The Comorbidity of Anxiety Disorders in Bipolar I Patients: Prevalence and Clinical Correlates

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Abstract: The purpose of this study was to determine the prevalence of lifetime anxiety disorders in bipolar I patients in Sanliurfa, Turkey, and to assess the association between comorbidity and several demographic and clinical variables. Seventy bipolar I patients in remission were assessed by means of the Structured Clinical Interview for DSM-IV axis I Disorders-Clinician Version (SCID-I-CV), Anxiety Disorder Module in order to detect lifetime comorbid anxiety disorders. Nineteen (27.1%) bipolar I patients were diagnosed with at least one lifetime comorbid anxiety disorder. The most common anxiety disorders in this sample were obsessive compulsive disorder (12.8%) and specific phobia (12.8%), followed by panic disorder (5.7%). Anxiety disorder comorbidity appears to be associated with greater number of hospitalizations, psychotic symptoms and suicide attempts in patients with bipolar I disorder. As comorbidity has a clear impact on the course of bipolar patients, special attention to this issue should be paid when interviewing bipolar patients.

Introduction

Clinical and epidemiological studies have provided convincing evidence that comorbid anxiety disorders are relatively prevalent among patients with bipolar disorder, found in up to 65% of cases (1-5). Comorbidity of anxiety disorders may be associated with greater suicidality, substance abuse, resistance to pharmacological treatment, and poor outcome (2, 6-8). Bipolar disorder patients with high level of anxiety symptoms may have an earlier onset of mood illness (1, 8). Comorbidity of anxiety disorders has been claimed to be the strongest predictor of poor compliance in bipolar patients (9).

Multiple anxiety disorder comorbidities occur in a significant minority of bipolar disorder patients. Tamam and Ozpoyraz (5) found lifetime multiple anxiety disorders in 39% of bipolar disorder outpatients in remission. Henry et al. (10) studied 318 inpatients including bipolar I, and found that 24% had at least one lifetime anxiety disorder and 11% of the patients had more than one such disorder.

The link between bipolar disorder and panic disorder has been demonstrated by genetic studies (11, 12). MacKinnon et al. (13) studied 203 families of probands with bipolar disorder and demonstrated that family history of bipolar disorder is a risk factor of panic disorder. Family studies also revealed an association between bipolar disorder and obsessive-compulsive disorder. Coryell et al. (14) diagnosed obsessive-compulsive disorder-OCD in 2.7% and 5.3% of relatives of bipolar I and bipolar II patients, respectively, compared to 0.8% among relatives of non-bipolar probands.

The purpose of this study was to determine the prevalence of lifetime anxiety disorders in bipolar I patients and to assess the association between comorbidity and several demographic and clinical variables. This study provides a view of lifetime anxiety disorder comobidity in bipolar I patients in Sanliurfa, Turkey.

Methods

Participants

All patients presenting at the Bipolar Disorder Outpatients Clinics of the Harran University, Sanliurfa, Southeastern Turkey, between 2002 and 2004 were considered for inclusion in the study. Patients diagnosed with bipolar disorder in the psychiatry clinics of Harran University Research Hospital (a tertiary level health institute which receives referrals from the southeastern part of Turkey) were recruited for the study. Among patients enrolled in this unit, those

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who met the following criteria were included in the study: 1) aged at least 18 years; 2) DSM-IV diagnosis of bipolar I disorder; 3) clinically in remission for at least one month before inclusion in the study as corroborated by routinely administered scales during follow-up visits (17-item Hamilton Rating Scale for Depression score of < 7 and Young Mania Rating Scale score of < 5 for at least one month in two consecutive visits were used as confirmative scores for remission); and 4) written informed consent obtained before participation in the study. The diagnosis of bipolar I disorder was clinically made according to DSM-IV criteria on admission of the patient to the follow-up routine of outpatient clinics and later confirmed by interviews conducted by the first and the second authors. Exclusion criteria were 1) history of seizure, head injury with loss of consciousness, or other neurologic disorder; 2) concurrent active medical disorder; 3) unwillingness to cooperate with investigators; and 4) contact loss.

Among the 116 cases who were enrolled in our bipolar disorder outpatient clinic, 70 patients (30 females and 40 males), aged between 18 and 59 years, fulfilled the inclusion criteria for the study. Our sample included 42 patients (60%) discharged from inpatient care and 28 patients (40%) who only received outpatient care. Out of 116 patients, 17 had other subtypes of bipolar disorder (i.e., bipolar II disorder, bipolar disorder not otherwise specified and schizoaffective disorder, bipolar type), four had a history of seizure, head injury with loss of consciousness, or other neurologic disorders, two had concurrent active medical disorders, 19 did not wish to be interviewed, and four were lost in follow-up. These cases, therefore, were excluded from the study.

Measures

1. Sociodemographic and clinical variables of the subjects including previous hospitalizations, number and type of previous episodes, presence of psychotic features, suicide attempts and age at onset of the disorder were obtained from inpatient and outpatient medical records of the cases, patient interviews, and from first-degree relatives when available.

2. The Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-I-

CV), Anxiety Disorder Module (15, 16) was used to diagnose lifetime comorbidities of anxiety disorders. All patients were interviewed by the first author, who was trained in the use of the SCID-I. Individuals who were found to present at least one lifetime anxiety disorder were included in the group "with comorbid anxiety disorder," and those without any comorbid anxiety disorder, in the group "without comorbid anxiety disorder."

3. Hamilton Rating Scale for Depression (HAM-D), a 17-item clinician-rated instrument (17, 18), was used to determine the level of depression.

4. Young Mania Rating Scale (YMRS) is a clinical rating scale containing 11 items assessing manic symptoms (19). Reliability ratings have been high with the Turkish version (20).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS 11.5, SPSS Inc., Chicago, IL) was used for all statistical analyses. Statistical methods consisted of chi square statistic with Yates' correction or Fisher's exact test for the comparison of categorical data, and Mann-Whitney test for dimensional variables. The 2-tailed significance level was set at .05.

Results

Of the 70 patients in the sample, 19 (27.1%) were diagnosed with at least one lifetime comorbid anxiety disorder. Of the 27.1% diagnosed with any anxiety disorder, 68.4% (18.5% of total sample) were found to have a single anxiety disorder, 31.6% (8.6% of the total sample) had two anxiety disorders, and 5.3% (1.4% of the total sample) had three anxiety disorders. The most common anxiety disorders in this sample, based on frequency, were OCD (12.8%, n=9) and specific phobia (12.8%, n=9), followed by panic disorder (5.7%, n=4), generalized anxiety disorder (1.4%, n=1), posttraumatic stress disorder (1.4%, n=1), social phobia (1.4%, n=1), and agoraphobia without panic disorder (1.4%, n=1).

When patients with and without anxiety disorder comorbidity were compared (Table 1), there were no significant differences between them with respect to demographic data. Neither were there significant

differences regarding most clinical variables such as age of onset, rapid cycling, seasonality and total number of episodes. Number of hospitalizations (p=0.003), psychotic symptoms (p=0.02), suicidal ideation (p=0.001) and number of suicide attempts (p<0.001) were associated with anxiety disorder comorbidity in patients with bipolar I disorder.

Table 1. *Comparison of bipolar I patients with and without anxiety disorder comorbidity with respect to demographic and clinical variables*

	BD with anxiety disorder comorbidity (n=19)	BD without anxiety disorder comorbidity (n=51)	Analysis	
	Mean (SD)	*Mean (SD)*	*U^a*	*p*
Age	34.73 (9.09)	33.88 (9.88)	-0.39	NS
Age of onset of BD	24.52 (7.80)	23.17 (7.80)	-0.72	NS
Total number of episodes	6.31 (3.66)	9.15 (12.91)	-0.35	NS
Number of hospitalizations	2.52 (2.63)	1.00 (1.42)	-3.01	0.003
	n (%)	*n (%)*	*χ^2(df=1)*	*p*
Sex			1.01	NS
Female	10 (53)	20 (39)		
Male	9 (47)	31 (61)		
First episode			0.03	NS
Manic	13 (68)	33 (65)		
Depressive	6 (32)	17 (35)		
Rapid cycling			*	NS
Present	1 (5)	2 (4)		
Absent	18 (95)	49 (96)		
Seasonal pattern			0.08	NS
Present	6 (32)	18 (35)		
Absent	13 (68)	33 (65)		
Psychotic symptoms			5.09	0.02
Yes	16 (84)	28 (55)		
No	3 (16)	23 (45)		
Suicidal ideation			10.92	0.001
Yes	13 (68)	13 (25)		
No	6 (32)	38 (75)		
Suicide attempts			12.47	<0.001
Yes	11 (58)	8 (16)		
No	8 (42)	43 (84)		
Family history of suicide			0.04	NS
Yes	3 (16)	7 (14)		
No	16 (84)	43 (86)		
Affective disorder in first-degree relatives			2.91	NS
Yes	11 (58)	18 (35)		
No	8 (42)	33 (65)		
Treatment			0.79	NS
Mood-stabilizer monotherapy	6 (32)	22 (43)		
Polymedicated	11 (58)	24 (47)		

BD = Bipolar I disorder;   SD = standard deviation;   NS = not significant. ^{a} Mann-Whitney test;   *Fisher's exact test.

Discussion

Our results on the rates of comorbidity (27.1% of patients had at least one comorbid diagnosis) are comparable to the rates reported elsewhere (10, 21). However, our rates are clearly lower than those reported in other studies (over 50%) conducted in acutely manic or psychotic samples (22, 23). This difference could be explained by the fact that we included patients in remission, avoiding the risk of mistaking acute affective symptomatology provided by a second illness. An alternative explanation may be that we recruited our group from an outpatient sample, avoiding the bias of a selected population of complicated bipolar patients in an inpatient sample.

Among anxiety disorders, OCD and specific phobia were the most common comorbid anxiety disorders with a lifetime comorbidity of 12.8% for each, followed by panic disorder (5.7%). The prevalence rates determined for OCD, specific phobia and panic disorder were in accordance with the results of prior studies. In the literature, comorbidity rates were 6-38%, 5-25%, 5-26% for OCD, specific phobia and panic disorder, respectively (1-3, 5, 22).

Chen and Dilsaver (24) analyzed data from the ECA study, and determined that lifetime rates of OCD among subjects with bipolar disorder was 21.0%, as compared to a lifetime rate of 12.2% in subjects with unipolar depression and a lifetime rate of 2.5% in the general population. They proposed that the clinical features defining bipolar disorder and OCD might represent manifestations of a single underlying diathesis.

Bipolar patients with psychiatric comorbidity were found to have a greater length of hospital stay, lower rate of recovery at discharge, and a worse response to somatic treatment than those without comorbidity (22, 25, 26). In parallel with these reports, we found that patients with comorbid anxiety disorders had more hospitalizations than those without such comorbid conditions.

The relationship between psychotic symptoms and anxiety disorder comorbidity among bipolar patients remains elusive. While Vieta et al. (27) reported no relationship between psychotic symptoms and comorbidity, Cassano et al. (8) found that paranoid ideations and psychoticism were associated with multiple anxiety comorbidity. Although our results indicate a positive relationship between comorbidity and psychotic symptoms in bipolar patients, we cannot determine if comorbity is causing psychotic symptoms or is resulting from psychotic symptoms.

In the present study, we found that suicidal ideation and suicide attempts were more common among patients with anxiety disorder comorbidity than those without comorbidity. It has been suggested that the presence of secondary psychiatric disorders is associated with a higher rate of past suicide attempts among bipolar I patients (27). Similar results have been reported by Vieta et al. (28) in a bipolar II sample. Bipolar patients with high anxiety scores have been found to have high rates of lifetime suicidal behaviors (29).

Little is known about the precise mechanism by which anxiety elevates suicidality, and study of this issue may need to precede the development of interventions specifically aimed at suicide prevention in this population. Patients with acute anxiety may be less capable of tolerating uncomfortable affects and utilizing other resources, such as social supports or cognitive strategies, to reduce suicidality. Psychological interventions to prevent suicide should focus in part on problem-solving skills and improved tolerability of distress (3, 30).

The main limitation of this study lays in the retrospective recall of some variables, which may certainly bias some results. Another limitation is the relatively small sample size that could limit our ability to generalize the results to bipolar patients in general.

This study suggests that the rates of comorbidity of anxiety disorders among bipolar I patients in Sanliurfa, Turkey are comparable to those from other places. Future large-scaled prospective clinical and epidemiological studies examining the prevalence and clinical variables of comorbid anxiety disorders in bipolar I patients and other bipolar subtypes in Turkey are required for a more general view on the subject.

In conclusion, anxiety disorder comorbidity is prevalent and it appears to be associated with greater number of hospitalizations, psychotic symptoms, and suicide attempts in patients with bipolar I disorder in Sanliurfa, Turkey. As comorbidity has a clear impact on the course of bipolar patients, special at-

tention to this issue should be paid when interviewing bipolar patients. Future studies will need to examine clinical correlates of comorbidity, and to focus on additional or alternate intervention for bipolar patients with comorbid anxiety disorders.

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