or more comorbid anxiety disorders on mood symptoms and general function was evaluated.

Results: In our sample, 55.8% of the patients had at least 1 comorbid anxiety disorder, and 31.8% had 2 or more anxiety disorder diagnoses. The most common anxiety disorder was generalized anxiety disorder, followed by panic disorder. The presence of an anxiety disorder led to significantly ($p < .05$) worse outcome on global as well as specific illness measures, including illness severity, proportion of patients characterized as euthymic, and proportion of the year spent ill. Number of anxiety disorders was less important than type, with generalized anxiety disorder and social phobia having the most negative impact on outcome.

Conclusion: Our data suggested that multiple anxiety disorder comorbidities were not infrequent in bipolar disorder and that generalized anxiety disorder and social phobia were more likely to be associated with poor outcome. We discuss some potential mechanisms and implications in our findings.

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There has been recent interest in comorbid anxiety disorders as a predictor of the course and treatment response of bipolar disorder. The rate of anxiety disorders in patients with bipolar disorder may exceed that associated with major depressive disorder,[1–3] suggesting that identifying and treating anxiety in patients with bipolar disorder may be a significant component of effective management of bipolar disorder. Clinical and population studies of bipolar disorder patients suggest current anxiety disorder comorbidity rates of between 30% and 40%.[4–6] The Epidemiological Catchment Area study found the lifetime prevalence for panic disorder in bipolar illness to be 20.8%, more than twice the rate of 10% reported in major depressive disorder patients.[5,7,8] The frequency of generalized anxiety disorder (GAD) approximates 30% in bipolar disorder as reported by 2 studies.[5,9] The prevalence of comorbid social phobia ranges between 7.8%[1] and 47.2%,[2] and obsessive-compulsive disorder (OCD) prevalence has been found to be between 3.2% and 35%.[1,5,8,10] Posttraumatic stress disorder (PTSD) associated with bipolar disorder has been less extensively studied, but may occur with a frequency as high as 40%.[10,11]

It also appears that multiple anxiety disorder comorbidities occur in a significant minority of bipolar disorder patients. For example, Young et al.[9] found multiple anxiety disorders in 32% of bipolar disorder outpatients. Cassano et al.[4] studied 77 inpatients presenting with severe mood disorders with psychotic features, including bipolar I, and found that 34% had 1 anxiety disorder and

14% of patients had 2 or 3. To what extent anxiety and the presence of single or multiple anxiety disorders impact on course and outcome in bipolar disorder has been studied only in a limited way.

The extant literature on anxiety disorders and anxiety symptoms in the treatment and clinical course of bipolar disorder suggests that patients with anxiety have longer, more frequent, and more difficult-to-treat mood episodes and may have greater functional impairment.[6,12–14] Others have noted an association between anxiety disorders and mixed as opposed to euphoric mania.[15,16] Bipolar disorder patients with high levels of anxiety symptoms experience more substance abuse and chronic suicidal ideation,[9] and these patients are less responsive to treatment with lithium[9,14,17] and may have an earlier onset of mood illness.[4,6] Taken together, these studies suggest that anxiety in bipolar disorder may have a negative influence on clinical outcome, though, importantly, the impact of multiple anxiety disorders has been understudied. In addition, little research has focused on whether 1 anxiety disorder, or combination of anxiety disorders, is particularly important for predicting clinical outcome.

In this study, we examined the rates of single and multiple anxiety disorders in a large sample of carefully diagnosed bipolar disorder patients. We describe the clinical characteristics of patients with single and multiple anxiety disorders over 3 years of prospective, longitudinal clinical surveillance and assess the contribution of anxiety disorder type and number of anxiety disorders as clinical correlates of mood symptoms and patient function. Anxiety disorders included in this study were GAD, panic disorder, social phobia, OCD, specific phobia, and PTSD. On the basis of previous research, we predicted that presence of anxiety disorders would lead, overall, to worse outcomes. We also examined whether the presence of multiple disorders was more problematic than a single anxiety disorder. Given the lack of data on multiple anxiety disorders and outcome, it was difficult to formulate specific hypotheses. It may be that there is a linear relation between number of anxiety disorders and outcome, but we also examined the possibility that specific anxiety disorders would be more problematic in terms of outcome than others.

METHOD

Participants

The study utilized a "life-charting" approach, the further details of which were described by MacQueen and colleagues.[18] Consecutive outpatients seen at the McMaster Regional Mood Disorders Program (Hamilton, Ontario, Canada) between 1994 and 1999 were screened for eligibility. The inclusion criteria for the sample were (1) age of 16 to 65 years and (2) diagnosis of bipolar disorder type I or II as assessed with the Structured Clinical Interview for DSM-IV (SCID).[19] Exclusion criteria were (1) history of seizure, head injury with loss of consciousness, or other neurologic disorder; (2) concurrent active medical disorder; and (3) substance abuse or dependence within 6 months of study entry. For this study, a total of 138 patients were available for analysis of the major independent and dependent variables. This number of patients resulted from cessation of recruitment to allow each participant to contribute a minimum of 1 year of follow-up data; however, most patients were followed for more than 2 years.

Clinical Treatment

The pharmacologic and nonpharmacologic treatments administered to participants are described in detail in a previous report by our group.[18]

Documentation of Illness Course and Measurement of Mood Status

The course of illness after inclusion in the study was documented for each participant using a modified life-charting technique based on the National Institute of Mental Health (NIMH) life-charting method that allows for a graphical representation of the longitudinal course of mood disorders.[18,20,21] Patients were treated according to published guidelines.[22,23] Definitions of depression, mania, hypomania, and euthymia from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[24] were utilized. Each time a patient was assessed, that patient's mood status was determined on a scale ranging from +3 to –3 using a method adopted from NIMH life-charting methods[20,21] and anchored with scores from either the Hamilton Rating Scale for Depression (HAM-D)[25,26] or Young Mania Rating Scale (YMRS)[27] as described below.

+3: *Severe mania/mixed symptoms* characterized by required close supervision due to lack of insight, unpredictability, impulsivity. Inability to work or function in a meaningful manner. Others insist that help is required. Needs little or no sleep, has excessive energy, and is unable to sit still. Feels out of control, all-powerful, invincible, explosive, potentially violent, angry, and reckless. May be psychotic or require hospitalization. Symptom levels equivalent to a YMRS score of > 25 or a score > 3 on YMRS questions 7 (language-thought disorder), 8 (content), or 9 (disruptive-aggressive behavior).

+2: *Moderate mania/hypomania/mixed symptoms* characterized by difficulty with goal-oriented activities and decreased productivity. Pleasure-seeking, risk-taking, poor judgment. Others notice euphoria, irritability, or grandiosity. Intrusive, disruptive, or reckless behavior. Pressured speech, racing thoughts, increased energy, sexual interest/activity, decreased need for sleep. Symptoms equivalent to a YMRS score of 10 to 25.

+1: *Mild mania/hypomania/mixed symptoms* characterized by minimal or no impairment, continues to function well. Functioning may even improve in some areas. Evidence of increased energy and activity, socialization. May feel enthusiastic, irritable, exuberant, and/or talkative. Feels more productive. Symptoms equivalent to a YMRS score of 5 to 10.

0: *Euthymic* characterized by no functional impairment, but may include mild subsyndromal symptoms. Symptom level equivalent to a YMRS score of < 5 and a HAM-D score of < 7.

–1: *Mild depression* characterized by minimal or no functional impairment, subjective distress, may have several symptoms but does not meet DSM-IV criteria for a major depressive episode (MDE). Symptom level equivalent to a HAM-D score of 7 to 15.

–2: *Moderate depression* characterized by significant impairment, marginal functioning, has to push self, missing work. Meets DSM-IV criteria for major depressive episode. Symptom level equivalent to a HAM-D score of 16 to 24.

–3: *Severe depression* characterized by not functioning at work, home, or school or in social situations. Meets criteria for MDE, including suicidal ideation/attempt, or unable to care for self, possibly psychotic or requiring hospitalization. Symptom level equivalent to a HAM-D score of > 25, or the suicide item of the HAM-D is rated 3.

Outcome Assessment

The primary dependent variables reported in this study were drawn from each individual's clinical status during the final available year of follow-up. As a first level of evaluation, each life-charted participant was categorized as being euthymic or noneuthymic for the duration of that outcome year. Patients were included in the euthymic group if they had no absolute scores exceeding +1 or –1 during the last year of follow-up and if any score of 1 occurred only once and lasted no longer than 1 week during the year; that is, patients could have only 1 week of symptoms in the mild hypomania or mild depression range during the entire last year of follow-up. All patients who did not meet this criterion were classified as noneuthymic.

The secondary level of outcome assessment involved a quantification of each patient's degree of illness during the last year of follow-up. Three measures were examined: (1) mean illness severity, based on the mood status ratings of depression and/or mania/hypomania; (2) percentage of the year spent with "mild" or worse mood symptoms; and (3) Global Assessment of Functioning (GAF)[24] score. The illness severity was equivalent to a patient's average mood status (as an absolute value) over the course of the entire last year of follow-up calculated as a percentage of the worst possible mood status, such that a person who had a "severe" mood status (depression or mania) for the entire year would have an illness severity of 100%, and a person who was euthymic for the entire year would have an illness severity of 0%. Illness severity constituent measures of depression severity and mania/hypomania severity were also calculated for each patient, based on mean negative and positive mood status values, respectively.

Measures

Structured Clinical Interview for DSM-IV. The SCID[28] is a diagnostic instrument that reflects DSM-IV diagnostic criteria for Axis I disorders.[24] Earlier versions of the SCID for DSM-III-R have been demonstrated to have good reliability, with kappas ranging from 0.84 to 0.40 and a mean of 0.61 for all disorders across a large number of samples, and adequate test-retest reliabilities.[29,30]

Hamilton Rating Scale for Depression. The HAM-D[25,26,31] is a 29-item clinician-rated instrument, of which 17 depression symptoms and features are considered for scoring. The HAM-D was chosen for the study because it is the most frequently used interviewer-administered measure of depression and because it is frequently used as a measure of change with treatment.[31] Therefore, its research utility is very high even though trained interviewers are needed.

Young Mania Rating Scale. The commonly used YMRS[27] was chosen to measure severity of mania. Trained interviewers rate the items, and reliability ratings have been high in multiple studies.[32] The scale has also been shown to correlate with more elaborate measures of mania and, particularly useful for this study, is sensitive to changes as a result of treatment.[32]

Clinicians were formally trained in the use of these rating scales using video and one-on-one training. Interrater reliability was recalculated every 3 to 4 months.

Statistical Analysis

To examine outcome, we began by focusing on the broadest possible overall classification variable of euthymic versus noneuthymic during the outcome year. When differences in the proportions of patients in each category were significant, more detailed tests were performed on the specific illness indicators that were part of the overall classification. Analyses of categorical variables were conducted using χ^2 tests. Continuous variables were analyzed using t tests, or 1-way analyses of variance followed by post hoc Newman-Keuls tests when more than 2 groups were compared. Critical levels of significance were set at .05.

RESULTS

Anxiety Disorder Comorbidity Rates

Of the 138 patients in the sample, 77 (55.8%) were diagnosed with at least 1 comorbid anxiety disorder, while

Table 1. Impact of Anxiety on Clinical Presentation in Bipolar Disorder Patients

Variable	No Anxiety	Comorbid Anxiety
Demographic variables		
N (% of sample)	61 (44.2)	77 (55.8)
Male, N (%)	24 (39.3)	20 (26.0)
Bipolar type		
I, N (%)	42 (68.9)	55 (71.4)
II, N (%)	19 (31.1)	22 (28.6)
Rapid cycling, N (%)		
Yes	13 (21.3)	28 (36.4)
No	48 (78.7)	49 (63.6)
Age at onset of depression, mean (SD), y	23.0 (10.0)	19.4 (10.3)
Age at onset of mania, mean (SD), y[a]	25.5 (10.8)	23.2 (11.1)
Age at onset of hypomania, mean (SD), y[a]	24.8 (12.2)	23.3 (9.3)
Age at last year of follow-up, mean (SD), y	46.0 (12.7)	42.0 (9.1)
Duration of illness, mean (SD), y[b]	24.0 (11.1)	22.9 (10.8)
Outcome variables		
Euthymic in outcome year, N (%)		
Yes	27 (44.3)	17 (22.1)
No	34 (55.7)	60 (77.9)
Percentage of year spent ill, mean (SD)	40.2 (39.8)	57.3 (37.4)
Illness severity, mean (SD)	14.6 (17.3)	21.5 (18.4)
Depression severity, mean (SD)	12.0 (16.5)	20.2 (18.5)
Mania/hypomania severity, mean (SD)	2.6 (6.2)	1.3 (3.5)
GAF score, mean (SD)	70.1 (6.6)	67.9 (6.8)

[a]Some patients reported data for both mania and hypomania.
[b]Based on earliest of onsets for depression, mania, and hypomania.
Abbreviation: GAF = Global Assessment of Functioning.

Table 2. Impact of Number of Anxiety Disorders on Outcome in Bipolar Disorder Patients[a]

Outcome Variable	1 Anxiety Disorder (N = 33)	2 Anxiety Disorders (N = 22)	3+ Anxiety Disorders (N = 22)
Euthymic in outcome year, N (%)			
Yes	8 (24.2)	7 (31.8)	2 (9.1)
No	25 (75.8)	15 (68.2)	20 (90.9)
Percentage of year spent ill	61.8 (38.3)	45.8 (38.7)	62.2 (33.5)
Illness severity	24.8 (20.8)	15.4 (14.3)	22.7 (17.3)
Depression severity	23.2 (21.2)	14.2 (13.7)	21.8 (17.4)
Mania/hypomania severity	1.6 (4.7)	1.2 (2.5)	0.9 (2.2)
GAF score	67.1 (7.3)	70.1 (6.3)	66.9 (6.4)

[a]Values shown as mean (SD) unless otherwise indicated.
Abbreviation: GAF = Global Assessment of Functioning.

the remaining 61 (44.2%) had no comorbid anxiety disorder. Of the 55.8% diagnosed with any anxiety disorder, 42.8% (23.9% of the total sample) were found to have a single anxiety disorder, 28.5% (15.9% of the total sample) had 2 anxiety disorders, and 28.5% (15.9% of the total sample) had 3 or more anxiety disorders. The most common anxiety disorder in this sample, based on frequency, was GAD (31.2%), followed by panic disorder (26.8%), social phobia (17.4%), PTSD (14.5%), specific phobia (10.1%), and OCD (8.7%).

Impact of Anxiety Disorder Comorbidity on Outcome

In the first set of analyses, we compared patients with and without anxiety disorders on a series of demographic variables as well as on the outcome variables drawn from the last year of follow-up (Table 1). Among the demographic variables, the age at onset of a first episode of depression differed significantly between the groups, $t = 2.04$, $df = 132$, as did the mean age at the beginning of the last year of follow-up, $t = 2.17$, $df = 136$. It is noteworthy that the younger age of the comorbid anxiety group at the start of the outcome year combined with their earlier age at onset resulted in no difference between the groups in overall duration of illness, $t = 0.56$, $df = 135$, $p > .55$. There were trends toward significant differences between the groups regarding the distributions of males and females, $\chi^2 = 2.80$, $p < .10$, and patients who were diagnosed with rapid cycling, $\chi^2 = 3.69$, $p < .06$.

Differences between the groups in medication use and past substance abuse were also analyzed. Statistically significant differences were found in the use of benzodiazepines for each group of patients with specific anxiety comorbidities compared with patients who had no anxiety disorder. When the number of anxiety comorbidities was considered, significant differences emerged for the number of mood stabilizer and antipsychotic trials for the group with 3 or more anxiety disorders only. The number of anxiety disorders was not related to past substance use; patients with comorbid GAD (37%), PTSD (45%), OCD (50%), and specific phobia (64%) had significantly higher rates of past substance abuse or dependence than participants without anxiety (20%).

Several significant differences emerged in the analyses of the outcome variables. Twice the proportion of patients without anxiety disorder was categorized as euthymic (44.3%) compared with patients with comorbid anxiety disorder (22.1%), $\chi^2 = 7.71$. Among the specific measures that constituted this broader classification of outcome, participants with comorbid anxiety had a significantly higher illness severity, $t = 2.25$, $df = 136$, which was accounted for by a greater number of depression symptoms (depression severity, $t = 2.73$, $df = 136$). Patients with comorbid anxiety disorders also spent a significantly greater proportion of the year ill, $t = 2.60$, $df = 136$, and tended to have lower mean GAF scores, $t = 1.94$, $df = 136$, $p < .06$.

Impact of Multiple Anxiety Disorder Comorbidities on Outcome

To examine our questions about the impact of single versus multiple anxiety disorders, we categorized the participants with anxiety disorders according to number of comorbid disorders, creating groups who met criteria for 1 (N = 33), 2 (N = 22), and 3 or more (N = 22) disorders. We then compared these groups on the outcome variables, and the results are displayed in Table 2. Contrary to the hypothesis that an increasing number of comorbid anxiety

Table 3. Impact of Type of Anxiety Comorbidity on Outcome in Bipolar Disorder Patients[a]

Variable	GAD (N = 43)	Panic Disorder (N = 37)	Social Phobia (N = 24)	PTSD (N = 20)	Specific Phobia (N = 14)	OCD (N = 12)
Euthymic in outcome year, N (%)						
Yes	7 (16.3)[b]	10 (27.0)	4 (16.7)[c]	2 (10.0)[b]	2 (14.3)[c]	3 (25.0)
No	36 (83.7)	27 (73.0)	20 (83.3)	18 (90.0)	12 (85.7)	9 (75.0)
Total no. of anxiety disorders	2.1 (1.2)	2.4 (1.2)	2.7 (1.2)	2.8 (1.2)	3.1 (0.8)	2.8 (0.9)
Percentage of year spent ill	62.8 (36.3)[b]	52.6 (38.0)	64.0 (35.1)[c]	62.7 (32.3)[c]	51.6 (36.8)	42.5 (36.9)
Illness severity	23.5 (19.2)[c]	18.2 (16.4)	25.8 (19.8)[c]	21.2 (12.9)	17.7 (15.8)	17.5 (18.6)
Depression severity	23.0 (19.1)[b]	16.9 (16.2)	24.6 (20.1)[b]	18.2 (13.6)	16.4 (15.4)	16.7 (18.4)
Mania/hypomania severity	0.5 (1.6)[c]	1.3 (3.0)	1.2 (2.4)	2.9 (5.6)	1.3 (2.8)	0.8 (2.8)
GAF score	67.5 (7.4)	68.9 (6.4)	66.4 (7.6)[c]	67.0 (4.3)	68.7 (5.8)	68.4 (8.3)

[a]Values are shown as mean (SD) unless otherwise indicated.
[b]Differed significantly from the no-anxiety group, $p < .01$.
[c]Differed significantly from the no-anxiety group, $p < .05$.
Abbreviations: GAD = generalized anxiety disorder, GAF = Global Assessment of Functioning, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.

disorders would be associated with an increasing burden of illness and worse outcome, there were no significant differences between the groups of patients with 1, 2, and 3 or more anxiety disorders for any of the outcome measures (all p values > .15).

Impact of Type of Anxiety Comorbidity on Outcome

Given that presence of any anxiety disorder, and not increasing numbers of anxiety disorders, had a negative impact on outcome, we next examined the effect of particular types of anxiety disorder on the major dependent variables in the study. The sample of participants with comorbid anxiety disorder was reorganized into a series of groups based on the presence of a particular anxiety disorder of interest. For example, all patients with comorbid GAD were placed in 1 group regardless of the presence of any other comorbid anxiety disorder diagnoses. This process was repeated for panic disorder, social phobia, specific phobia, PTSD, and OCD. Each resulting group was then compared with the no-anxiety group. Mean values for the outcome variables for each of the anxiety disorder groups, and statistically significant differences from the no-anxiety group, are shown in Table 3.

As can be seen, GAD, social phobia, PTSD, and specific phobia were associated with a smaller proportion of euthymic participants across the entire last year of follow-up ($\chi^2 = 8.98$, 5.66, 7.69, and 4.31, respectively). Analyses of the other outcome variables indicated that patients with comorbid GAD had higher illness severity, $t = 2.48$, $df = 102$, and higher depression severity, $t = 3.14$, $df = 102$, and spent more time ill, $t = 2.95$, $df = 102$, than their nonanxious counterparts. In contrast, the GAD patients had significantly lower mania/hypomania severity, $t = 2.15$, $df = 102$.

Similar to the participants with GAD, those individuals with comorbid social phobia also had higher illness severity, $t = 2.58$, $df = 83$, and higher depression severity, $t = 2.98$, $df = 83$; spent more time ill, $t = 2.55$, $df = 83$; and had lower GAF scores, $t = 2.24$, $df = 83$, than the patients in the no-anxiety group. The only other comparison between a comorbid anxiety disorder group and the no-anxiety group to reach statistical significance revealed that patients with PTSD spent more time ill, $t = 2.28$, $df = 79$.

DISCUSSION

This report is consistent with previous studies[3,4] that found that anxiety disorders are common in bipolar disorder and frequently co-occur with other anxiety disorders. Over half (55.8%) of our sample had an anxiety disorder, and close to one third (31.9%) had multiple anxiety disorders. We found that an increasing number of diagnosed anxiety disorders did not predict worse outcomes for our participants. In contrast, it appeared that presence of certain anxiety disorders, GAD and social phobia specifically, were more likely to be associated with negative outcomes on a variety of illness measures.

The frequency of comorbid anxiety disorders we identified is somewhat elevated compared with rates found in other samples of bipolar patients (48%[4] and 42%[6]). One of these studies was conducted in an inpatient setting,[6] which may have had some impact on observed comorbidity rates. In contrast, our sample was from a specialty mood clinic with a focus on refractory mood disorders. It may be that differences in comorbidity rates between this study and others are accounted for by the different patient population followed in this tertiary care clinic.

Patients with comorbid anxiety disorder(s) had an earlier age at onset of illness, had more depressive symptoms, spent a significantly greater proportion of the year ill, and tended to have lower GAF scores (and benzodiazepine use). There was also a trend for anxiety disorders to be associated with rapid cycling. Similar findings have been described in other studies[5,6,9,33,34] that also reported that bipolar disorder with comorbid anxiety disorder is associated with earlier onset, more severe mood illness, rapid cycling, and poorer outcome.

There are several ways that the presence of an anxiety disorder could be theorized to negatively impact on symptom levels and functioning in patients with bipolar disorder. For example, anxiety disorder comorbidity may be associated with an earlier age at onset of bipolar disorder. Given the study design, we cannot comment on whether the comorbid anxiety disorder appeared after the time of bipolar illness onset or preceded it. Certainly, psychiatric illness with an onset during adolescence has the potential to affect the long-term trajectory of development processes in a number of domains, possibly making individuals more vulnerable to more severe mood illness in later life. Additionally, individuals with an earlier onset of illness would have had less time to develop coping strategies and a stable sense of identity independent of illness. These hypotheses have not been tested in the literature and need to be further explored, as early-life anxiety has been reported in children with bipolar disorder[20] and may be a risk factor for bipolar disorder severity in adulthood.

Other ways anxiety has been described to complicate the course of bipolar disorder are through lengthening the duration of depressive episodes[14,32] and elevating the rate of interepisode subsyndromal mood symptoms.[35] These studies suggest that anxiety may worsen the course of bipolar disorder by making patients more unwell during an episode, more likely to have frequent and protracted episodes, and more likely to have interepisode impairment.

Importantly, our results also suggested that the impact of anxiety disorders on outcome does not fit an additive linear model. This apparent paradox, that anxiety disorder is associated with negative outcome, but that increasing numbers of anxiety disorders do not combine to create worse outcome, appears to be explained by examination of the type of anxiety disorder present. When we more carefully parsed the data to examine types of anxiety disorder and outcome, both social phobia and GAD were most reliably associated with more symptoms and dysfunction. On the basis of our data alone, it is difficult to draw definitive conclusions about why GAD and social phobia would be associated with more severe impairment in bipolar disorder. The typical ages at onset of GAD and social phobia are not necessarily earlier than the onset of bipolar disorder.[2,36] However, this epidemiologic information does not come from bipolar samples; thus, it is possible that GAD and social phobia are associated with more illness impairment in our patients because these disorders were premorbid to the onset of bipolar disorder. To examine this point, the National Comorbidity Study (NCS)[2] investigated the course of social phobia in mood disorders and found that social phobia clearly predated the onset of unipolar depression and dysthymia (in 72% and 76% of patients, respectively) and bipolar disorder (in 40% of patients). No studies have looked at the course of GAD in bipolar disorder.

The adverse impact of GAD and social phobia may be explained by the clinical course of these anxiety disorders. Both of these disorders are described as persistent rather than episodic; indeed, they may have traitlike aspects. For example, there is a significant overlap in symptoms between social phobia and avoidant personality disorder[37]; thus, for patients with GAD or social phobia, symptoms of negative emotionality, worry, and tension are likely to persist into euthymic periods. Several studies in the literature support this possibility. In a study by Kessler et al.,[2] those patients with social phobia also had more frequent episodes of depression over their lifetime and more persistent and severe depressive symptoms during a mood episode. Findings about the course of GAD in mood disorders, also from NCS comorbidity data,[38] suggest that GAD was the only anxiety disorder studied in which persistence of anxiety symptoms was unrelated to whether other disorders were present. Furthermore, Yonkers et al.[36] studied 135 patients with GAD and with or without other anxiety and mood disorders and found that when GAD was comorbid with any other disorder, the chance of remission was 3 times less than when GAD was absent. It also may be that GAD and social phobia prolong or provoke self-defeating coping styles (anticipation of negative outcomes, negative self-evaluation, avoidance of functional interactions). Finally, it could be that GAD and social phobia are not treated as successfully by conventional interventions for bipolar disorder, such as mood stabilizers and antipsychotics.

To better understand the mechanisms by which specific anxiety disorders can affect bipolar illness severity, it will be important to expand on current knowledge about the course of mood and anxiety symptoms in bipolar disorder and how they relate to each other in the clinical presentation. This investigation would include development of methodologies to better differentiate symptoms that are specific to anxiety disorders and those that may represent subsyndromal mood disorders. This knowledge can best be obtained through carefully constructed longitudinal studies that track the emergence of symptoms of anxiety and mood disorder and track functional impairment. Furthermore, as proposed by Frank et al.,[39] future studies should consider the spectrum of anxiety symptomatology that may coexist in bipolar disorder patients, as categorical classification of anxiety disorders may not capture contribution of subsyndromal anxiety symptoms to the clinical course and outcome.

Despite the consistencies and significant patterns in our findings, our study does have several limitations. First, the analysis would have benefited from more information about the course of anxiety disorders in our patients; knowing date of onset and whether anxiety disorder preceded or followed the emergence of bipolar disorder would have been useful. Second, our naturalistic sample is from a tertiary care clinic. Patients seen in the

study had multiple disorders at presentation and had experienced many years of psychiatric illness prior to treatment. Findings about comorbidity, course, and response to treatment may not be generalizable to community or primary care samples with bipolar disorder. Finally, although our sample size was adequate, a larger sample would have allowed us to better examine very specific combinations of bipolar disorder and anxiety disorder rather than having to compare heterogeneous mixtures of disorders; this would have allowed us to examine some of our explanatory hypotheses with less ambiguity. Conversely, anxiety disorder comorbidity in bipolar disorder is clearly complex, and findings about "pure" cases may not generalize to bipolar disorder patients who present with multiple anxiety disorders.

The presence of anxiety disorder, particularly GAD and social phobia, exerts an important influence in the outcome of bipolar disorder. These disorders occur with high frequency in patients with bipolar disorder and appear to contribute significantly to poor symptomatic outcome and reduced overall function. It is obviously important clinically to screen for and treat anxiety disorders in patients with bipolar disorder; future studies will need to focus on optimal pharmacologic and nonpharmacologic approaches to treating these comorbid conditions, as currently there are few data describing the best management of any anxiety disorder in a patient with bipolar illness.

Drug name: lithium (Lithobid, Eskalith, and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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