REVIEW ARTICLE

Bipolar disorder and anxiety disorders

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Abstract

BACKGROUND: Anxiety disorders are common in patients with bipolar disorder and show considerable influence on the course of the disease and response to treatment.
METHOD: We conducted a series of literature searches using key words, such as bipolar disorder and anxiety disorders, as items in indexed fields. The studies were obtained through a MEDLINE search from 1970 to 2012. We also examined additional studies cited in articles from these searches or our previous studies.
RESULTS: Several studies have shown poorer outcomes for patients with bipolar and comorbid anxiety disorders. Some studies have indicated worse outcomes in patients with bipolar disorder and associated anxiety disorders. Shorter periods of euthymia, increased suicidal thoughts and an increased number of suicide attempts were observed. Whether the effective treatment of anxiety reduces suicide and the severity of bipolar disorder or improves the response to treatment remains unknown. There are no well-designed intervention studies in bipolar patients with anxiety symptoms.
CONCLUSION: Further studies concerning the influence of anxiety on the course of bipolar disorder would be useful.

INTRODUCTION

Bipolar disorder (BD) is considered as a mood disorder characterized by episodes of mania, hypomania, and depression. Bipolar disorder has been associated with diseases that share common characteristics, including variations in mood or affective disorders, impulsivity, propensity towards substance abuse, and predisposition for other psychiatric conditions (McElroy *et al.* 2005; Maremmani *et al.* 2006). It has recently been suggested that dysfunctions in BD are not strictly associated with mood episodes (Tohen *et al.* 2000; Tohen *et al.* 2003). As the sixth leading cause of disability worldwide (Murray & Lopez 1996), dysfunction is high in BD, and the occurrence of anxiety disorders with BD is a frequent psychiatric condition. Several epidemiological studies have revealed higher prevalence rates of generalized anxiety disorder, social phobia, obsessive-compulsive disor-

der, panic disorder and post-traumatic stress disorder in BD. Moreover, the course and outcome of BD are negatively affected through anxiety disorders, which challenge conventional therapeutic approaches.

METHODS

In this study, we reviewed studies on the comorbidity between anxiety disorders and BD published between 1970 and 2012, identified through the Web of Science and Medline databases. We conducted a series of literature searches using terms, such as bipolar disorder, anxiety disorders, social phobia, panic disorder, obsessive compulsive disorder, agoraphobia, generalized anxiety disorder, and posttraumatic stress disorder, as key words or items in indexed fields. In addition, we examined other studies cited in articles from these searches or our previous studies. The studies were prioritized for inclusion based on the following considerations: sample size, use of standardized diagnostic criteria and validated methods of assessment, and sequencing of disorders.

BIPOLAR DISORDER AND ANXIETY DISORDERS

Data from both epidemiological and clinical samples indicate elevated rates of anxiety disorders among bipolar patients (Dilsaver *et al.* 1997; Kessler *et al.* 1997; McElroy *et al.* 2001; Pini *et al.* 1999). From a physiopathological point of view, the association between both psychopathologies remains unclear. Increased severity, earlier age-at-onset, residual symptoms presentations, and poor functional outcomes are associated with anxiety symptoms in BD. In addition, suicidal behavior, insufficient response to pharmacological treatment, and a reduced quality of life are observed (Zutschi *et al.* 2006; Simon *et al.* 2004a,b; Parmentier *et al.* 2012).

Bipolar children also have high rates of comorbid anxiety disorder (Harpold *et al.* 2005). The mean number of anxiety syndromes per child was 2 among 297 children with an unspecified BD referred for clinical management. Separation anxiety (44%) and overanxious disorder (43%) were the most common syndromes. Agoraphobia (28%), social phobia (26%), and simple phobia (23%) were also common, and obsessive-compulsive disorder (15%), panic disorder (14%) and PTSD (12%), were less common.

Epidemiological studies show that as many as 74.9% of bipolar individuals have at least one anxiety disorder during their lifetime (Cardoso *et al.* 2008; Merikangas *et al.* 2007). Smaller clinical samples suggest that between 27.2% and 55.8% of bipolar individuals have a comorbid anxiety disorder, while 31.8% to 37% of bipolar individuals have two or more disorders (Boylan *et al.* 2004; Simon *et al.* 2004a, b). Suicidality is particularly elevated in comorbidity with social phobia and generalized anxiety disorder (Perroud *et al.* 2007). The National Comorbidity Survey Replication (NCS-R) reported that among bipolar patients who have a comorbid anxiety disorder, social anxiety, specific phobia and generalized anxiety disorder were the most frequent symptoms, at 37.8%, 35.5% and 29.6% respectively. Other prevalent anxiety disorders in this population include post-traumatic stress disorder at 24.2%, panic disorder at 20.1% and obsessive-compulsive disorder at 13.6% (Merikangas *et al.* 2007).

Anxiety disorders are common in bipolar adults and bipolar adolescents, and associated anxiety symptoms negatively impact the severity, course, and response to treatment.

Panic disorder

The impact of panic disorder and comorbidity of panic spectrum symptom during the course of BD has been assessed in some studies. Lifetime panic symptoms were associated with an increased intensity of pharmacological treatment required to recover from an acute episode of bipolar disorder type I (BD-I) (Feske *et al.* 2000). High scores in the Panic-Agoraphobic Spectrum Scale Self-Report were associated with more depressive episodes (but not manic) during the course of BD-I, and longer time to remission were observed from the index episode (Frank *et al.* 2002). A panic disorder diagnosis or history of panic attacks was associated with younger age at the onset of BD-I or bipolar disorder type II (BD-II) (18 years or younger), but no associations were observed between these comorbidities and the number of hospitalizations, psychotic symptoms, suicide attempts, and current or past addictive behaviors (Henry *et al.* 2003). Another study showed more previous episodes, suicide attempts and panic attacks in groups with early disease onset (Coryell *et al.* 2013). A history of panic attacks was associated with the comorbidity of substance dependence according to the National Comorbidity Survey of individuals with BD (Goodwin & Howen 2002). The age at the onset of BD-I or BD-II was significantly lower in the presence of a lifetime panic disorder diagnosis in a large sample (Simon *et al.* 2004b). In this study, the comorbidity of lifetime panic disorder was associated with higher rates of lifetime alcohol dependence, suicide attempts, and current panic disorder, with diminished quality of life and role functioning.

Toniolo *et al.* (2009) studied 95 outpatients with bipolar disorder and compared the clinical and demographic variables of 27 BD-I patients with panic disorder (PD) to 68 BD-I patients without any anxiety disorders. The results showed that BP-I patients with panic disorder exhibited an increased number of mood episodes and higher frequencies of drug misuse, and eating disorders, indicating that the comorbidity of panic disorder is associated with a poorer course and outcome of BD-I.

The two disorders have a familial relationship. In a study of 109 bipolar probands and 226 of their siblings, Doughty *et al.* (2004) showed that only affectively ill

subjects, whether probands or siblings, had panic disorder. None of the unaffected siblings of bipolar probands (i.e., siblings that did not have a mood disorder) had full syndromic panic disorder, and panic attacks were rarely observed (3.4% vs. 28% of bipolar I subjects). Thus, panic disorder was exclusively associated with bipolar illness and did not occur independently.

Moreover, panic disorder might share a special relationship with bipolar disorder.

Generalized anxiety disorder

Generalized anxiety disorder (GAD) occurs in nearly a third of bipolar patients according to the National Comorbidity Replication Study (29.6% of all bipolar disorders) and is more frequently observed in type I bipolar patients (38.7%) (Merikangas *et al.* 2007). Furthermore, the children of bipolar subjects might be particularly at risk for developing GAD. In a study of 117 children of parents affected with bipolar disorder and major depression and 171 children of parents without these disorders, children of affectively ill parents had an increased risk of developing GAD and social phobia (Henin *et al.* 2005).

Social phobia

Social anxiety is particularly associated with poor long-term outcome in patients with bipolar disorder (Boylan *et al.* 2004). Social phobia occurred in 47–51.6% of bipolar I subjects who participated in the original and replicated National Comorbidity Surveys (Kessler *et al.* 1994; Merikangas *et al.* 2007). In addition, the National Epidemiologic Survey on Alcohol and Related Conditions Study, which surveyed 43,093 community adults, showed 5.0% lifetime prevalence of social anxiety, with comorbid bipolar I illness occurring frequently (Grant *et al.* 2005).

Obsessive compulsive disorder

The comorbidity between obsessive-compulsive disorder (OCD) and bipolar disorder is highly prevalent. In BD patients, the lifetime rates of comorbid OCD range between 3.2% and 35%, depending on the characteristics of the subjects (with or without psychotic features, BD type I or II or mixed samples) (Cassano *et al.* 1998; Cosoff *et al.* 1998, Pini *et al.* 1999; Kruger *et al.* 2000; McElroy *et al.* 2001; Craig *et al.* 2002; Henry *et al.* 2003; Simon *et al.* 2003; Simon *et al.* 2004b). In contrast, the rate of lifetime comorbid BD in clinical samples of OCD patients ranges between 3.8% and 21.5%, with a higher prevalence of BD type II (7.8–17.7%) (Ronchi *et al.* 1992; Perugi *et al.* 1997; Bogetto *et al.* 1999; Fireman *et al.* 2001; Diniz *et al.* 2004).

In an ECA study, OCD was common in 21% BD-I and BD-II patients (Chen *et al.* 1995), nearly 10-fold greater than the prevalence of OCD in the general population at 2.6%. The National Comorbidity Survey Replication (lifetime comorbidity 16.6%) confirmed this finding (Merikangas *et al.* 2007).

The onset of bipolar illness and OCD may occur during childhood in many patients (Masi *et al.* 2004).

Family members of BD-I and BD-II probands have a higher rate of OCD, suggesting a familial or genetic association (Coryel *et al.* 1985).

The comorbidity of personality disorders in a group of patients with OCD and comorbid BD was observed in a sample of 204 patients primarily diagnosed with OCD (Maina *et al.* 2007). Antisocial and narcissistic personality disorders were more frequent in patients with comorbid BD.

The peculiar characteristics of these patients contribute to their poorer response to or compliance with common pharmacological and psychological anti-obsessional strategies (Mataix-Cols *et al.* 2002), suggesting the need for alternative interventions for these subjects.

Posttraumatic stress disorder

Bipolar subjects might be at a higher risk of experiencing traumatic events, reflecting problematic behavior during mania or increased childhood trauma (Brown *et al.* 2005, Goldberg & Garno 2005). Furthermore, traumatic events that occur during a manic or hypomanic episode likely induce PTSD symptoms (Kennedy *et al.* 2002; Pollack *et al.* 2006). PTSD is highly prevalent in the general population, but might be more common in bipolar patients, ranging from 16% to 39% of BD-I patients according to the National Comorbidity Replication study (Otto *et al.* 2004; Merikangas *et al.* 2007). Bipolar women are nearly twice as likely to have PTSD compared with bipolar men (20.9% vs. 10.6% in the STEP-BD study) (Baldassano *et al.* 2005).

Complicated grief is characterized by both separation and traumatic distress symptoms (Boelen *et al.* 2003; Boelen & den Bout 2008). Increased rates (24%) of complicated grief comorbidity have been observed in individuals with bipolar disorder (Simon *et al.* 2005, Simon *et al.* 2007b; DellÓsso *et al.* 201), demonstrated by the increased severity of bipolar disorder, worse functional outcome, and lifetime suicidal tendencies.

IMPACT ON THE TREATMENT

Comorbid anxiety disorders also substantially impact the course of illness and response to treatment. Comorbid anxiety disorders or considerable anxiety symptoms are associated with longer and more frequent affective episodes (Azorin *et al.* 2009; Zutshi *et al.* 2006), slower time to remission, poorer treatment outcome (Feske *et al.* 2000; Henry *et al.* 2003), increased risk of substance abuse and psychosis (Kauer-Sant'Anna *et al.* 2007), suicidal ideations (Simon *et al.* 2007a), and suicide attempts (Simon *et al.* 2004a, 2004b; Simon *et al.* 2007a). Indeed, subclinical anxiety negatively impacts the treatment response (El-Mallakh & Hollifield 2008).

The treatments for anxiety disorders comorbid to bipolar disorder have also been observed, although a

number of studies have shown that anxiety comorbidity negatively impacts the treatment response (El-Mallakh & Hollifield 2008; Provencher *et al.* 2012).

Antidepressants are first-line agents for treating anxiety disorders, but whether the compounds retain efficacy for patients with social anxiety and bipolar disorder is not known (Provencher *et al.* 2012).

The controversy surrounding the use of antidepressants in patients with bipolar disorder has predominantly focused on whether these substances play a role in treating bipolar depression (Gijsman *et al.* 2004; Sidor & MacQueen 2011; Frye 2011); however, there are currently no studies on the role of antidepressants in treating anxiety, which is highly comorbid with bipolar disorder.

Indeed, as a major pharmacological treatment for anxiety, antidepressants might aggravate the side effects of mood stabilizers in many patients and even worsen or trigger mania (El-Mallakh & Hollifield 2008; Freeman *et al.* 2002; Sasson *et al.* 2003). There is evidence that the risk of these complications increases when bipolar patients receive antidepressants during periods of euthymia (Kukopulos *et al.* 1983) or with the long-term use (Altshuler *et al.* 1995), as would occur when these substances are primarily used to treat anxiety disorders, but this result has not been experimentally demonstrated.

The limited treatment options available for patients with comorbid anxiety suggest that the benefits of antidepressant treatment might outweigh the risks, particularly when psychotherapy has not generated an adequate response. Nevertheless, there are concerns about affective switch or increasing cycle frequency (Gijsman *et al.* 2004), particularly in patients not adherent to mood stabilizers. Studies and meta-analyses have not confirmed that SSRIs (Selective Serotonin Reuptake Inhibitors) significantly increase the risk for an affective switch in patients taking mood stabilizers (Gijsman *et al.* 2004; Sidor & MacQueen 2011), although some studies have been criticized for poor monitoring of affective switch rates.

Other agents, such as the anticonvulsant gabapentin, used to treat social phobia and panic disorder, have shown some efficacy in the treatment of anxiety disorders (Pande *et al.* 1999; Pande *et al.* 2000). There is emerging evidence for the use of atypical antipsychotics, such as olanzapine or quetiapine, and mood stabilizers, such as lamotrigine, to control anxiety symptoms in bipolar patients. The second-generation antipsychotics, olanzapine, and quetiapine might be used to treat panic disorder, OCD, nonspecific anxiety symptoms, and PTSD (Oruc *et al.* 2003; Bystritsky *et al.* 2004; Hamner *et al.* 2004, Hollifield *et al.* 2005, Sepede *et al.* 2006; Hirshfeld *et al.* 2006). Primary mood stabilizers might also be effective, but these agents have not been extensively studied (e.g., PTSD or panic disorder (Keck *et al.* 1992). Benzodiazepines are frequently utilized and have demonstrated short-term efficacy in many studies (Munjack et al.1989). Clonazepam, in particular, is commonly used in bipolar patients because this substance acts faster than lithium for the treatment of acute mania (Chouinard 1988). However, benzodiazepines, including clonazepam, have multiple potential limitations. The use of benzodiazepines (predominantly the fast-acting agents) among bipolar patients with a history of substance use has increased. These agents might contribute to the destabilization of bipolar illness, reduced compliance, and increased likelihood of relapse into comorbid substance use disorder (Weiss *et al.* 1998; Turkington & Gill 1989); thus, the use of benzodiazepines is generally not recommended. Benzodiazepines are also ineffective for the treatment of PTSD and might interfere with the long-term goals of psychotherapeutic approaches in panic disorders, and phobias. Moreover, benzodiazepine withdrawal (e.g., with short-acting benzodiazepines) might cause rebound anxiety.

Benzodiazepines induce dependence (Chouinard 2004), which may make these substances contraindicated, as bipolar patients are at a particularly higher risk of developing substance dependencies (Brunette *et al.* 2003; Goodwin & Jamison 2007; Schaffer *et al.* 2012).

Psychotherapy is a promising alternative, as the pharmacological treatment of comorbid anxiety interacts with bipolar disorder.

Attention should be paid to psychosocial treatments. Psychosocial treatments (for a review, see Provencher *et al.* 2011), such as Cognitive Behavioral Therapy (Mueser *et al.* 2007; Rosenberg *et al.* 2004) and Mindfulness-Based Cognitive Therapy (Miklowitz *et al.* 2007; 2009) have a great deal of potential. Several forms of psychotherapy, and particularly cognitive behavioral psychotherapy, are effective anxiolytic treatments (Blanchard *et al.* 2003; Linden *et al.* 2005; Mitte 2005; Shuurmans *et al.* 2006; Dusseldorp *et al.* 2007; Anderson *et al.* 2007). Psychotherapeutic interventions have a long-lasting treatment effect, where improvement continues beyond the termination of treatment (Hollon *et al.* 2006). There are no studies concerning psychotherapy in comorbid anxiety/bipolar patients, but a few studies have examined the use of psychotherapy for mood in bipolar patients.

CONCLUSIONS

The comorbidity of anxiety disorder is prevalent and serves as an independent marker for the increased severity of bipolar illnesses and suicide attempts. The presence of anxiety comorbidity signal the need for enhanced clinical monitoring of suicidality, and an increased understanding of this association is critical. The coexistence of these disorders is associated with a poorer prognosis of BD, and reduced social and occupational functioning. It is unclear whether the pathology of BD involves two independent disorders, or the additive interaction of the coexisting disorders. Little is

known about whether the effective treatment of anxiety symptoms lessens bipolar severity, improves the response to treatment of manic or depressive symptoms, or reduces suicidality. To date, there are no well-designed intervention studies in bipolar patients with comorbid anxiety.

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