

Comorbid Anxiety Disorders in Bipolar Disorder Patients: A Review

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Abstract

In recent years, a growing number of clinical and epidemiological studies have reported high rates of comorbid anxiety disorder in patients with bipolar disorder. These studies have stated that comorbid anxiety disorder in bipolar patients is the rule rather than the exception. Lifetime anxiety disorder comorbidity rates among bipolar disorder patients are estimated to be between 24% and 93%, based on several different clinical and epidemiological studies. Bipolar patients usually are diagnosed with comorbid multiple anxiety disorders rather than a single one. Anxiety disorder comorbidity is associated with greater psychopathology, decreased treatment response, poor outcome, and increased suicidality. Current prevalent treatment approaches almost always give priority to the symptomatic treatment of bipolar episodes, which inevitably influences the provision of adequate attention and care to the diagnosis and treatment of a comorbid anxiety disorder. This approach has important therapeutic and clinical implications, such as delays in treatment leading to resistance to drugs and severe functional losses. Therefore, the treating psychiatrist needs to carefully evaluate, diagnose, and treat comorbid anxiety disorders in the early stages to avoid any unpleasant consequences and to improve the quality of life of patients. In this paper, an overview of comorbid anxiety disorder in bipolar disorders is presented, with a special emphasis on its prevalence, its relationship to sociodemographic and clinical variables, and possible therapeutic approaches.

Key Words: Bipolar disorder, anxiety disorder, comorbidity

INTRODUCTION

The clinical and phenomenological relationship between major depression and anxiety disorders is well-known (Issler et al., 2004). On the other hand, the relationship between bipolar disorder (BPD) and anxiety disorders is not well-documented in the literature. The Epidemiological Catchment Area (ECA) study conducted in the USA is among the pioneering research studies in the field of Itamamaxis I comorbidities in psychiatric patients. (Chen and Dilsaver, 1995a). In this study, it was reported that the frequency of additional panic disorder (PD) diagnosis is higher in BPD patients than in patients with unipolar depression. Subsequently, the number of studies on the relationship between BPD and anxiety disorders rapidly increased (Boylan et al., 2004; Cassano et al., 1999; Cosoff and Haffner, 1998; McElroy et al., 2001; Feske et al., 2000; Himmelhoch et al., 1998; Pini et al., 1997, 1999). The two common

findings of these studies are the high comorbidity rate between these two disorders and higher prevalence rate of anxiety disorders in patients with BPD than in the general population (Bauer et al., 2005). In addition, acknowledgment of this comorbidity has important contributions in making an accurate diagnosis and determining the best treatment approach (Myers and Thase, 2000). It has been proposed that when this comorbidity remains undiagnosed, the presented symptoms might be evaluated as a personality disorder, mixed episodes can be ignored, and treatment response will be low (Myers and Thase, 2000).

In this review study, an overview of comorbid anxiety disorders in BPD is briefly presented, with special emphasis on its prevalence, its relationship to sociodemographic and clinical variables, and possible therapeutic approaches. With this aim, national and international studies were reviewed. International articles in PubMed,

EMBASE, ISI Web of Science, and Google Scholar databases were searched using the following keywords; “anxiety disorder, social phobia, phobia, post traumatic stress disorder, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, bipolar disorder, anxiety, and bipolarity”. In particular, articles on the various aspects of BPD and anxiety disorder comorbidity, such as epidemiology, clinical aspects, and response to treatment were obtained in full-text. Studies conducted in Turkey were searched in ULAKBİM using the same keywords among the thesis studies conducted between 1995 and 2005, in the Turkish Medicine Index, and Çukurova Psychiatry Index, and full texts of the relevant articles were obtained.

We have focused on determining the prevalence of anxiety disorders in general and which anxiety disorders are diagnosed in BPD patients, the relationship between comorbidity and various sociodemographic and clinical variables, and treatment approaches in the light of the available findings.

Epidemiological findings

There are various large-scale, epidemiological or clinic studies on the frequency and other aspects of comorbid anxiety disorders in BPD (Boylan et al., 2004; Henry et al., 2003; Simon et al., 2004). In Turkey, there are at least 3 different clinical cross-sectional studies on the subject (Altındağ et al., 2006; Tamam and Ozpoyraz, 2002; Ünal, 2002). Lifetime anxiety disorder comorbidity rates among BPD patients are estimated to be 24%-93%, based on several different clinical and epidemiological studies (Henry et al., 2003; Kessler et al., 199; McElroy et al., 2003; Pini et al., 1997). In a large international study, Boylan et al. (2004) reported that 55.8% of 138 BPD patients had at least one additional anxiety disorder and 31.8% had more than one. In a clinical study conducted in Turkey, Tamam and Ozpoyraz (2002) found that the prevalence rate of at least one additional anxiety disorder diagnosed in 70 BPD-I patients in remission was 61.4%, and the prevalence rate of multiple additional anxiety disorder diagnoses was 38.6%. In another study conducted with a similar population that used a similar research design, these rates were reported as 27.1% and 10%, respectively (Altındağ et al., 2006).

When anxiety disorders are considered separately, it is difficult to determine which diagnosis is most commonly comorbid with BPD. The findings on this subject differ (Issler et al., 2004). One of the most difficult problems in determining the most common comorbid anxiety dis-

order is that the majority of BPD patients meet the diagnostic criteria for more than one comorbid anxiety disorder (Boylan et al., 2004). In a comorbid diagnosis study conducted with 288 BPD patients in the USA by McElroy et al. (2001), the most common additional diagnosis was PD (20%), followed by social phobia (SP) (16%), specific phobia (10%), obsessive-compulsive disorder (OCD) (9%), post-traumatic stress disorder (PTSD) (7%), and generalized anxiety disorder (GAD) (3%). In contrast, while GAD was found to be the least frequent additional diagnosis (with a rate of 31%) in McElroy et al.'s study (2001), it was the most frequent additional diagnosis according to a study conducted by Boylan et al., (2004). In Boylan et al.'s study, GAD (?%) was followed in frequency by PD (27%), SP (17%), PTSD (15%), specific phobia (10%), and OCD (9%). Conversely, a study conducted in Turkey between 1999 and 2001 (Tamam and Ozpoyraz, 2002) reported that the most frequently seen anxiety disorder in BPD patients was OCD (39%). The lifetime prevalences of other comorbid anxiety disorders in this study were SP (26%), specific phobia (20%), PTSD (14%), GAD (14%), and PD (10%).

These varying results are believed to be related to the different research methods and populations studied (Simon et al., 2003). Of note, the distribution of study populations is believed to have an important role in these differences. While some studies recruited only BPD-I patients (Tamam and Ozpoyraz, 2002), others included BPD-II and BPD- not otherwise specified (BPD-NOS) patients (McElroy et al., 2001), or some included schizoaffective and unipolar depression patients (Pini et al., 1997). In addition, it is believed that the socioeconomic characteristics of the study populations also affected the results (Simon et al., 2003). Other possible clinical variables that might have had an effect on the findings are patients being in a depressive or manic episode during the course of the study, and different treatment approaches used (Gaudiano and Miller, 2005). Lack of access to the structured interviews, such as SCID-I (The Structured Clinical Interview for DSM-IV) used in the earlier studies complicates the comparisons among different study findings (Cosoff and Haffner, 2000; Tamam and Ozpoyraz, 2002).

The relationship between bipolar disorder and separate anxiety disorders

Obsessive-Compulsive Disorder

In the past, OCD was associated with major depression more so than it was associated with BPD; however, currently it is accepted that OCD has a stronger relation-

Table 1. Clinical and Demographic Variables Related to Comorbid Anxiety Disorders in BPD Patients.

Demographic variables

Low socioeconomic status
Being female
Low education level

Clinical variables

Less euthymic durations
Increase in lifetime substance use
Increase in symptoms
Early onset
Severe symptoms
More depressive or mixed episodes *
Higher number of total episodes *
More severe general psychopathology level
Increase in suicide risk
Rapid cycling
Deterioration of quality of life
Lack of adherence to treatment
Necessity to use higher doses of medications
High levels of insight

(Cited and adapted from Bauer et al., 2005)

*(than BPD patients without comorbid anxiety disorders)

ship with BPD (Freeman et al., 2002; Myers and Thase, 2000). A landmark study (Chen and Dilsaver, 1995b) on the subject reported that the risk of OCD development in BPD patients is 2 times higher than the risk in unipolar depression patients and 3 times higher in non-depressive patients or patients without BPD. Various studies showed that an additional diagnosis of OCD in BPD patients varies between 7% and 39%, and that the lifetime prevalence of comorbid OCD in BPD patients is at least 10% (Krüger et al., 1995; 2000; Simon et al., 2004; Tamam and Ozpoyraz, 2002). Similarly, in a recent study that presented findings of STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) conducted in the USA, the prevalence of OCD among 500 BPD patients was 11% (Simon et al., 2004).

The relationship between episodic OCD and BPD, which is frequently mentioned in the literature, the effect of similar neurotransmitter systems in the etiologies of both disorders, and the fact that both disorders respond to mood stabilizers and antidepressants show that both disorders might have a similar underlying etiology (Krüger et al., 2000; Perugi et al., 1997, 1998; Tamam and Ozpoyraz, 2002). Studies have shown that in BPD patients with a comorbid OCD diagnosis, OCD symptoms begin more slowly than in OCD patients and dis-

play episodic characteristics. Additionally, BPD patients with a comorbid OCD diagnosis experience more depressive periods and a higher number of suicidal ideation and attempts than OCD patients (Perugi et al., 1999a, 2001; Perugi and Toni, 2004).

It was found that aggressive, religious, and sexual obsessions, as well as controlling, collecting, and repeating compulsions are more frequent in BPD patients with comorbid OCD than in OCD patients (Perugi and Toni 2004). It was reported that mixed mania is more frequent in BPD patients with comorbid OCD (McElroy et al., 2001). Furthermore, comorbidity of these 2 disorders makes the treatment more difficult, especially in the use of antidepressants, and BPD patients with comorbid OCD are considered to be difficult patients (Raja and Azzoni, 2004).

Panic Disorder

Epidemiological and clinical studies have shown a clear relationship between PD and BPD. The prevalence of comorbid PD in BPD patients varies between 6% and 43% (Freeman et al., 2002; Perugi et al., 1999a, 1999b; Sasson et al., 2003). PD is the most frequently seen comorbid anxiety disorder diagnosed in BPD patients according to numerous studies (Issler et al., 2004; McElroy et al., 2001). Other studies found a higher BPD prevalence (between 6% and 21%) in PD patients in comparison to the general population (Dick et al., 1994; Brieger, 2000). In addition, results of family and genetic studies also support the PD/BPD relationship (Doughty et al., 2004; MacKinnon et al., 1997; Rotondo et al., 2002). MacKinnon et al. (1997, 2002) found that in families of both PD patients and BPD patients, the second diagnosis (of BPD or PD) is more prevalent than in the general population. Based on these findings, it was hypothesized that patients who are diagnosed with PD and BPD might represent a familial genetic subgroup of BPD (Issler et al., 2004; MacKinnon et al., 1997; Rotondo et al., 2002). MacKinnon et al., (1997, 1998) proposed that the 18th chromosome has a specific role in the proposed subtype. In another study (Rotondo et al., 2002), it was found that BPD patients with PD and without PD differ in terms of catechol-O-methyltransferase (COMT) and serotonin transmitter (5-HTT) gene polymorphism. On the other hand, Doughty et al.'s (2004) study conducted with 109 bipolar patients and 226 of their relatives did not support the hypothesis that BPD-PD comorbidity represents a subtype of BPD. Some authors recommended the administration of a panic-provoking test in order to reach a definite conclu-

Table II. Treatment Interventions for Comorbid Anxiety Disorders in BPD Patients.

OCD-BPD

1st line: MS (especially valproate)¹ + CBT
 2nd line: MS² (SSRI or clomipramine) and /or atypical AP³
 Alternative: lamotrigine/topiramate as MS

PD-BPD

1st line: MS (especially valproate-gabapentin combination)¹
 2nd line: AD²
 Additional treatments: CBT, benzodiazepines⁴

SP-BPD

1st line: MS (especially valproate and gabapentin combination)¹
 2nd line: AD² (especially SSRI, Moclobemide)
 Additional treatments: CBT
 Alternative: topiramate, pregabalin, or levetiracetam as MS

PTSD-BPD

1st line: MS
 2nd line: AD² (SSRIs)
 3rd line: Atypical AP (olanzapine, risperidone, quetiapine)
 Additional treatments: benzodiazepines⁴

AD: Antidepressants; AP: Antipsychotics; BPD: Bipolar disorder; OCD: Obsessive-compulsive disorder; SP: Social phobia; PD: Panic disorder; PTSD: Posttraumatic stress disorder; MS: Mood stabilizer, CBT: Cognitive behavioral therapy.

* It is suggested that second line medications should be used together with first line medications.

¹All mood stabilizers can be used as combination treatments if necessary. Valproate is the first choice in monotherapy.

²Mania risk should be considered, SSRIs should be the first choice.

³Risk of exacerbation of obsessive-compulsive symptoms should be considered.

⁴Alprazolam carries the risk of causing mania. Clonazepam or lorazepam should be preferred.

sion, to identify correlated variables, and to identify any possible hidden tendency for panic attacks.

Generalized Anxiety Disorder

The lifetime prevalence of BPD with GAD comorbidity ranges between 3% and 43% according to the results of both epidemiological and clinical studies (Boylan et al., 2004; Kessler, 1999; Pini et al., 1997). Boylan et al. (2004) reported that GAD has the highest lifetime prevalence (31.2%) rate among other additional anxiety disorder diagnoses. In the same study, GAD was found to lead to more functional disorders and severe symptoms in comparison to other anxiety disorders in BPD patients, and that there was a lack of research on the effect of GAD on BPD. Although it is accepted that there is a significant relationship between BPD and anxiety disorders, genetic, epidemiological, and phenomeno-

logical studies conclude that the relationship between unipolar depression and GAD is stronger than its relationship with other disorders, including BPD (Brieger, 2000).

Posttraumatic stress disorder

The lifetime prevalence of comorbid PTSD in BPD patients varies between 7% and 21% in clinical studies; in epidemiological studies this rate increases up to 40% (Issler et al., 2004; Kessler et al., 1997; McElroy et al., 2001; Muesser et al., 1998; Tamam and Ozpoyraz, 2002). In a review study conducted with 1214 BPD patients (Otto et al., 2004), the prevalence of comorbid PTSD was 16%, which is approximately 2 times more than the lifetime prevalence of PTSD in the general population. In the same study, a higher rate of Axis-I disorders (DSM-IV) and frequency of experienced trauma, lower levels of social support, higher neurotic scores, and lower extraversion scores were observed in BPD patients with comorbid PTSD. It is believed that BPD patients, especially during a manic period, may have negative experiences related with the illness, which leads to traumatizations, and therefore, the BPD itself can be the cause of PTSD (Shear, 1997). Moreover, it should not be overlooked that negative life events can result in depressive or manic episodes in BPD patients (Perugi and Toni, 2004). There are no extensive studies on the specific relationship between PTSD and BPD.

Social Phobia

The lifetime prevalence of comorbid SP diagnosis in BPD patients ranges from 5% to 47.2%. (Bauer et al., 2005; Freeman et al., 2002). It is believed that the onset of SP is earlier than BPD in the majority of these patients (Perugi et al., 1999b). Yet, regressive behavior in BPD patients during depressive episodes can be similar to the clinical presentation of SP (Himmelhoch, 1998). It is accepted that social anxiety symptoms observed during depressive episodes are representative of a condition that is the opposite of hypomania (Himmelhoch, 1998). In the same article, it was proposed that a phobic patient group composed of SP patients might belong to the BPD spectrum. SP patients that were considered to be in this spectrum displayed difficulties in post treatment inhibition, especially following antidepressant treatment, and at some point in time their BPD II symptoms resurfaced. In addition, the risk of developing treatment resistance, alcohol dependency, and other anxiety disorders are quite high. (Issler et al., 2004; Perugi et al., 1999a, 1999b; Perugi and Toni, 2004).

The Relationship of Anxiety Disorders Comorbidity to Sociodemographic and Clinical Variables

The majority of studies support the idea that additional anxiety disorder diagnoses in BPD greatly affect the diagnosis, treatment, and the course of the illness. (Bauer et al., 2005; Boylan et al., 2004). As in unipolar depression, comorbid anxiety disorder in BPD leads to an increase in the severity of the disorder, chronicity, and poor response to treatment (Gaudiano and Miller, 2005). Although there are differences in the findings of various studies, the additional diagnosis of anxiety disorder is related to various clinical and sociodemographic variables.

The relationship between sociodemographic variables

Studies conducted to date have found a significant relationship between only a few sociodemographic variables and the additional diagnosis of anxiety disorder (Simon et al., 2004; Strakowski et al., 1998; Tamam and Ozpoyraz, 2002). While 2 studies reported a relationship between being female and additional anxiety (Strakowski et al., 1998; Tamam and Ozpoyraz, 2002), other studies found a relationship between comorbid anxiety disorder and low level of education (Simon et al., 2004), and low socioeconomic status (Strakowski et al., 1998). As the current number of studies reporting significant relationships is limited, it is not possible to definitively state the strength of the relationship between sociodemographic variables and comorbid anxiety disorder diagnosis.

Relationship with the clinical variables

Relationship with the age of onset

Although there are studies that found an earlier age of onset in BPD cases with comorbid anxiety disorders (Boylan et al., 2004), others report the opposite (Tamam and Ozpoyraz, 2002). In particular, psychiatric disorders that begin during adolescence were believed to have various effects on the long-term developmental process of the patient, and therefore, caused more serious mood disorders in the future (Boylan et al., 2004; Wozniak et al., 2002). In addition, it was thought that individuals who develop psychiatric disorders in their youth do not have the opportunity to develop an independent, self-determined personality structure, which is necessary for coping with the illness. In this situation, patients are defenseless towards the illness. Although this theory has not yet been proven, it is compatible with the findings of the

studies that found a more severe illness course in younger BPD patients who reported anxiety symptoms during early childhood (Dickstein et al., 2005). In a study conducted with pediatric BPD patients, it was proposed that the presence of an anxiety disorder might be a harbinger of very early onset BPD (Wozniak et al., 2002).

The relationship between the episodes, course, and severity of the illness and the relationship with prognosis

It was found that anxiety or anxiety disorders in patients with BPD worsens the prognosis of the disorder by increasing the number of episodes, the frequency and duration of depressive episodes, and the frequency of inter-episode below-threshold mood symptoms (Boylan et al., 2004; Feske et al., 2000; Tamam and Ozpoyraz, 2002). In addition, it is believed that a comorbid anxiety disorder diagnosis is related to rapid cycling BPD, mixed episodes, or dysphoric BPD (Freeman et al., 2002).

In a study conducted with 318 cases, Henry et al. (2003) found that comorbid anxiety disorder did not have an effect on the course of BPD, and said it was because the majority of the study population (74%) was BPD-I cases. In various studies, it was reported that some anxiety disorders were more common in BPD-II than others and that the rate of comorbidity of anxiety disorders in BPD-II patients is significantly higher (Doughty et al., 2004; Manning et al., 1997; Perugi et al., 1999; Rihmer et al., 2001). Conversely, McElroy et al. (2001) reported that there was no difference between BPD-I and BPD-II cases (42% and 45%, respectively) in terms of the prevalence of lifetime comorbid anxiety disorders.

In a Turkish study, it was reported that the levels of general psychopathology and anxiety in BPD patients with comorbid anxiety disorders are related to the number of comorbid diagnoses (Tamam and Ozpoyraz, 2002). In the same study, despite this significant finding, there was no significant relationship with suicidal ideation, or duration of illness and hospitalization, and therefore, it was concluded that the effects of comorbid anxiety disorder on the course and outcome of BPD still remains unclear. Boylan et al. (2004) suggested that comorbid anxiety disorder diagnoses have a general negative effect on the course of BPD, but there is no significant relationship between the number of additional diagnoses and severity and outcome of the disorder. At this point, it is important to consider the type of anxiety disorder rather than the number of comorbid diagnoses. It is known that comorbidity with GAD and SP, which are more chronic in

nature than other anxiety disorders, result in more symptoms, greater loss of functionality, and have a negative impact on the course of BPD (Boylan et al., 2004; Feske et al., 2000). Reasons for the dominance of SP and GAD in BPD populations are their negative effects on mood, and the continuation of anxiety and tension feelings during euthymic periods (Boylan et al., 2004).

Relationship with temperament

It was proposed that there is a relationship between the clinical characteristics of BPD and temperament (Henry et al., 2003), especially the relationship between the frequency of attacks and hyperthymic temperament. Henry et al. (2003) found a strong relationship between depressive temperament and comorbid anxiety disorder diagnosis. In the same study, based on these results, it was proposed that hyperthymic and depressive temperaments could be 2 distinct subgroups of BPD. In addition to these 2 groups, it is also believed that there is a close relationship between depression with labile mood and cyclothymic temperament, and frequent anxiety symptoms, which are observed in BPD-II patients, in particular (Akiskal, 2002).

Relationship with insight It was found that an additional anxiety disorder diagnosis is more frequent in BPD patients who have good insight towards their illness (Pini et al., 2003). In the same study, it was found that patients with comorbid OCD-SP have more insight, less hospitalization, and experience less illness episodes than patients with SP. It was proposed that the low level of insight in BPD patients with comorbid PD is related to a tendency for somatization.

Relationship with substance use

The lifetime prevalence of diagnosed substance abuse in patients with comorbid BPD and anxiety disorders is quite high (Keller, 2006). It was reported that even in BPD patients without comorbid anxiety disorders, the frequency of substance abuse is higher than in the general population and that diagnosis of substance abuse is related to mixed episodes, prolonged episodes, higher rate of comorbid physical illness, and suicidal ideation (Krishnan, 2005). In cases with comorbid anxiety disorders, the lifetime prevalence of diagnosed substance abuse in BPD increases by a factor of 2 or more. (Bauer et al., 2005; Simon et al., 2004). The additional diagnosis of substance abuse in BPD patients was related to the disruption of functionality, increased hostile behavior, and resistance to treatment (Keller, 2006). In addition

to studies reporting a significant relationship between these 2 conditions, some studies reported that there is no significant relationship between substance abuse and comorbid anxiety disorders diagnosis (Henry et al., 2003; Tamam and Ozpoyraz, 2002).

In addition, it was reported that anxiety disorder comorbidity increases suicide risk and ideation, decrease the number of euthymic periods, has negative effects on professional, social, and general functionality, decreases quality of life, and has important negative effects on the patients' families and their social environments (Bauer et al., 2005; Keller, 2006).

The most important and significant variables found to be related to comorbidity of anxiety disorders and BPD are summarized in Table I.

Explanatory models of the comorbidity of bipolar disorder and anxiety disorders

There are various theories and relational models of the relationship between BPD and anxiety disorders. Yet, there are no models that are widely accepted, which explain the relationship between these 2 disorders. Freeman et al. (2002) discussed 3 conceptual models, which have the capacity to explain the overlap between BPD and anxiety disorders.

The first model suggests that these 2 disorders are separate disorders and that their pathophysiological basis and comorbidity is the result of a high prevalence of both disorders in the general population. Findings that support this model include lower levels of lithium response in highly anxious patients, and the fact that benzodiazepines do not have a long-term effect on mood stabilization (Freeman et al., 2002). On the other hand, results of large-scale epidemiological studies show that the comorbidity of these 2 disorders cannot be coincidental and do not support Freeman's model (Chen and Dilsaver, 1995a, 1995b; Kessler et al., 1997). Findings regarding a genetic relationship between comorbid PD additional in BPD patients proposed by MacKinnon et al. (1997), and supported by other authors (Doughty et al., 2004; Rotondo et al., 2002), also do not support this model.

The second model proposes that the 2 disorders are separate, but pathophysiologically related (Freeman et al., 2002). Genetic and epidemiological findings support the validity of this model. Another important data source that supports this model is the common biological processes that are thought to be responsible in the

etiology of both disorders. It is believed that neurotransmitter and neuromodulator systems that play a role in the development of both disorders overlap. These systems are the noradrenergic, dopaminergic, GABAergic, and serotonergic systems. It is useful to talk about the characteristics of these systems as they relate to BPD and anxiety disorders.

An anomaly in noradrenergic functions in PD and PTSD has been detected and it was reported that there is a reduction in the levels of plasma noradrenaline and metabolites (Bremner et al., 1998; Southwick et al., 1993). In BPD, noradrenergic functions were reported to increase, not only in manic episodes, but also in all episodes of the disorder (Young et al., 1994). These findings show that as a common point of these 2 disorders, noradrenergic functions increase during episodes of each illness (Freeman et al., 2002). In contrast to the noradrenergic system, functionality of the dopaminergic system increases only during the manic episodes of BPD and during periods in which anxiety symptoms are evident. Although there are controversial findings, it was also believed that GABA might explain some of the relationship between BPD and anxiety disorders comorbidity (Freeman et al., 2002). Some studies reported that GABA levels decrease during manic and depressive episodes in BPD, while others failed to find such a decrease (Petty et al., 1990; Roy et al., 1991). Studies of GABA levels in patients with anxiety disorders consistently found lower levels than in control groups. The majority of findings on the role of the GABAergic system in these 2 disorders were the result of examining the mechanisms of the medications that are effective in treating the 2 disorders. For example, the proven effectiveness of valproate, which increases the level of GABA, in the treatment of BPD and the existence of studies showing the effectiveness of valproate in the treatment of anxiety disorders, indicate that this system is involved in the pathophysiology of both disorders (Keck et al., 2006).

Although the effect of the serotonergic system on the development and treatment of all anxiety disorders has been demonstrated by the prominent effectiveness of SSRI's in the treatment of anxiety, its role in BPD is still unclear (Kent et al., 1998; Mahmood and Silverstone, 2001). Although it is known that one of the action mechanisms of lithium and valproate is increasing serotonergic transmission, the role of SSRI's is believed to be complex and requires further research (Freeman et al., 2002).

The third model proposed by Freeman et al. consid-

ers bipolar disorder and anxiety disorders to be different reflections of a common pathophysiological anomaly (Freeman et al., 2002). This model views general anxiety, social anxiety, panic attacks, and compulsions as pathological affective conditions similar to the mania and depressive episodes observed in BPD. The symptoms of anxiety frequently seen in mixed and dysphoric mania supports this model. It is believed that this model would be helpful in explaining the unresponsiveness of manic patients with comorbid anxiety symptoms to lithium, as well as manic attacks due to antidepressant use in anxiety disorder patients.

Freeman et al. (2002), stressed that each of these models explains different patient subgroups and it is not possible to have a common explanatory model.

Treatment Approaches

Putting less emphasis on the comorbidity of anxiety disorders and BPD obviously affects treatment approaches. Although a number of important studies were conducted in the last few years, the findings are not sufficient to develop a universal treatment protocol (Perugi and Toni, 2004). Despite this, in the light of the findings of uncontrolled studies, case presentations, and clinical experience, there is a consensus on certain issues.

Priorities should be set in the treatment of BPD–anxiety disorders cases. Anxiety disorders should be assessed in BPD patients and following the assessment, treatment should be adjusted accordingly (Myers and Thase, 2000). Initiating an antidepressant treatment without controlling mood might intensify anxiety symptoms by exacerbating the BPD episodes, because the majority of medications used in the treatment of anxiety disorders (for example SSRIs and tricyclic antidepressants (TCA)) might result in mania or rapid cycling in BPD patients (Sasson et al., 2003). Taking these factors into consideration before initiating pharmacotherapy is essential.

The number of studies conducted on the treatment of BPD and anxiety disorder comorbidity is limited in the psychiatric and psychopharmacologic literature, as patients with comorbid disorders are excluded from study samples in controlled studies (Issler et al., 2004). In reviews, case presentations, open studies, and clinical observations there are valuable discussions and suggestions for the treatment of such patients with comorbid diagnoses. In one of these reviews, Perugi and Toni (2004) proposed that controlling BPD is primarily im-

portant and suggested initiating treatment with mood stabilizers, and then continuing with antidepressants. Other authors suggested the use of other non-pharmacological treatments, such as cognitive behavioral therapy (CBT) in these patients (Sasson et al., 2003). As this option is not valid for manic patients, the best solution is adding low-risk anti-anxiolytics, such as SSRI's, instead of TCA's, to the treatment after the remission of manic episodes with mood stabilizers and antipsychotics.

In addition to these general treatment approaches, there are also some suggestions for the treatment of different combinations of anxiety disorders and BPD. Suggestions and approaches for this issue are summarized in Table II and below are explanations about these suggestions. While considering these suggestions and examining the table, certain points are important. The anxiolytic effects of mood stabilizers have been proven. In addition, there are no controlled studies on the effects of mood stabilizers in treating comorbid anxiety disorders in BPD (Freeman et al., 2002). Most of the findings on this issue are based on studies conducted only with anxiety disorder patients, only patients with BPD, or data from case presentations. Therefore, there are no findings demonstrating the particular affect of a mood stabilizer on comorbid anxiety disorders.

Obsessive Compulsive Disorder–Bipolar Disorder

The most complex disorder among the comorbid anxiety disorders associated with BPD is OCD. As in other comorbid anxiety disorder diagnoses, mood symptoms should be treated first in BPD patients with OCD (Myers and Thase, 2000). In BPD patients with OCD, treatment should be initiated with an appropriate mood stabilizer, though none have been proven to be effective alone in the treatment of OCD (Issler et al., 2004). In addition, there are no studies that show a more effective mood stabilizer for the treatment of OCD-BPD comorbidity; however, some mood stabilizers seem to be more effective than others according to some research findings and clinical evaluations. Two separate studies reported that BPD patients with high anxiety scores respond less to lithium than those with lower scores (Feske et al., 2000; Young et al., 1993). In addition, it has been reported that mixed episodes, which are generally related to high anxiety levels, respond less to lithium treatment and more to valproate (Keck et al., 2006). Although there are certain case reports and open studies on the effectiveness of car-

bamazepine on OCD patients (Keck et al., 2006), there are no controlled studies on the subject. Sasson et al. (2003), referring to the positive case studies, suggested that the effectiveness of lamotrigine/topiramate should be examined in detail in OCD-BPD patients.

There are studies reporting the effectiveness of the majority of atypical antipsychotics (amisulpride, olanzapine, risperidone, quetiapine, aripiprazole) in treatment resistant OCD cases (Bystritsky et al., 2004; Connor et al., 2005; Denys et al., 2002; Metin et al., 2003; Pfanner et al., 2000). Similarly, these atypical antipsychotics were found to be effective in the acute phase of PBD, or as a preventive treatment (Perugi and Toni, 2004). Therefore, atypical antipsychotic medications can be used as an additional treatment to mood stabilizers in OCD- BPD patients, especially in patients with psychotic mania symptoms or presenting OCD symptoms without insight. In this process, it should be remembered that some antipsychotic medications could cause obsessive-compulsive symptoms or exacerbate existing symptoms (Lykouras et al., 2003).

It has been frequently stressed that the continuation of obsessive-compulsive symptoms during the treatment process will result in chronic depressive symptoms and will deteriorate the clinical presentation (Issler et al., 2004). As SSRI's are the only medication group with proven effectiveness in the treatment of OCD, it is inevitable to add antidepressants to the treatment after a certain time. In this process, all antidepressant medications carry a high risk of causing mania or rapid cycling in OCD-BPD patients and the treatment should be used only after establishing the cost-benefit ratio.

In conclusion, in BPD patients with comorbid OCD, it has been suggested that the treatment should start with mood stabilizers, especially valproate, and should continue with CBTs that are proven to be effective in OCD. During the treatment process, especially when OCD symptoms are resistant, the treatment of first choice is SSRI's, and atypical antipsychotics, after first considering their possible side-effects (the risk of mania with SSRI's and an increase in obsessive compulsive symptoms with antipsychotics), can be added to the treatment. New potential mood stabilizers (lamotrigine or topiramate) can also be an alternative.

Panic Disorder–Bipolar disorder

The ideal treatment approach in this patient group is to use medications or medication combinations that both prevent panic attacks and stabilize mood (Sasson

et al., 2003). There are some preliminary studies that show the antiepileptic medications valproate and carbamazepine are effective in both controlling panic attacks and in stabilizing mood (Guay, 1995; Tondo et al., 1989). There are reports that gabapentin is an effective mood stabilizer in acute mania, bipolar depression, or in BPD (Karataş et al., 2003). In addition, it is known that adding gabapentin to the treatment regimes of BPD patients with comorbid anxiety disorders or substance abuse disorders is effective (Perugi et al., 2002). It has been accepted that due to their GABAergic characteristics, valproate-gabapentin combination treatment is the best treatment approach for anxiety symptoms in BPD patients (Perugi and Toni, 2004).

For panic symptoms that cannot be controlled with mood stabilizers, adding antidepressant medications might be necessary. Although nearly all antidepressants are effective in the treatment, SSRIs, which carry less risk in terms of causing manic episodes, should be preferred. In these patients, adding benzodiazepines to the treatment might be an option. As the benzodiazepine alprazolam might cause mania or hypomania, clonazepam or lorazepam should be preferred. In addition, CBT is suggested as an adjunct to the treatment for suitable patients (Freeman et al., 2002).

Social Phobia–Bipolar Disorder

Despite limited data, the treatment approach in this patient group is believed to be similar to the PB-BPD patient group. Although there is a placebo-controlled study indicating the effectiveness of gabapentin in SP (Pande et al., 1999), there are no studies on its effectiveness in BPD-SP comorbidity. However, depending on the available data reviewed, it can be proposed that gabapentin is an effective choice in BPD-SP comorbidity (Sasson et al., 2003). Additionally, all mood stabilizers known to be effective in these patients (lithium, valproate, carbamazepine) can be used. In resistant cases, various antidepressants, with knowledge of their known risks (SSRIs and the monoamine oxidase inhibitors, RIMA and MAOI), can be added to the treatment. It was proposed that various antiepileptic agents that have mood-stabilizing effects (topiramate, pregabalin, and levetiracetam) might be effective in SP symptoms, and this issue should be further investigated (Keck et al., 2006).

Post traumatic stress disorder–Bipolar disorder

Treatments for this patient group are similar to other patient groups. There are various case presentations

and open-ended studies in the literature showing the effectiveness of lithium, valproate, carbamazepine, and gabapentine, alone or as a combination treatments (Forster et al., 1995; Fesler, 1991; Hamner, 2001; Karataş et al., 2003; Lipper, 1988). In cases in which symptoms cannot be controlled, adding antidepressants, especially SSRIs, to the treatment regime was suggested (Issler et al., 2004). There are various studies showing the effectiveness of some atypical anxiolytics (risperidone, olanzapine, and quetiapine) as monotherapies or as combination therapies for the treatment of PTSD symptoms, such as irritability or hypervigilance (Hamner et al., 200; Monnelly et al., 2003; Stein et al., 2002). Based on these findings, it is logical to use atypical antipsychotics with antidepressants or mood stabilizers in resistant PTSD-BPD cases. As in the treatment of all other anxiety disorders, adding benzodiazepines to the treatment is another choice.

DISCUSSION

Relevant studies show that BPD with comorbid anxiety disorders occurs frequently, and that both the severity and the course of BPD are negatively affected by this comorbidity. Despite this general common understanding, it is difficult to say that there is a consensus on the prevalence of comorbid anxiety disorders diagnoses, its relationship with clinical variables, or underlying etiological models.

Studies that have reported on the frequency of PD in BPD patients and which stress the genetic basis of the relationship between the 2 disorders, propose that PD-BPD patients represent a subgroup of BPD (MacKinnon et al., 1997; 1998). On the other hand, in other studies, comorbid OCD was found to be more frequent (Tamam and Ozpoyraz, 2002). Two studies with a similar research design, both conducted in Turkey, found that OCD was the most frequent additional anxiety disorder diagnosis in BPD patients (Altındağ et al., 2006; Tamam and Ozpoyraz, 2002). Differing from studies conducted in other countries, Turkish studies examining comorbid personality disorders in BPD patients found higher occurrence rates of obsessive-compulsive personality disorder (Tamam et al., 2004; Üçok et al., 1998). When these 2 separate findings are evaluated together it can be hypothesized that in Turkey, obsessive-compulsive traits in BPD patients are more frequent in comparison to other countries. These results should be evaluated from a cultural perspective and further examined in a large-scale national survey, as well as with cross-cultural studies.

Currently, there is no generally accepted model that explains the relationship between anxiety disorders and BPD. As mentioned earlier, models proposed to date are insufficient in explaining the conditions of all BPD patients and the comorbidity of these 2 disorders. In particular, family and genetic studies are very important in the explanation of the molecular basis of this comorbidity and the nature of the disorders. Another limitation of studies conducted to date is that most do not evaluate the effect of all additional anxiety disorder diagnoses on the BPD process. Some authors proposed that PD should be evaluated as a genetic subgroup related to BPD, whereas other authors (Boylan et al., 2004) proposed that comorbid anxiety disorders have the greatest effect on the course and outcome of BPD. Examining BPD cases with different additional anxiety disorders from a phenom-

enological, clinical, and molecular level, and with larger populations will result in better explanations.

Today, it is suggested that in the treatment of comorbid disorders, the symptoms of BPD should be the priority and that additional diagnoses should be handled with the appropriate care. Generally, the treatment of comorbid anxiety disorder is overlooked and this situation might lead to the development of treatment resistance and significant loss of functionality. In order to prevent these problems and to increase the quality of life for these patients, it is very important to recognize comorbid anxiety disorders in the early phase, by using screening tests if necessary, and to initiate the appropriate treatment. Physicians working with BPD patients should remain cognizant of this issue and choose the most appropriate intervention.

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