

Anxiety Disorders in 318 Bipolar Patients: Prevalence and Impact on Illness Severity and Response to Mood Stabilizer

Chantal Henry, M.D., Ph.D.; Donatienne Van den Bulke, M.A.;
Frank Bellivier, M.D., Ph.D.; Bruno Etain, M.D.;
Frédéric Rouillon, M.D.; and Marion Leboyer, M.D., Ph.D.

Objective: The aim of this study was to assess the frequency and impact of anxiety disorders on illness severity and response to mood stabilizers in bipolar disorders.

Method: 318 bipolar patients consecutively admitted to the psychiatric wards of 2 centers as inpatients were recruited. Patients were interviewed with a French version of the Diagnostic Interview for Genetic Studies providing DSM-IV Axis I diagnoses and demographic and historical illness characteristics. Logistic and linear regressions to adjust for age and sex were performed.

Results: In a population with mostly bipolar type I patients (75%), 24% had at least 1 lifetime anxiety disorder (47% of these patients had more than 1 such disorder), 16% of patients had panic disorder (with and without agoraphobia, and panic attacks), 11% had phobia (agoraphobia without panic disorder, social phobia, and other specific phobias), and 3% had obsessive-compulsive disorder. Comorbidity with anxiety disorders was not correlated with severity of bipolar illness as assessed by the number of hospitalizations, psychotic characteristics, misuse of alcohol and drugs, and suicide attempts (violent and nonviolent). Bipolar patients with an early onset of illness had more comorbidity with panic disorder ($p < .05$). Anxiety disorders were detected more frequently in bipolar II patients than in other patients, but this difference was not significant ($p = .09$). Bipolar patients with anxiety responded less well to anticonvulsant drugs than did bipolar subjects without anxiety disorder ($p < .05$), whereas the efficacy of lithium was similar in the 2 groups. There was also a strong correlation between comorbid anxiety disorders and depressive temperament in bipolar patients ($p = .004$).

Conclusion: Patients with bipolar disorders often have comorbid anxiety disorders, particularly patients with depressive temperament, and the level of comorbidity seems to decrease the response to anticonvulsant drugs.

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Received May 16, 2002; accepted Sept. 3, 2002. From the Department of Adult Psychiatry, Charles Perrens Hospital, Bordeaux (Dr. Henry and Ms. Van den Bulke); INSERM U-394, Integrative Neurobiology, Bordeaux (Dr. Henry and Ms. Van den Bulke); Albert Chenevier Hospital, Créteil (Drs. Bellivier, Etain, Rouillon, and Leboyer); and the INSERM U-513, University of Medicine, Créteil (Drs. Bellivier, Etain, Rouillon, and Leboyer), France.

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Corresponding author and reprints: Chantal Henry, M.D., Service Universitaire de Psychiatrie, CH Charles Perrens, 121 rue de la Béchade, 33076 Bordeaux, France (e-mail: chantal.henry@bordeaux.inserm.fr).

Numerous studies have indicated a high prevalence of comorbidity for anxiety disorders and depressive disorders. Less attention has been paid to the relationship between anxiety disorders and bipolar disorders. Several studies have reported prevalences of comorbidity between bipolar disorder and obsessive-compulsive disorder (OCD),¹ panic disorder,² generalized anxiety disorder,³ or social phobia,^{4,5} but only a few studies have assessed prevalence of lifetime anxiety disorders in a large cohort of bipolar patients. Only 1 recent study, performed by the Stanley Foundation Bipolar Treatment Outcome Network,⁶ assessed all of the components of Axis I psychiatric comorbidity in bipolar patients. However, that study did not focus on anxiety disorders, and little is known about the relationship between bipolar disorder and anxiety disorder and the impact of this comorbidity on the symptoms, course, and treatment response of bipolar disorders. However, data on mood disorders as a whole and partial data on bipolar disorders have suggested that anxiety disorders may be associated with greater severity of illness. For example, multiple anxiety disorder comorbidity has been shown to be associated with more severe psychopathologic characteristics in patients with mood spectrum disorders with psychotic features.⁷ Anxiety disorders also seem to be associated

with a poor outcome in the acute treatment of bipolar type I disorder, with a longer remission, more severe side effects of medication, and a larger number of drugs required for effective treatment.⁸ Moreover, severe bipolar illness with early age at onset was found to be associated with panic disorder,⁹ and bipolar patients with OCD were found to have a higher incidence of prior suicide attempts than bipolar patients without OCD.¹⁰

MacKinnon et al.^{11,12} suggested that it may be possible to further explore genetic heterogeneity in bipolar disorders on the basis of comorbidity, as panic disorder and bipolar illness are cotransmitted in some families. For example, a polymorphic genomic duplication on chromosome 15 was recently found in a large population of patients with panic and phobic disorders.¹³ It thus seems important to determine the level of comorbidity with anxiety disorders in a population of bipolar patients to identify possible genetic factors common to both disorders.

The aim of this study was to determine the prevalence of anxiety disorders in bipolar patients and to assess the impact of this comorbidity on factors relating to severity and treatment response. We also assessed the possible relationship between temperament characteristics of bipolar patients and the occurrence of anxiety disorders.

METHOD

Bipolar patients (N = 318) were recruited from consecutive admissions to the psychiatric inpatient centers of 2 university-affiliated hospitals (Charles Perrens Hospital, Bordeaux, and Chenevier Hospital, Créteil, France).

The study was described in detail to the subjects, from whom informed written consent was then obtained. Patients were interviewed by trained psychiatrists or psychologists using the French version of the Diagnostic Interview for Genetic Studies,¹⁴ which provides lifetime DSM-IV Axis I diagnoses and sociodemographic data. Age at onset was defined as the age at which the patient met full DSM criteria for the disorder for the first time, and patients were subdivided into 3 subgroups (early onset, 18 years of age or before; intermediate onset, 19 to 45 years; and late onset, 46 years of age or later), as defined in Bellivier et al.¹⁵ Family history was assessed using a French version of the Family Interview for Genetic Studies.¹⁴ We assessed temperament using the French version of the Semi-Structured Interview for Hyperthymic Temperament criteria developed by Akiskal and Mallya.¹⁶ This interview consists of 22 items concerning usual mood, cognition, motor activity, personal interrelationships, attitudes toward social norms, sleep requirements, and sexual appetite. Answers were selected by the patient, not by the scorer, and the interview was administered when patients were euthymic. One point was counted for each item with a positive response. We used this characterization of temperament as a dimension rather than a category.^{17,18}

In our initial analysis, we pooled all anxiety disorders except posttraumatic stress disorder and generalized anxiety disorder (not assessed). We then assigned these disorders to 3 groups: (1) the “panic disorders group” (panic disorders with and without agoraphobia, and panic attacks), (2) the “phobia disorders group” (social phobia, agoraphobia without history of panic disorder, and specific phobia), and (3) “the obsessive-compulsive disorder group.”

We investigated response to mood stabilizers (lithium or anticonvulsants) as follows. Good responders were defined as patients displaying a subjective and objective improvement over at least 2 years of treatment (decrease in frequency and severity of episodes), or a relapse at termination of treatment, or no relapse during at least 2 years. Poor responders were patients who did not respond to these criteria and for whom a new therapeutic strategy was used.

Violent suicidal acts were defined as at least 1 violent suicidal act involving the use of firearms, the use of a knife, hanging, jumping out of a window, or throwing oneself under a train.

Statistical Analysis

Statistical analyses were performed with SPSS V.10.0 (SPSS Inc., Chicago, Ill.) using the chi-square test and the t test for group comparisons. Logistic and linear regression were used to analyze the effect of the various factors on the presence or absence of anxiety disorders. Sex and age were considered as covariates.

RESULTS

Sample Characteristics

The sample of 318 bipolar patients was composed of 41% men and 59% women, with a mean age at interview of 53.3 ± 15.1 years (range, 24–89 years) (Table 1).

Educational level was high school graduate-level or higher (≥ 12 years of education) for 68% of patients. Occupational status was “unemployed or disability pension” for 39% of patients and “currently working, student, or retired” for 59% of patients. As far as marital status was concerned, 39% of patients had always been single, and 61% of patients were married, divorced, or widowed.

Bipolar Illness Characteristics

Most patients had type I bipolar disorder (74.5%). The mean age at onset was 27 ± 11 years (range, 6–66 years). Fifty-five percent of subjects met the criteria for at least 1 episode with psychotic features, and 40% had attempted suicide at least once, with 22% of these subjects (N = 28) having carried out a violent suicidal act. The mean number of hospitalizations was 4.5 ± 4.8 (range, 1–31). Twenty-one percent of patients had a present or past history of alcohol or drug misuse (Table 1).

Table 1. Demographic Characteristics and Bipolar Disorder Characteristics (N = 318)

Characteristic	Value
Gender, %	
Male	41
Female	59
Age at interview, y ^a	53.3 ± 15.1 (24–89)
Education (≥ 12 years), %	68
Occupational status (currently working, student, retired), %	59
Marital status (always been single), %	39
Bipolar type I, %	74.5
Age at onset of bipolar disorder, y ^a	27 ± 11 (6–66)
At least 1 suicide attempt, %	40
Age at first suicide attempt, y ^a	32 ± 13 (13–69)
Number of hospitalizations ^a	4.5 ± 4.8 (1–31)
At least 1 psychotic episode, %	55
Present or past history of substance misuse, %	21
Familial history of affective disorders, %	67.6

^aValue represents mean ± SD (range).

Table 2. Lifetime Comorbidity for Anxiety Disorders in Bipolar Patients (N = 318)

Comorbid Disorder	N	%
At least 1 anxiety disorder	75	24
Panic disorder/agoraphobia	52	16
Phobia	35	11
Obsessive-compulsive disorder	9	3

Comorbidity Prevalences

Twenty-four percent (N = 75) of bipolar patients had at least 1 anxiety disorder, and 47% (N = 35) of these patients had more than 1 such disorder. The most frequent association of bipolar disorder with at least 1 anxiety disorder involved panic disorders and phobia (20%, N = 15). The prevalence of comorbidity for panic disorder (including panic disorder with and without agoraphobia and panic attacks) was 16% (N = 52), that for phobia (including agoraphobia without panic disorder, social phobia, and other specific phobia) was 11% (N = 35), and that for OCD was 3% (N = 9) (Table 2).

Clinical Impact of Anxiety Disorders on Bipolar Disorder

We first investigated the clinical impact of the presence of any anxiety disorders (Table 3). We found that these disorders had no effect on the number of hospitalizations (B = -0.012, p = .8), presence of psychotic features (B = -0.047, p = .8), past or present history of alcohol or drug misuse (B = 0.36, p = .9), suicide attempts (B = -0.056, p = .8), or violence of suicide attempts (B = -0.08, p = .18). Although the trends were not significant, bipolar II patients tended to be more likely to have comorbid anxiety disorders compared with bipolar I patients (B = 0.5, p = .09). Patients with an early onset of illness were characterized by comorbid panic disorders (B = -0.187, p < .05), and there was a tendency toward

Table 3. Clinical Impact of Anxiety Disorders on Bipolar Illness

Variable	At Least 1 Anxiety Disorder (N = 75)		Panic Disorder (N = 52)		Phobia (N = 35)	
	B	p	B	p	B	p
Bipolar diagnosis (I vs II)	0.504	.09	0.316	.3	0.4691	.2
Age at onset of bipolar disorder	-0.099	.09	-0.187	.049	-0.127	.25
Number of hospitalizations	-0.012	.8	-0.056	.3	0.006	.9
Psychotic symptoms	-0.047	.8	-0.132	.7	0.3745	.3
Current or past addictive behavior	0.368	.9	0.278	.5	0.5259	.2
Suicide attempts	-0.056	.8	-0.2902	.4	0.4466	.2
Violence of suicide attempts	-0.08	.18	-0.4	.5	-0.8	.3

Table 4. Treatment Response as a Function of Comorbid Status

Response	Bipolar Without Anxiety Comorbidity	Bipolar With Anxiety Comorbidity	p Value
Good response to lithium	88% (91/103)	87% (27/31)	1
Good response to anticonvulsant drugs	85% (29/34)	54% (6/11)	< .05

an association with any anxiety disorders (B = -0.099, p = .09). Similar analyses were carried out for the other groups of anxiety disorders, but we found no evidence of impact on the severity of bipolar disorder.

Impact of Comorbid Anxiety Disorders on Mood Stabilizer Efficacy

There was no difference in the efficacy of lithium treatment between patients with comorbid anxiety disorders (87% good responders) and patients with no comorbid anxiety disorders (88% good responders) (p = 1) (Table 4). The response to anticonvulsants appeared to be different between bipolar patients with comorbid anxiety disorders (54% good responders) and patients with no anxiety disorder (85% good responders) (p < .05).

Temperament, Familial History of Affective Disorders, and Anxiety Comorbidity

We found a strong association between depressive temperament and comorbidity with all anxiety disorders. Patients with a low score for hyperthymic temperament as defined by Akiskal and Mallya,¹⁶ i.e., presenting depressive temperament characteristics, were at high risk of anxiety disorders (B = -0.131, p = .004). This relationship also held true for panic disorders (B = -0.11, p = .015) and for phobias (B = -0.23, p = .009). By contrast, we found no association between positive family history of affective disorders and any comorbid anxiety

disorders ($B = -0.074$, $p = .79$) for panic disorders ($B = -0.168$, $p = .60$) or for phobia ($B = -0.019$, $p = .9$).

DISCUSSION

In this study, we found that 24% of bipolar patients had at least 1 anxiety disorder: 16% of patients had panic disorder (with and without agoraphobia and panic attacks), 11% had phobia (agoraphobia without panic disorder, social phobia, and other specific phobias), and 3% had OCD. We found that 47% ($N = 35$) of the patients with anxiety disorders had more than 1 anxiety disorder. Bipolar disorder began at an earlier age in bipolar patients with panic disorder than in bipolar patients without panic disorder. A poor response to anticonvulsants was observed in bipolar patients with anxiety disorder compared with bipolar patients without anxiety disorders, whereas no difference was observed between the 2 groups in response to lithium treatment. Depressive temperament was identified as a risk factor for the development of comorbid anxiety disorders in bipolar patients.

This study was the first to focus on the comorbidity of all anxiety disorders and bipolar disorders in a large cohort, exploring specifically its impact on outcome and the response to various mood stabilizers. Our findings are consistent with others suggesting that anxiety disorders are frequent in bipolar illness. Surprisingly, with the exception of the earlier age at onset for the bipolar disorder observed in patients with comorbid panic disorder, comorbid anxiety disorders had no great impact on the outcome of bipolar illness. This may be due to our cohort's consisting mainly of patients with type I bipolar disorder. In a sample with more bipolar II patients, it might be possible to detect a greater impact of anxiety disorders on the outcome of bipolar illness. Indeed, our results are consistent with those of Perugi et al.,¹⁹ showing higher levels of anxious comorbidity in bipolar II patients than in bipolar I patients.

Our results conflict with those of certain other studies. Comorbidity with anxiety disorder was less frequent in our study than in a study by McElroy et al.,⁶ who reported anxiety disorders in 42% of their cohort, versus only 24% in ours. The main difference between the 2 sets of results is that McElroy et al. reported social phobia in 16% of patients and simple phobia in 10% of patients, whereas only 11% of our patients were found to have any type of phobia. The frequency of OCD was also lower in our study (3%) than the prevalences reported by Krüger et al.^{1,10} (35% and 7%) and McElroy et al.⁶ (9%). Thus, OCD prevalence appears to be highly variable across studies. The prevalence of panic disorder, the anxious disorder most frequently studied in patients with bipolar disorder, is generally reported to be around 20% (20% by McElroy et al.,⁶ 21% by Chen and Dilsaver²), which is consistent with our findings (16%). Some of the differences between

the prevalences of anxiety disorders in our study and in the most comparable study by McElroy et al. may be accounted for by the fact that fewer of our patients had a current or past history of substance misuse (21% vs. 42%).

To our knowledge, ours is the first study that has dealt with the impact of anxiety comorbidity as a whole on the course of bipolar disorder. McElroy et al.⁶ assessed the impact of Axis I comorbidity as a whole on bipolar clinical features, and others' studies have only partially explored aspects of this issue. Patients with panic disorder²⁰ or high anxiety scores²¹ have been found to have high rates of lifetime suicide attempts, and patients with panic disorder who attempted suicide were significantly more likely to have suffered from major depressive episodes and alcohol or other substance abuse in their lifetime than were patients with panic disorder who did not attempt suicide.²² However, the relative effects of panic disorder on suicidality among individuals with bipolar disorder are unknown.² In our study, we found no difference in the number or type of suicide attempts between bipolar patients with and without panic disorders, possibly because bipolar disorder is strongly associated with suicide attempts even in the absence of panic disorder.

Our study is the first to show that bipolar patients with anxiety disorders may have a poorer response to long-term treatment, depending on the type of mood stabilizer given. However, our results require confirmation in a larger group of patients treated with anticonvulsant drugs, and, because ours was an open study without randomization for treatment, the results must be taken with caution. Such studies may help for developing guidelines for the management of these complex patients.

We have previously shown that temperament characteristics are associated with certain clinical features of bipolar illness¹⁶ and with a higher risk of mood switch for hyperthymic bipolar patients.¹⁷ Anxiety disorder comorbidity also seems to be strongly associated with depressive temperament. Overall, these results indicate that hyperthymic and depressive temperament may correspond to 2 different subgroups of bipolar disorder.

In conclusion, a few recent studies have suggested that bipolar disorders with and without comorbid panic disorder correspond to distinct genetic forms of this mood disorder. Rotondo et al.²³ found that bipolar patients with and without panic disorder had different genetic profiles for the catechol-*O*-methyltransferase and serotonin transporter (5-HTT) gene polymorphisms. Moreover, in a large familial study, MacKinnon et al.¹² confirmed their previous results¹¹ and showed that the risk of panic disorder with familial bipolar disorder appears to be co-inherited. As some comorbid anxiety disorders seem to identify a genetic subtype of bipolar disorder, Nemeroff²⁴ emphasized in a recent editorial the need to know whether anxiety comorbidity interferes with the course of bipolar

illness and treatment response. This study provides some elements of the response to this question.

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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