

Comparison of clinical and sociodemographic features of bipolar disorder patients with those of social anxiety disorder patients comorbid with bipolar disorder in Turkey

Tonguç D. Berkol, MD, Ebru Kırılı, MD, Serkan Islam, MD, Rasim Pınarbaşı, Student, İlker Özyıldırım, MD.

ABSTRACT

الأهداف: لتقييم تأثير اضطرابات القلق الاجتماعي (SAD) والاعتلال المشترك على المظاهر السريرية، شدة المرض، والاستجابة إلى مثبتات الاضطراب المزاج الثنائي القطب (BD) في المرضى.

الطريقة: شملت هذه الدراسة بأثر رجعي المرضى القطبين اللذين كانوا في قسم الطب النفسي، مستشفى الأبحاث والتدريب Haseki اسطنبول، تركيا في عام 2015م، والذين قدموا على موافقتهم للمشاركة في هذه الدراسة. وقد أجريت الدراسة من خلال تقييم ملفات المرضى بأثر رجعي. تم تقييم مائتي مريض ثنائي القطب باستخدام المقابلة السريرية المنظمة للدليل التشخيصي والإحصائي للاضطرابات العقلية، الطبعة 4 المحور الأول (SCID-I) من أجل الكشف عن كل تشخيص الحالات للأمراض النفسية. تم تقسيم العينة نسبة إلى وجود الاعتلال المشترك SAD ومقارنة المجموعتين.

النتائج: تم الكشف عن الاعتلال المشترك SAD في 17.5% (35/200) من المرضى BD. وكان المرضى المصابين بثنائي القطب SAD أكثر تعليماً، وكان لديهم سوابق من BD، انخفاض عدد نوبات الهوس، وزيادة شدة النوبات. لم يكن هناك اختلاف بين المجموعات من حيث عدد النوبات، والاستشفاء، الانتحار، كونه مريض نفسي، استجابة العلاج لالليثيوم ومضادات الاختلاج.

الخلاصة: قد يرتبط اضطراب القلق الاجتماعي بالاعتلال المشترك مع نوبات أشد وقت مبكر من بداية BD. ومع ذلك، قد لا تكون مرتبطة بالاعتلال المشترك SAD في الاستجابة للعلاج عند مرضى ثنائي القطب.

Objectives: To assess the impact of social anxiety disorder (SAD) comorbidity on the clinical features, illness severity, and response to mood stabilizers in bipolar disorder (BD) patients.

Methods: This retrospective study included bipolar patients that were treated at the Department of Psychiatry, Haseki Training and Research Hospital, Istanbul, Turkey

in 2015, and who provided their informed consents for participation in this study. The study was conducted by assessing patient files retrospectively. Two hundred bipolar patients were assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition axis-I (SCID-I) in order to detect all possible comorbid psychiatric diagnoses. The sample was split according to the presence of SAD comorbidity and the groups were compared.

Results: The SAD comorbidity was detected in 17.5% (35/200) of the BD patients. The SAD comorbid bipolar patients were more educated, had earlier onset of BD, lower number of manic episodes, and more severe episodes. There was no difference between groups in terms of total number of episodes, hospitalization, suicidality, being psychotic, treatment response to lithium and anticonvulsants.

Conclusion: Social anxiety disorder comorbidity may be associated with more severe episodes and early onset of BD. However, SAD comorbidity may not be related to treatment response in bipolar patients.

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From the Department of Psychiatry (Berkol), DışkapıYıldırım Beyazıt Research and Training Hospital, Ankara, the Department of Psychiatry (Kırılı), Arnavutköy State Hospital, the Department of Psychiatry (Islam), Haseki Research and Training Hospital, the Faculty of Science, Department of Biology (Pınarbaşı), Istanbul University, and the Department of Psychiatry (Özyıldırım), Öteki Psychotherapy Center, Istanbul, Turkey.

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Address correspondence and reprint request to: Dr. Tonguç D. Berkol, Department of Psychiatry, DışkapıYıldırım Beyazıt Research and Training Hospital, Ankara, Turkey. E-mail: tberkol@gmail.com

Data from both epidemiologic and clinical samples indicate elevated rate of social anxiety disorder (SAD) among patients with bipolar disorder (BD).^{1,2} Comorbid SAD patients have been reported at the rate of 5-47.2% in BD patients.³⁻⁷ Also BDs, especially BD type II (BD-II) is frequent among SAD patients.⁸ Anxiety disorder comorbidity in BD seems to be associated with many indicators of severity in the clinical course and outcome of mood disorder.^{2,6,9-11} However, only a few studies have examined the impact of SAD comorbidity in particular, in the course and outcome of BD.¹² Some studies with clinical samples report that bipolar patients comorbid with SAD compared with bipolar patients not comorbid with SAD, may be more likely to have suicide attempts,¹³ diminished quality of life,¹⁴ mixed states,¹⁵ substance abuse,¹² and earlier age of onset.^{12,15} It has been reported by some authors that SAD additional diagnosis, showing a continuous and chronic progress rather than periodical episodes, leads to more symptoms and more loss of function, and negatively affects the progress of the illness.^{4,7,9} The SAD was reported to have earlier onset than BD among patients with comorbidity.¹⁵ In the present study, we evaluated the impact of lifetime SAD comorbidity on a sample of BD outpatients in Turkey regarding demographic and clinical variables.

Methods. *Study sample and psychiatric diagnosis.*

After receiving informed consent, 200 patients with BD admitted at the Department of Psychiatry, Haseki Training and Research Hospital, Istanbul, Turkey in 2015 were interviewed by trained psychiatrists using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) Axis I Disorders (SCID-I). The preparation of the patient files in a manner appropriate for the study was carried out between March 2013 and March 2015. The study was conducted on outpatients. They were assessed in the inter-episodic interval of BD, and were euthymic at the time of the study entry. The included patients is part of a "BD prospective follow up program", which also covers the treatment of the patients. Semi-structured interview charts that assess sociodemographic and clinical features (family history, presence of psychotic features, age of onset, predominant

episode type, number and type of episodes, ratio of episode types, the total number of episodes, number of hospitalizations, duration and outcome of prophylactic treatment among others) of the patients based on data obtained from the patient, his/her family on admission, and previous medical records, as well as "mood chart" that includes graphical records for the outcome of the disorder and outcome of treatments since the onset of BD are filled out. These charts have been updated in every follow-up visits. During the follow-up, patients and their accompanying relatives are interviewed once a month in the first 6 months, once in every 2 months for the following 6 months, and once in every 3 months for the rest of the maintenance period for remitted patients. If there is recurrence, the visits were more frequent according to the needs of the treatment. The life charts of the patients and all the records were screened for the present study, and the missing parts were completed in an update visit when necessary. Age of onset was the age that met mood episode criteria of DSM-IV for the first time, and predominant episode type is the most frequent episode amongst all. The interviews are semi-structured, not clinical scales, whose charts are prepared by the authors, and are designed to measure socio-demographic and clinical data. Evaluation of patient files was carried out retrospectively. Patients who are diagnosed with BD-I and BD-II according to DSM-IV, as well as BD-I and BD-II with SAD comorbidity, and aged between 18 and 65 years were our inclusion criteria. Patients with schizophrenia, schizoaffective, and schizophreniform disorders, organic mental illnesses, medical comorbidity, and substance use disorders, and axis I comorbidity in patients with BD-I and BD-II were excluded from the study. The BD patients diagnosed with social phobia who have previously received treatment for SAD were excluded from the study. The BD with SAD group was created with 35 patients with lifetime SAD comorbidity. The BD patients without SAD that presented another anxiety disorder (AD) comorbidity were excluded to have a control group without any comorbid AD, similar to the analysis that were conducted in previous studies.^{2,11}

Maintenance treatment response. In the present study, "mirror-image evaluation" method was used for the assessment of patients' response patterns to prophylactic treatments. Life chart-data of patients were evaluated for each prophylactic treatments (such as, lithium, valproic acid, and others); comparing number and duration of manic, depressive, and mixed episodes prior to prophylactic treatment and after initiation of treatment.¹⁶ Zero point was indicated to

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be the time when maintenance treatment has started, and maintenance treatment period was compared with the same drug-free period prior to zero point. For patients whose multiple prophylactic treatments were investigated, response type was assessed for each treatment separately, and each treatment period was compared with the same drug-free untreated period prior to treatment. Based on the response features as explained above, patients were divided into 2 groups: A) treatment responder group - composed of patients who never had any recurrence (good response), or those who had a recurrence during maintenance treatment period with a decrease in severity, duration, and frequency of episode (moderate response) with regard to the same period prior to maintenance treatment; and B) treatment non-responder group - included patients who had recurrence during maintenance treatment period similar or even worse in severity, duration, and frequency of episode with regard to the period prior to maintenance treatment (poor response). Minimum duration for the maintenance treatment was one year. However, shorter durations were included if a clear conclusion can be made according to the mirror design when treatment changed earlier because of recurrences. The ethics committee approval for the study was obtained from Haseki Training and Research Hospital.

Statistical evaluation. Descriptive statistics were computed as mean \pm standard deviation (SD), count and percent frequencies according to type of variables. Independent samples t-test was used to compare differences between the 2 groups in terms of numerical variables, which have normal distribution. In addition, Mann-Whitney-U test was used for differences between the 2 groups in terms of numerical variables, which have no normal distribution. The relationship between groups and categorical features was evaluated by Pearson chi-square test. Statistical significance level was accepted as $p < 0.05$. All statistical computations were performed using NCSS version 2007 (Salt Lake City, Utah, USA) package program.

Results. Out of 200 patients, 178 had BD-I, and 22 had BD-II. The mean age was 39.3 ± 9.6 . Females comprise 64% of the study population. Demographic and clinical features of the study sample are shown in Tables 1 & 2. There were 31 patients (88.6%) in the BD-SAD group diagnosed with BD-I, 147 patients (89.1%) in the BD group diagnosed with BD-I, 4 patients (11.4%) in the BD-SAD group diagnosed with BD-II, and 18 patients (10.9%) in the BD group diagnosed with BD-II (Table 3). The ratio of BD-I and BD-II

Table 1 - Descriptive statistics of demographic features, and comparison results of the 2 groups.

Demographic features	Bipolar disorder-social anxiety disorder (n=35)	Only bipolar disorder (n=165)	P-value
	n (%)		
Age*	38.1 \pm 9.2	40.5 \pm 10.2	0.252
Gender, female [†]	17 (48.57)	111 (67.27)	0.058
Polarity[†]			0.699
Bipolar disorder I	30 (86.7)	148 (89.7)	
Bipolar disorder II	5 (14.3)	17 (10.3)	
Marital status[†]			0.573
Married	16 (45.7)	77 (46.7)	
Divorced	3 (8.6)	24 (14.5)	
Single	16 (45.7)	64 (38.8)	

Mean \pm standard deviation. *independent sample t-test, [†]Pearson chi-square test

in both groups was observed to be similar ($p=0.929$). The prevalence of comorbid social anxiety was 17.5% ($n=35$). There was no difference among groups in terms of total number of episodes, hospitalization, suicidality, being psychotic, treatment response to lithium and anticonvulsants. No statistically significant difference was observed in the distributions of mean age, gender ($p > 0.05$), and marital status ($p=0.573$) among BD-SAD and only BD groups (Table 1).

In Table 2, the prevalence of comorbid social anxiety was 17.5% ($n=35$). There was no difference among groups in terms of total number of episodes ($p=0.465$), hospitalization ($p=0.095$), suicide attempt ($p=0.352$), being psychotic symptoms ($p=0.365$), treatment response to lithium ($p=0.831$) and anticonvulsants ($p=0.636$). An average episode severity (severe) ($p=0.014$) of BD group was found to be significantly higher than those in the BD-SAD groups and the onset age (BD) of BD group was found to be significantly higher than those in the BD-SAD groups ($p=0.001$). No statistically significant difference was observed in time of onset between BD and only BD groups ($p=0.856$). There was no difference among groups of manic episodes ($p=0.211$), number of mixed episodes ($p=0.082$), and number of depressive episodes ($p=0.589$) (Table 2).

Discussion. Recent epidemiological and clinical studies indicated that the comorbidity of SAD was frequent in BD. However, there is little information on the differences in clinical, socio-demographic features, and treatment resulting from the presence of this comorbidity. In our study, SAD was observed in 35 (17.5%) of the 200 BD patients.

Table 2 - Descriptive statistics of clinical features and comparison results of the 2 groups.

Clinical features	Bipolar disorder-social anxiety disorder (n=35)	Only bipolar disorder (n=165)	P-value
<i>Primary psychiatric disorder*</i>			
Bipolar disorder present versus absent	13 (37.1) versus 22 (62.9)	37 (22.42) versus 128 (77.6)	0.068
Any affective disorder present versus absent	17 (48.6) versus 18 (51.4)	58 (35.2) versus 107 (64.8)	0.136
Suicide present versus absent	1 (2.9) versus 34 (97.1)	8 (4.9) versus 157 (95.2)	0.606
Psychotic symptoms present versus absent*	29 (82.9) versus 6 (17.1)	125 (75.8) versus 40 (24.2)	0.365
Suicide attempt present versus absent*	9 (24.3) versus 26 (74.3)	31 (18.8) versus 134 (81.2)	0.352
<i>Prophylactic lactic treatment response*</i>			
Lithium monotherapy	15/28 (53.6)	65/112 (58.0)	0.831
Anticonvulsant monotherapy	12/17 (75.0)	4 5/74 (60.8)	0.636
Average episode severity (severe) [†]	22 ± 78.6	68 ± 53.1	0.014
Onset age (bipolar disorder) [‡]	20.1 ± 4.7	24.5 ± 8.6	0.001
Time of onset [‡]	17.0 ± 9.3	16.9 ± 10.2	0.856
Hospitalization [†]	3.2 ± 2.7	2.6 ± 2.3	0.095
Total number of episodes [‡]	8.7 ± 5.4	9.5 ± 7.6	0.465
Number of manic episode [†]	3.5 ± 2.6	4.3 ± 4.6	0.211
Number of mixed episodes [†]	0.8 ± 1.3	0.7 ± 1.8	0.082
Number of depressive episodes [†]	3.0 ± 3.6	2.6 ± 3.2	0.589

Mean ± standard deviation. *Pearson chi-square test, [†]Mann-Whitney U test, [‡]Independent samples t-test

Table 3 - Distribution of bipolar I and II patients according to social anxiety disorder and only bipolar disorder.*

Groups	Bipolar disorder-social anxiety disorder	Only bipolar disorder	Total	P-value
	n (%)			
Bipolar I	31 (88.6)	147 (89.1)	178 (89.0)	0.929
Bipolar II	4 (11.4)	18 (10.9)	22 (11.0)	
Total	35	165	200	

*Chi-square test was used.

The frequency of SAD comorbidity with BD was described in the literature to be between 5% and 47%, which is compatible with our results.¹⁻⁷ Discrepant findings in these studies are likely to be originated from different methodological approaches, such as bipolarity phase at comorbidity assessment, utilization of epidemiological or clinical data, involvement of inpatients or outpatients, assessment method used in diagnosis, and evaluation of the presence of lifetime, or current comorbidity. Generally, an increase in comorbidity has been found to negatively affect academic success, especially in diseases, such as SAD, which start at an early age. However, the way SAD comorbidity affects adults with BD has not been studied yet. In our study, we have found that BD patients with SAD comorbidity are relatively better educated than those without SAD comorbidity. Further studies are needed to verify this finding.

We found a significantly younger age at onset of BD in those with lifetime SAD comorbidity. These data are consistent with previous reports that found a similar association of SAD with early onset of BD.^{2,12,15} Provencher et al¹² found that SAD comorbidity leads to the early onset of bipolar depressive episodes in patients, especially those admitted to the emergency. In 2 studies that assessed temporal relationship of onset of SAD with BD, one found 88%,⁷ and the other 95%¹² of BD-SAD comorbidity had earlier onset of SAD than BD. Furthermore, a recent study¹⁷ found that SAD comorbidity is a meaningful predictor of relapse of BD in patients with major depression. These findings support the suggestions that there might be a neurobiological association between SAD and BD, anxiety accelerates emergence of BD, and SAD symptoms might be prodromal symptoms of BD.¹⁷

In our study, bipolar patients' comorbidity with SAD had more frequent severe episodes. That finding might imply that SAD comorbidity has a negative impact on the course of BD. In some studies⁷ however, it has been found that the negative effects of SAD comorbidity on BDs are more limited, even non-existent, when compared with other anxiety disorders, such as panic, or obsessive compulsive disorder. Thus, further studies are needed to clarify these contradictory suggestions.

A significant amount of data exists on the relationship between BD, manic switch, and SAD, however, there still remain a number of vague areas. In our study, it has

been found that BD patients with SAD comorbidity have fewer manic episodes throughout their lives. This result has not been observed in previous studies. In another study¹² with similar methodology with the present study, a difference in the number of manic episodes of the 2 groups was not found. In a study by Himmelhoch¹⁸ monoamine oxidase inhibitors have been given to 32 patients with social phobia, and of the 18 patients who have benefited from the treatment, 14 have shown hypomanic signs. Based on this, it has been speculated that a group of patients with social phobia could belong to the bipolar spectrum, and that BD symptoms appear with antidepressant treatment.¹⁸ Furthermore, as stated above, SAD comorbidity has been found to be a meaningful predictor of a relapse of BD on patients with major depression observed over 5 years.¹⁸ It has been stated that this is more than just comorbidity, but rather a predictor of inhibition caused by social anxiety related depressive bipolarity in patients with this switch.¹⁸ All of these studies suggest that SAD is related to bipolarity. Our study, however, does not have enough data to support these findings, which might indicate that the relationship between SAD and the extents of BD is more complex than it has been suggested before. Very little is known about possible SAD comorbidity in the effectiveness of mood-stabilizing agents in BD. In our study, there was no significant difference between the 2 groups in terms of response to lithium and anticonvulsant maintenance treatment. However, the rate of response to anticonvulsant treatment was higher in BD-SAD group. This finding is in line with recent studies¹⁹ reporting that antiepileptic agents are effective for SAD treatment.

We acknowledge several limitations of this study. A major limitation is the retrospective nature of data collection. The reliability and validity of patients' reports of clinical history, such as age of onset, or number of prior episodes is uncertain. However, the life charts of the patients were filled prospectively as part of the follow up program, and assessments were carried out retrospectively. The life chart method is often used in studies for the long-term course of BD. The reliability and validity of life chart method was confirmed in the literature.²⁰ Another limitation is the fact that analyses of comorbidity in BD subjects were carried out without discriminating between generalized and specific SAD. In spite of these limitations, our study has an advantage on previous investigations by specifically evaluating the effects of comorbid SAD on socio-demographic and clinical features of BD. These investigations, on the

contrary, included more heterogeneous patient groups for the evaluation of combined effects of comorbid anxiety disorders in bipolar patients.

In conclusion, SAD comorbidity is not rare among patients with BD-I, and is likely to affect age of onset and phenomenology of BD. These findings may influence treatment planning and the possibility of discovering a pathophysiological relationship between SAD and bipolarity.

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