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ORIGINAL PAPER

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Comorbidity of anxiety disorders in patients with remitted bipolar disorder

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Abstract Comorbidity between bipolar disorder and anxiety disorders has attracted considerable attention in recent years. However, a majority of the earlier studies examined anxiety disorders in acutely ill patients resulting in a possible confounding effect of the affective episodes. This study examines the prevalence of anxiety disorders in remitted bipolar subjects recruited from a psychiatric hospital in India and their effect on the severity of bipolar illness. A total of eighty remitted DSM-IV adult bipolar subjects and 50 non-psychiatric controls were recruited over a 10-month period. They were evaluated using a structured interview and various scales. The effect of anxiety disorders on bipolar severity was analyzed using multiple regression analyses. Anxiety disorders were highly prevalent in bipolar subjects compared to controls (49 [61%] vs. 7 [14%], $\chi^2 = 28.01$, $P < 0.001$). Commonest lifetime anxiety disorder was obsessive-compulsive disorder (35%). Lifetime anxiety disorder had significant effect on all four indices of severity of illness, that included (1) percentage of time spent in episodes (Beta = 18.67, SE = 5.11, $P < 0.001$), (2) maximum period of continuous euthymia in the preceding 2 years (Beta = −5.26, SE = 1.71, $P = 0.003$), (3) presence of psychosis (Beta = 3.22, SE = 1.02, $P = 0.002$), and 4) response to mood stabilizers (Beta = −2.11, SE = 0.76, $P = 0.006$). The findings of this study confirm previous observations of the high prevalence and negative impact of co-morbid anxiety disorders in bipolar disorder and also demonstrate that the findings are similar in culturally diverse settings. Future studies should systematically examine the various treatment options for anxiety disorders in bipolar patients. It is also necessary to examine the neurobiological and family/genetic correlates of anxious bipolar subjects to validate if they are a subgroup of bipolar disorders.

Key words bipolar disorder · anxiety disorders · comorbidity · obsessive-compulsive disorder

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Introduction

In recent years, comorbidity between bipolar disorder and anxiety disorders has drawn considerable attention [1]. Several clinical and epidemiological studies have reported elevated rates of anxiety disorders in bipolar disorder [2–12]. Common comorbid anxiety disorders include panic disorder (PD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), social phobia (SP), and post-traumatic stress disorder (PTSD). Some reports have suggested a specific association between bipolar II disorder and anxiety disorders [13, 14], but recent studies have challenged this view by reporting high rates of anxiety disorders in bipolar I disorder [2–4]. Comorbidity of anxiety disorders in bipolar disorder has important clinical and theoretical implications [1]. Clinically, it is vital to recognize and treat anxiety disorders because anxiety disorders may contribute to poor recovery, poor treatment response, less time in euthymia and high rates of suicide attempts and substance abuse [3, 8, 15, 16]. Theoretically, it is possible that bipolar disorder with comorbid anxiety disorders may be a severe subtype of the bipolar disorder, or the two may be distinct disorders but co-occur by chance in greater frequency because both are common disorders [1].

A majority of the earlier studies included acutely ill patients and typically did not have controls. In this study, we examined comorbid patterns of anxiety disorders in remitted adult bipolar patients attending a large psychiatric hospital in India in comparison with the rates in non-psychiatric controls. We also examined the effect of current and lifetime anxiety disorders and the individual anxiety disorders on the measures of bipolar severity that include percentage of time spent in episodes, maximum duration of continuous euthymia in the preceding 2 years, presence of psychotic symptoms and response to mood stabilizers. We hypothesized that anxiety disorders would be more prevalent in bipolar subjects compared to controls and that they could have detrimental effect on the course of bipolar illness.

Methods

Subjects

A total of 80 subjects fulfilling the inclusion criteria were recruited from the adult psychiatric services of the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India between March 2004 and January 2005. Three other subjects also fulfilled the inclusion criteria but could not be evaluated because they did not keep up the appointments and expressed their unwillingness. The inclusion criteria included (1) age 18–45 years, (2) DSM-IV diagnosis of bipolar disorder, (3) clinical remission corroborated by the clinical notes in the charts, information from the patient and relatives, and a score of less than 8 on both the Hamilton Depression Rating Scale (HDRS) [17] and the Young Mania Rating Scale (YMRS) [18], and (4) informed consent to participate in the study. We recruited only patients between 18 and 45 years for two reasons. Firstly, the purpose of this study was to study anxiety disorder comorbidity in adults and not in juvenile population; therefore, juvenile population had to be excluded. Secondly, we used an upper cut-off age of 45 years to exclude older bipolar subjects. Older bipolar subjects fall into two groups. The first group could include older bipolar subjects who have had their onset before 45 years and in these subjects, it is often difficult to get a good history about the life course of bipolar disorder and comorbidities because of poor recall and unavailability of relatives who can give a reliable history about the early course of illness. The second group could include elderly bipolar subjects who often have associated cerebrovascular diseases and cognitive dysfunction.

We recruited 50 consenting second or third degree relatives of the neurologically ill patients admitted in the neurology and neurosurgery wards of the NIMHANS as controls. The controls were recruited during the same time frame. The controls had to be between age 18 and 45 years. We chose relatives of neurologically ill patients as controls and not the patients themselves because there is a possibility that they may have had higher rates of anxiety and depression because of the neurological illness. In other words, neurologically ill patients may not be similar to general population and therefore, not suitable as controls. On the other hand, their distant relatives would be closer to the general population characteristics. The purpose was to have a control group, which is similar to the general population. We did not chose the immediate relatives (first degree) as controls, because they are often the primary care takers of the neurologically ill patients and there is a possibility of higher rates of psychiatric morbidity in them due to the burden associated with caring for the ill. It is a common practice in Indian hospitals for the relatives to visit patients to enquire about their health. We just used this situation to recruit controls for this study.

Procedures

Initial diagnosis of bipolar disorder was made according to the DSM-IV criteria after detailed unstructured clinical evaluation by at least two clinicians one of whom was a senior consulting psychiatrist of the clinical team. Since the patients were already attending the clinical services of the NIMHANS hospital, we had access to the clinical records of all the patients. The diagnosis was reconfirmed at the time of evaluation by administering the Structured Clinical Interview for DSM-IV Axis I disorders-Clinical Version (SCID-CV) [19].

Sociodemographic and clinical variables of the subjects were obtained from the medical records, and from the interviews of the patients and their relatives. Life charting of the course of bipolar illness was made for each subjects based on the information available from all the sources [20]. The assessments were done when subjects were in clinical remission to avoid the possible confounding factors that may be associated with the episode.

Comorbidity was assessed using the SCID-CV. Where appropriate, subjects with comorbid anxiety disorders were also administered the Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) [21, 22], the Hamilton rating Scale for Anxiety (HARS) [23], the Liebowitz Social Phobia Anxiety Scale (LSAS) [24], and the Panic Disorder Severity rating Scale (PDSS) [25]. The SCID-CV and the various scales were administered by the first author (AZ), a psychiatrist who was trained to administer them by one of the senior authors (YCJR).

Four predetermined indices of the severity of bipolar illness were used.

1. Percentage of time spent in episodes since onset
2. Maximum duration of continuous euthymia in the preceding 2 years [3]
3. Response to mood stabilizer [26]. Good response was defined as patients displaying a subjective and objective improvement during the treatment period (decrease in frequency and severity of episodes as determined by the accounts of patients and their relatives and from the clinical charts), or a relapse at termination of treatment, or no relapse while on treatment. Poor responders were patients who did not fulfill these criteria and for whom a new therapeutic strategy was used
4. Presence of psychotic symptoms in any of the episodes [26]

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 11.0. The χ^2 test was used to compare categorical variables. The continuous variables were analyzed using the independent sample t test. Multiple linear regression and multiple logistic regression were employed to find the effect of anxiety disorder(s) on the continuous and categorical dependent variables, respectively. All p values were two-tailed and statistical significance was set at $P < 0.05$.

Results

The study included 80 subjects with bipolar disorder and 50 controls. Of the 80 bipolar subjects, a majority was in remission for at least 2 months ($n = 72$, 90%) and the remaining were in remission for at least 1 month at the time of assessment of comorbidity and severity measures. The median time in remission was 4 months. The sociodemographic and clinical profile of the sample is given in Table 1. The bipolar sample included bipolar I, bipolar II and bipolar-not otherwise specified (NOS). We included five subjects with

Table 1 Sociodemographic and clinical profile of bipolar subjects and controls

Variable	Bipolar subjects ($n = 80$)	Controls ($n = 50$)	X^2/t	P
Mean age in years (SD)	30.06 (7.77)	31.44 (7.85)	0.997	0.331
Mean age at onset in years (SD)	21.51 (5.91)	–	–	
Illness duration in months (SD)	99.03 (70.65)	–	–	
Sex, *n* (%)				
Male	57 (71)	38 (76)	0.353	0.553
Female	23 (29)	12 (24)		
Marital status, *n* (%)				
Married	40 (50)	33 (66)	3.978	0.053
Single	38 (48)	17 (34)		
Divorcee	2 (2)	0		
Background, *n* (%)				
Rural	22 (28)	15 (30)	0.004	0.951
Urban	58 (72)	35 (70)		
Years of education, *n* (%)				
<5 years	9 (11)	6 (12)	1.891	0.360
5–12 years	34 (43)	25 (50)		
>12 years	35 (44)	19 (38)		
Illiterate	2 (2)	0		
History of failure in education	30 (38)	2 (4)	18.60	<0.001
Occupation, *n* (%)				
Student	11 (13)	3 (6)	12.084	0.017
Housewife	14 (18)	9 (18)		
Employed	17 (21)	20 (40)		
Farmers/laborers/petty business	24[a] (30)	17[b] (34)		
Unemployed	14 (18)	1 (2)		
Bipolar type, *n* (%)				
Bipolar I	65 (81)			
Bipolar II	10 (13)			
Not otherwise specified	5 (6)			
Single bipolar episode	3 (4)			
Polarity of recent episode				
Mania	43 (54)			
Hypomania	13 (17)			
Depression	18 (22)			
Mixed	6 (8)			
Current treatment				
Mood stabilizer + antipsychotic	40 (50)			
Mood stabilizers alone	37 (46)			
Profile of mood stabilizer use				
Lithium	38 (48)			
Valproate	15 (19)			
Carbamazepine	5 (7)			
Lamotrigine	1 (1)			
Combination	18 (22)			
Atypical antipsychotics[c]	25 (31)			
Typical antipsychotics[d]	15 (19)			

[a]Farmers (agriculturists) and laborers = 21, Petty businessmen = 3
[b]Farmers and laborers = 10, Petty businessmen = 7
[c]Olanzepine = 12, Risperidone = 13
[d]Chlorpromazine = 13, Chlorpromazine + Fluphenazine = 1, Zuclophenthixol = 1

bipolar NOS because our inclusion criteria were any subjects with DSM-IV diagnosis of bipolar disorder. These five subjects were diagnosed bipolar NOS because four had developed hypomania in the background of antidepressant use and one subject developed hypomania following administration of electroconvulsive therapy (ECT), but the bipolar episodes persisted much beyond the reasonable period of one month even after withdrawal of medication/ECT. Therefore, their bipolarity could not be attributed to medication use or ECT. The DSM-IV recommends that these patients be classified as bipolar NOS. The bipolar subjects were similar to controls with respect to age, gender ratio, rural/urban background, and number of years of education. However, bipolar subjects were more likely to be unmarried and unemployed with a history of 'failures' in school and colleges.

Comorbidity

Table 2 displays lifetime and current prevalence of anxiety disorders in bipolar subjects compared to controls. All the anxiety disorders except panic disorder were significantly more prevalent in bipolar subjects than in the controls. The most prevalent

Table 2 Lifetime and current comorbid anxiety disorders in subjects (n = 80) and controls (n = 50)

Anxiety disorder	Lifetime		χ^2	P	Current		χ^2	P
	Subjects n (%)	Controls n (%)			Subjects n (%)	Controls n (%)		
OCD	28 (35)	1 (2)	19.334	<0.001	20 (25)	1 (2)	12.071	0.001
Social phobia	24 (30)	4 (8)	8.812	0.003	23 (29)	4 (8)	8.051	0.005
GAD	20 (25)	3 (6)	7.628	0.006	19 (24)	3 (6)	6.895	0.009
Panic disorder	6 (7)	0	3.931	0.081	4 (5)	0	2.579	0.298
Anxiety NOS	4 (5)	0	2.579	0.298	0	0	–	–
Any anxiety disorder	49 (61)	7 (14)	28.015	<0.001	40 (50)	7 (14)	17.276	<0.001

lifetime anxiety disorder in bipolar subjects was OCD, followed by SP, GAD and PD. The most common current anxiety disorder was SP, followed by OCD, GAD and PD. Bipolar subjects had significantly higher rates of multiple anxiety disorders (two or more) compared to controls. None of the bipolar subjects had clinically diagnosable specific phobias. Three subjects did report specific phobias but were subclinical because there was no significant distress or interference because of fears.

The mean age at onset (SD) of lifetime OCD, SP, GAD and PD were 19.48 (4.60), 15.96 (2.18), 17.86 (2.46) and 22.67 (5.20) years, respectively, whereas the mean age at onset of bipolar disorder was 21.51 (5.91) years. In 15 subjects with OCD (54%), 21 with SP (88%), 17 with GAD (85%), and 2 with PD (33%), the onset of anxiety disorder preceded the onset of bipolar disorder.

Other comorbid diagnoses in the bipolar subjects included alcohol dependence (n = 4, 5%), and somatization disorder (n = 7, 9%). None of the subjects had post-traumatic disorder or eating disorders. The controls did not report any other comorbid diagnoses.

Bipolar disorder with and without anxiety disorder

The clinical profile of bipolar subjects with and without lifetime and current anxiety disorders is shown in Table 3. The bipolar subjects with anxiety disorders were younger, had earlier age at onset of illness, and were overrepresented by male subjects and those with juvenile onset illness compared to those without anxiety disorder. They also had a higher rate of history of hospitalization, and academic failures. There was no significant difference with respect to the prevalence of bipolar subtypes in those with and without anxiety disorder. First episode polarity was mainly depression in those with anxiety. Bipolar subjects with and without anxiety did not differ with respect to the number of manic and hypomanic episodes, but mixed episodes were more frequent in those with anxiety disorder. Those with current anxiety disorder also had greater number of depressive episodes.

Compared to those without anxiety disorder, those with anxiety disorder (1) spent greater percentage of time in episodes, (2) had lesser duration of continuous euthymia in the preceding 2 years, (3) had a higher rate of psychotic features, and (4) poorer response to mood stabilizers. Those with anxiety disorder also reported a greater use of antipsychotics, antidepressants and benzodiazepines currently than those without. History of antidepressant-induced switch was also greater in those with anxiety disorder.

Effect of age at onset and gender

We examined the profile of anxiety disorders and bipolar illness variables according to age at onset of bipolar disorder and gender because those with anxiety had earlier age at onset and were overrepresented by juvenile onset and male subjects (Table 3). The bipolar subjects included 32 subjects with juvenile onset of illness (≤18 years) and the remaining 48 with adult onset illness (>18 years). The juvenile onset bipolar subjects were younger (25.03 ± 6.45 vs. 33.42 ± 6.72, t = 5.553, P < 0.001), and less likely to be married (28% vs. 65%, P = 0.003) compared to the adult onset subjects. They also spent a higher percentage of time in episodes (34.62 ± 28.32 vs. 22.8 ± 22.18, t = 2.087, P = 0.04) with a high rate of 'history of hospitalization' (72% vs. 44%, χ^2 = 6.136, P = 0.013). Although the prevalence of anxiety disorders was comparable in juvenile onset and adult onset subjects, the juvenile onset subjects had earlier onset of SP (14.92 ± 2.27 vs. 17 ± 1.54 years, t = 2.269, P = 0.015), GAD (16.60 ± 2.32 vs. 19 ± 2.05 years, t = 2.518, P = 0.021) and OCD (18 ± 4.39 vs. 21.07 ± 4.41 years, t = 1.878, P = 0.071). The severity of anxiety disorders measured by the Y-BOCS (15 ± 8.14 vs. 13.82 ± 6.54, t = −0.382, P = 0.707), the LSAS anxiety (31.50 ± 12.96 vs. 31.90 ± 15.12, t = 0.067, P = 0.947) and avoidance sub scales (23.06 ± 12.45 vs. 26.60 ± 15.70, t = 0.558, P = 0.564), the HARS (19.80 ± 4.47 vs. 21.64 ± 4.95, t = 0.890, P = 0.385), and the PDSS (14 ± 0 vs. 13.50 ± 0.71, t = −0.577, P = 0.667) was similar in both the juvenile onset and adult onset bipolar subjects.

The prevalence of SP, lifetime (37% vs. 13%, χ^2 = 4.42, P = 0.036) and current (37% vs. 9%, χ^2 = 6.338, P = 0.012) and GAD lifetime (32% vs. 9%, χ^2 = 4.577, P = 0.032) and current (30% vs. 9%, χ^2 = 4.040, P = 0.044) was significantly greater in the

Table 3 Clinical profile of bipolar subjects with and without lifetime and current anxiety disorders

Variable	Lifetime anxiety		Analysis	Current anxiety		Analysis
	Yes (n = 49) Mean (SD)/n (%)	No (n = 31) Mean (SD)/n (%)		Yes (n = 40) Mean (SD)/n (%)	No (n = 40) Mean (SD)/n (%)	
Age, years	28.29 (7.09)	32.87 (8.06)	t = 1.134 P = 0.009	25.03 (6.45)	33.42 (6.72)	t = 5.553 P < 0.001
Age at onset, years	20.47 (5.07)	23.16 (6.80)	t = 2.023 P = 0.047	19.83 (4.64)	23.20 (6.59)	t = 2.649 P = 0.010
Juvenile onset	25 (45)	7 (23)	χ^2 = 6.399 P = 0.018	22 (55)	10 (25)	χ^2 = 7.5 P = 0.006
Gender, male	40 (82)	17 (55)	χ^2 = 6.655 P = 0.013	32 (80)	25 (63)	χ^2 = 2.990 P = 0.084
History of hospitalization	32 (65)	12 (39)	χ^2 = 5.427 P = 0.020	27 (68)	13 (33)	χ^2 = 5.051 P = 0.025
Academic failure	27 (55)	3 (10)	χ^2 = 16.716 P < 0.001	25 (63)	5 (13)	χ^2 = 21.333 P < 0.001
Bipolar type			χ^2 = 0.79			χ^2 = 1.938
Bipolar I	39 (80)	26 (84)	P = 0.674	31 (77)	34 (85)	P = 0.379
Bipolar II	6 (12)	4 (12)		5 (13)	5 (13)	
Others	4 (8)	1 (3)		4 (10)	1 (02)	
First episode			χ^2 = 7.177			χ^2 = 8.917
Mania	18 (37)	20 (65)	P = 0.008	14 (35)	24 (60)	P = 0.02
Hypomania	5 (10)	3 (10)		3 (08)	5 (13)	
Depression	23 (47)	8 (26)		22 (55)	9 (22)	
Mixed	3 (6)	0		1 (2)	2 (5)	
No. of manic episodes	2.41 (4.46)	2.87 (2.33)	t = 0.532 P = 0.596	2.55 (4.87)	2.63 (2.25)	t = 0.088 P = 0.930
No. of hypomanic episodes	0.73 (1.20)	0.84 (1.39)	t = 0.354 P = 0.724	0.85 (1.29)	0.70 (1.26)	t = −0.525 P = 0.601
No. of depressive episodes	1.90 (2.48)	1.10 (1.34)	t = −1.518 P = 0.133	2.10 (2.68)	1.13 (1.24)	t = −2.089 P = 0.04
No. of mixed episodes	0.78 (1.28)	0	t = 3.368 P = 0.001	0.75 (1.28)	0.20 (0.72)	t = −2.372 P = 0.02
History of antidepressant switch	12[a] (25)	0	χ^2 = 8.932 P = 0.008	10[b] (25)	2[c] (05)	χ^2 = 6.275 P = 0.012
% of time spent in episodes	35.49 (26.57)	14.95 (17.12)	t = −3.827 P = 0.001	34.06 (25.09)	20.99 (24.12)	t = −2.376 P = 0.02
Maximum duration of continuous euthymia in last 2 years, in months	11 (6.54)	16.65 (6.77)	t = 3.682 P < 0.001	11.23 (6.45)	15.15 (7.34)	t = 2.54 P = 0.013
Presence of psychotic features	47 (96)	19 (61)	χ^2 = 15.770 P < 0.001	39 (98)	27 (68)	χ^2 = 12.468 P < 0.001
Suicide attempts	8 (16)	1 (03)	χ^2 = 3.264 P = 0.149	6 (16)	3 (8)	χ^2 = 1.127 P = 0.481
Response to mood stabilizer	23 (56)	26 (84)	χ^2 = 10.912 P = 0.001	20 (50)	29 (73)	χ^2 = 4.266 P = 0.039
Current use of antipsychotics	34 (69)	8 (26)	χ^2 = 14.462 P < 0.001	28 (70)	14 (36)	χ^2 = 9.825 P = 0.002
Current use of antidepressants	17 (35)	2 (6)	χ^2 = 8.363 P = 0.004	15 (38)	4 (10)	χ^2 = 8.352 P = 0.004
Current use of benzodiazepines	8 (16)	0	χ^2 = 5.624 P = 0.020	7 (18)	1 (3)	χ^2 = 5 P = 0.018

[a]Bipolar I = 4, Bipolar II = 4, Bipolar NOS = 4
[b]Bipolar I = 3, Bipolar II = 3, Bipolar NOS = 4
[c]Bipolar I = 1, Bipolar II = 1

male than in the female subjects. Male bipolar subjects also had a higher rate of multiple anxiety disorders (32% vs. 9%, χ^2 = 7.810, P = 0.02). Although the severity of anxiety disorders measured by the Y-BOCS (14.50 ± 7.51 vs. 14.29 ± 7.27, t = 0.64, P = 0.950), the LSAS anxiety (31.90 ± 14.27 vs. 29.50 ± 4.95, t = 0.232, P = 0.819) and the avoidance (24.85 ± 14.45 vs. 23 ± 4.24, t = 0.177, P = 0.861) sub scales, the HARS (29.95 ± 4.81 vs. 19 ± 4.24, t = 0.548, P = 0.590) and the PDSS (13.50 ± 0.71 vs. 14 ± 0, t = −5.770, P = 0.667) was comparable in male and female bipolar subjects, male subjects had somewhat earlier onset of OCD (19.76 ± 4.10 vs. 21.07 ± 4.41, t = 1.878, P = 0.071) and PD (20.8 ± 2.77 vs. 32, t = −3.685, P = 0.021) and had a greater number of anxiety disorders (1.18 ± 1.07 vs. 0.57 ± 0.9, t = 2.411, P = 0.018) compared to female subjects.

Independent effect of anxiety disorders on the illness severity

The effect of anxiety disorders, lifetime and current on four illness severity variables was examined by employing multiple linear regression for continuous outcome variables and multiple logistic regression for categorical variables after controlling for the possible confounding effects of age, age at onset, gender, and polarity of the recent episode (Table 4). Lifetime anxiety disorder had significant effect on all four indices of severity of illness. Presence of current anxiety had significant effect on 'psychosis' and a trend towards significance on percentage of time spent in illness and longest euthymia. Understandably lifetime anxiety was a better predictor of severity of illness than the current anxiety since the indices of severity were reflective of the course and not the current clinical status.

In addition to the effect of any anxiety disorder on the illness severity, we also examined the effect of individual anxiety disorders on the same indices of illness severity after controlling for the effect of age, age at onset, gender, polarity of the recent episode and presence of other anxiety disorders (Table 4). Percentage of time in illness was predicted by current and lifetime OCD and current and lifetime PD. Current OCD and lifetime GAD predicted maximum euthymia in the preceding 2 years. Lifetime OCD also showed a trend toward prediction of maximum euthymia. Similarly, there was a trend toward prediction of response to mood stabilizers by lifetime OCD and GAD.

Discussion

The study aimed to investigate the prevalence of anxiety disorders in bipolar disorder and their influence on the illness severity. The sample consisted of mainly bipolar I subjects (81%). The study demonstrated that (1) anxiety disorders are highly prevalent in bipolar subjects and are more prevalent than in controls, (2) OCD is the commonest lifetime anxiety disorder followed by SP and GAD, all the three disorders being more prevalent than in the controls, (3) the bipolar subjects with comorbid anxiety tend to have a poorer course and are less responsive to treatment, and (4) individual anxiety disorders, particularly OCD and PD seem to have an effect on illness severity. Rates of suicide attempts and substance/alcohol dependence were low. The main strengths of the study include availability of controls, assessment during remission removing the possible confounding effects of the episode, and availability of multiple sources of information (patient and relatives' interview, and clinical charts). Additionally, the study controlled for the effects of confounding factors, including the polarity of the recent episode in determining the effect of anxiety disorder on the indices of bipolar severity.

The high rate of lifetime (61%) and current (50%) anxiety disorders in our study is consistent with the findings of recent studies that reported lifetime and current anxiety disorders in 42–61% and 31–52% of the subjects, respectively [2–4]. The findings of our study suggest that the pattern of anxiety disorder comorbidity and its negative impact in bipolar disorder are similar in culturally diverse settings. Our study also confirms the findings of the previous studies [2–4] that anxiety disorder comorbidity is not specific to bipolar II disorder as reported previously [13, 14], but equally prevalent in bipolar I subjects. It is possible that the specific association between anxiety disorder comorbidity and bipolar II disorder reported previously is the result of having studied primary anxiety disorder samples and not primary bipolar cohorts. In our study, although bipolar II

Table 4 Multiple regression analysis of the effect of anxiety disorders on illness severity

	% Time in episodes			Maximum continuous euthymia in 2 years			Response to mood stabilizers			Presence of psychosis		
	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*
Lifetime anxiety	18.67	5.11	<0.001	−5.26	1.71	0.003	−2.11	0.76	0.006	3.22	1.02	0.002
Current anxiety	9.87	1.93	0.056	−3.17	1.65	0.059	−0.82	0.57	0.149	3.22	1.18	0.006
OCD												
Lifetime	11.15	5.06	0.031	−2.88	1.73	0.099	−1.09	0.64	0.088	1.71	1.08	0.112
Current	17.79	5.12	0.001	−3.78	1.83	0.043	−1.08	0.67	0.108	0.75	0.87	0.384
SP												
Lifetime	6.42	5.15	0.217	−2.13	1.76	0.229	−0.61	0.67	0.369	0.99	1.12	0.376
Current	0.61	5.15	0.905	−1.06	1.84	0.565	−0.23	0.66	0.724	0.59	0.97	0.543
GAD												
Lifetime	5.78	5.45	0.292	−3.77	1.86	0.047	−1.21	0.67	0.073	0.26	1.04	0.799
Current	3.49	5.54	0.531	−2.51	1.98	0.210	−0.89	0.69	0.203	0.49	0.98	0.619
PD												
Lifetime	22.09	8.64	0.013	−1.97	2.95	0.507	−0.31	1.23	0.796	0.75	1.21	0.531
Current	30.62	9.83	0.003	−4.71	3.52	0.185	−0.87	1.45	0.548	2.12	1.27	0.094

OCD = Obsessive-compulsive disorder, SP = Social phobia, GAD = Generalized anxiety disorder, PD = Panic disorder

subjects were few in number, their prevalence was similar in those with and without anxiety disorder. However, it is interesting to note that those bipolar subjects who reported antidepressant induced switch were somewhat overrepresented by bipolar II and bipolar NOS subjects (Table 3) and this aspect deserves further study.

Although the prevalence of anxiety disorders in our study is comparable to those in previous studies, the pattern of anxiety disorder comorbidity is somewhat different. In our study, OCD was the commonest anxiety disorder and PD was the least prevalent with no significant difference compared to the rate in controls. Many previous studies have reported PD as the most frequent comorbid anxiety disorder in bipolar subjects [2, 5, 15, 26, 27]. In the recent large study by Simon et al. [3] lifetime prevalence of PD was 17%, a rate much higher than the 7% rate in our study. Even in the Epidemiological Catchment Area (ECA) study, the lifetime prevalence of PD was 21% in those with bipolar I disorder [9]. However, a low prevalence of PD in our study is consistent with the findings of two recent studies that reported a rate of 6–7% [4, 28].

In our study, OCD was the commonest lifetime anxiety disorder (35%). The finding is consistent with the high rates reported in two previous studies. In the studies by Tamam and Ozpoyraz [4] and Kruger et al. [12], the prevalence of OCD was 35% and 39%, respectively. The increased prevalence of OCD is also consistent with the ECA rate of 21% in those with primary diagnosis of bipolar disorder [10]. Curiously, in a recent study by Kruger et al. [28], OCD comorbidity was only 7% in recovered bipolar group as a whole, but did not find even a single case in a subgroup of 109 subjects with bipolar I disorder. The likely explanations for the conflicting findings with regard to pattern of anxiety disorders comorbidity could be due to the nature of the sample studied (primary anxiety disorder samples vs. primary bipolar cohorts, bipolar I versus bipolar II versus mixed group versus bipolar depressives), sample size (large versus small sample sizes), the clinical status at the time of assessment (in episode vs. in remission) and the types of instruments used. For example, some studies, including our study recruited both bipolar I and II subtypes [3, 26], whereas a recent study included only bipolar I samples [2, 4]. Similarly, samples could be from primary bipolar cohorts [2–4] or anxiety disorder cohorts [13, 14, 29]. Sample sizes have varied from just 20 [30] to a large sample of 500 subjects [3]. The clinical status at the time of assessment has also varied from study to study, some studies including ours have assessed patients while in remission [4] and others both while in episode and euthymic period [3].

Our finding that those with anxiety have earlier onset of bipolar disorder is consistent with the previous data [2, 3, 7]. However, the exact nature of the relationship between anxiety disorder comorbidity and bipolarity is not clear although in our study, a significant proportion of subjects with anxiety disorders reported onset of anxiety much before the onset of bipolar disorder. It is possible that the earlier onset of anxiety disorders may represent either a prodrome of bipolar disorder or may even suggest that the anxiety disorders are risk factors for worse bipolar course. Alternatively, anxiety and bipolarity may share an associated biology or genetic risk [31, 32]. It is also possible that anxiety symptoms are an inherent component of severe bipolar disorder which often has a juvenile onset and not distinct disorders. An analogy could be the case of depression where anxiety is a frequent accompaniment. Whether such patients who have multiple symptom domains should be given multiple diagnoses or a single diagnosis is debatable although current classificatory systems encourage diagnosis of multiple comorbid conditions.

The detrimental effect of anxiety on all the four indices of bipolar severity is obvious. That comorbid anxiety has detrimental effect on the course of bipolar disorder has important clinical implications. Firstly, anxiety disorders are often not diagnosed in routine clinical assessment of bipolar subjects with the resultant negative effect on the course of the illness. Therefore, it is essential for the clinicians to be sensitive to the fact that anxiety disorders are highly comorbid in bipolar disorder and that the goal of treatment is not just remission of bipolar episodes but also remission of comorbid anxiety. Secondly, a comorbid diagnosis of anxiety disorder leads to the difficult issue of management. It is well known that antidepressants, particularly SSRIs are effective in treating anxiety disorders. However, the issue of concern is the manic/hypomanic switch associated with their use. Although a recent meta-analysis demonstrated that switch rate is not unusually high with SSRIs in bipolar disorder [33], it is evident from our data (Table 3) that switch rates are higher in bipolar subjects with comorbid anxiety. In routine clinical practice, such subjects are often prescribed antidepressants under the cover of mood stabilizers. Whether such subjects benefit with a combination of mood stabilizer(s) and a SSRI is an issue that needs systematic exploration. Alternatively, efficacy of cognitive behavior therapies (CBT) in treating anxiety in bipolar disorder needs to be studied systematically since CBT has shown to be effective in treating anxiety disorders [34].

Our study has also demonstrated the effect of individual anxiety disorders, particularly OCD and PD on some indices of bipolar severity. Curiously, SP, although highly prevalent, did not have any effect on the severity indices of the bipolar course. We speculate that the perceived distress and interference in daily life due to social anxiety could be somewhat less because of the nature of the occupations of our sample. Only a minority was students and majorities

were housewives, unemployed, laborers or agriculturists (Table 1). In these patients, social anxiety may not be a source of great problem because they are not involved in socially demanding occupations. A high rate of OCD and its impact on the severity of bipolar illness is consistent with the findings of a previous study [29]. Presence of comorbid OCD, unlike other anxiety disorders pose special problems in management. Other anxiety disorders such as GAD, PD and SP do respond to benzodiazepines but OCD responds only to high doses of SSRIs. Therefore, the use of SSRIs often becomes an inevitable part of management particularly when there is no facility for CBT. In the study by Perugi et al. [29], the incidence of switch in bipolar subjects with OCD was 39% with clomipramine and 14% with SSRIs. Residual affective and OCD symptoms remained in many subjects despite treatment with mood stabilizers, and in some, multiple mood stabilizers were required. This highlights the problems involved in treating bipolar subjects with comorbid OCD. There is a need to study systematically the role of CBT, and the clinical utility of combining SSRIs and mood stabilizers in bipolar subjects with OCD. Additionally, role of atypical antipsychotics in treating OCD in bipolar disorder deserves systematic exploration since they have been shown to have anti-obsessional effect in controlled clinical trials [35].

The results of this study have to be interpreted in the background of certain limitations. The sample was relatively small and was recruited from a psychiatric hospital setting. A majority was hospitalized sometime during their illness. Therefore, the findings may not be generalizeable to patients in the general hospital psychiatry settings and community. Our clinical sample may have overrepresented the anxiety disorder comorbidity relative to non-treatment-seeking bipolar population. It is possible that those with anxiety disorders may have sought consultation more often than those without anxiety resulting in Berkson's bias. A majority of our patients (96%) also had multiple episodes, which could increase overall anxiety disorder comorbidity determined. However, the findings concur with the high levels of comorbidity seen in epidemiological sample [7]. Unfortunately, there is no epidemiological data from India to compare our findings. We excluded juvenile and older bipolar subjects. It is possible that the comorbid patterns could be different in these populations. The assessments were cross-sectional. The course of illness reconstructed by life-charting method is less likely to be accurate and open to recall bias. Due to the cross-sectional method, issues of causality cannot be clearly addressed.

In conclusion, our study has demonstrated that anxiety disorders are highly prevalent in bipolar disorder and are associated with greater bipolar severity. The study highlights the need for recognition and treatment of comorbid anxiety disorders. However, the methods of treating comorbid anxiety in bipolar disorder need systematic examination. Future studies should focus on neurobiological and family/genetic correlates of anxious vs. non-anxious bipolar subjects to examine if bipolar disorder with comorbid anxiety disorders is a subtype of the bipolar disorders. This is important because the existing data on the anxiety disorder comorbidity in bipolar disorders does not help us to understand the nature of relationship between the two groups of disorders.

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