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Research Article

A Lifetime Prevalence of Comorbidity Between Bipolar Affective Disorder and Anxiety Disorders: A Meta-analysis of 52 Interview-based Studies of Psychiatric Population

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ABSTRACT

Background: Bipolar affective disorder has a high rate of comorbidity with a multitude of psychiatric disorders and medical conditions. Among all the potential comorbidities, co-existing anxiety disorders stand out due to their high prevalence.
Aims: To determine the lifetime prevalence of comorbid anxiety disorders in bipolar affective disorder under the care of psychiatric services through systematic review and meta-analysis.
Method: Random effects meta-analyses were used to calculate the lifetime prevalence of comorbid generalised anxiety disorder, panic disorder, social anxiety disorder, specific phobia, agoraphobia, obsessive compulsive disorder and posttraumatic stress disorder in bipolar affective disorder.
Results: 52 studies were included in the meta-analysis. The rate of lifetime comorbidity was as follows: panic disorder 16.8% (95% CI 13.7–20.1), generalised anxiety disorder 14.4% (95% CI 10.8–18.3), social anxiety disorder13.3% (95% CI 10.1–16.9), post-traumatic stress disorder 10.8% (95% CI 7.3–14.9), specific phobia 10.8% (95% CI 8.2–13.7), obsessive compulsive disorder 10.7% (95% CI 8.7–13.0) and agoraphobia 7.8% (95% CI 5.2–11.0). The lifetime prevalence of any anxiety disorders in bipolar disorder was 42.7%.
Conclusions: Our results suggest a high rate of lifetime concurrent anxiety disorders in bipolar disorder. The diagnostic issues at the interface are particularly difficult because of the substantial symptom overlap. The treatment of co-existing conditions has clinically remained challenging.

1. Introduction

Bipolar disorders with the prevalence rate of 4% are among the most common psychiatric disorders (Ketter, 2010). It is considered to be the sixth leading cause of disability worldwide due to its significant economic, social, familial and individual burdens (Woods, 2000). Lifetime prevalence of bipolar disorder type I or type II (which includes at least one hypo/manic episode during a lifetime) has been estimated at 2% (Oldani et al., 2005). The relationship between bipolar disorder and anxiety disorders can create a more difficult course of treatment if comorbid (McIntyre et al., 2006). Studies suggest that the rate of anxiety disorders in individuals with bipolar disorder is in fact greater than those of the general population (Keller, 2006).

Bipolar disorder and anxiety disorders, including panic disorder, generalised anxiety disorder (GAD), social anxiety disorder (SAD), specific phobia, agoraphobia, obsessive–compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) are psychiatric illnesses that individually cause significant mortality and morbidity, as reflected in suicide rates (Allgulander and Lavori, 1991; Schneier et al., 1992; Osby et al., 2001), substance abuse rates (Chengappa et al., 2000; Grant et al., 2004), total medical burden (Klerman et al., 1991; Tolin et al., 2008; Lauterback et al., 2005), economic costs (Souètre et al., 1994; Wyatt and Henter, 1995) and quality of life (Wittchen et al., 1992; Mendlowicz and Stein, 2000).

Clinical and epidemiological studies have reported lifetime prevalence rates for comorbid anxiety disorders in bipolar disorder of 50% (Cassano et al., 1999; Pini et al., 1997; McElroy et al., 2001). The Epidemiological Catchment Area study found the lifetime prevalence for panic disorder in bipolar illness to be 20.8%, more than twice the rate of 10% reported in patients with major depressive disorder (Pini et al., 1997; Chen and Dilsaver, 1995a,b; Perugi et al., 2001). The frequency of GAD at 30% in bipolar disorder is reported by two studies (Pini et al., 1997; Young et al., 1993). The prevalence of comorbid social

Abbreviations: GAD, generalised anxiety disorder; PTSD, posttraumatic stress disorder; OCD, obsessive–compulsive disorder; SAD, social anxiety disorder; DSM, Diagnostic and Statistical Manual; ICD, International Classification of Diseases.

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anxiety disorder ranges between 7.8% (Szadoczky et al., 1998) and 47.2% (Kessler et al., 1997) and the prevalence rate of OCD has been found to be between 3.2% and 35% (Pini et al., 1997; Perugi et al., 2001; Szadoczky et al., 1998; Krüger et al., 1995). Although the association between PTSD and bipolar disorder has been less extensively studied, the rate of comorbidity between these two conditions may exceed by 40% (Musser et al., 1998).

Previous studies have suggested that multiple anxiety disorder comorbidities occur in a significant minority of patients with bipolar disorder. For example, Young et al. (1993) found multiple anxiety disorders in 32% of bipolar disorder outpatients. Cassano et al. (1999) studied 77 inpatients presenting with severe mood disorders with psychotic features, including bipolar I, and found the presence of one anxiety disorder in 34% of cases, while 14% of patients had two or three. Similarly, Henry et al. (2003) studied 318 inpatients most of whom had bipolar I disorder and found the rate of one or more lifetime comorbid anxiety disorders to be 24% and 11%, respectively. The extent to which anxiety and the presence of single or multiple anxiety disorders impact on course and outcome in bipolar disorder has been studied only in a limited way (Ghoreishizadeh et al., 2009; Deckersbach et al., 2014).

Compared to those with uncomplicated bipolar disorder, this co-occurrence with anxiety disorders is associated with increased suicide attempts and ideation (Young et al., 1993; Simon et al., 2003; Lee and Dunner, 2008; Frank et al., 2002; Angst et al., 2005), substance abuse (Young et al., 1993; Simon et al., 2003; Lee and Dunner, 2008; Angst et al., 2005; Toniolo et al., 2009), increased severity of mood episodes (Frank et al., 2002; Angst et al., 2005; Toniolo et al., 2009; Gaudiano and Miller, 2005), and more mood episodes. Young et al. (1993) and Feske et al. (2000) also found a decrease in lithium responsiveness in the presence of anxiety disorders. Other studies showed this combination has led to a longer recovery time (Feske et al., 2000; Otto et al., 2006) and an earlier age at the onset of bipolar illness (Simon et al., 2003; Lee and Dunner, 2008; Pini et al., 2006).

The co-occurrence of an anxiety disorder leads to a particularly difficult challenge in the treatment of bipolar illness since antidepressant medication, the mainstay of pharmacologic treatments for anxiety, may adversely alter the course of bipolar disorder. Furthermore, the common co-occurrence of alcohol and substance use disorders with bipolar disorder, limits the utility of benzodiazepines. Identification of anxiety disorders in bipolar patients is important. The treatment plan needs to balance the potential benefits to harm of antidepressant administration (El-Mallakh and Hollifield, 2008) and benzodiazepines (Brunette et al., 2003) administration.

In view of the presence of a high heterogeneity about the lifetime prevalence of anxiety disorders in patients with bipolar disorder, we aimed to quantitatively summarise the lifetime prevalence of robustly defined anxiety disorders in co-occurrence bipolar disorder (mainly type I) in psychiatric inpatient and outpatient population.

2. Methods

2.1. Search Strategy and Selection Criteria

BN and AJM designed the review protocol and extraction form in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A systematic search of PsycINFO, Medline, and CINAHL abstract databases was done by BN, from 1992 to 2013.

We included studies with data for the lifetime comorbidity between bipolar affective disorder and anxiety disorders among population of patients with bipolar affective disorder under the care of psychiatric services, and we excluded the data from any community-based samples. When it was possible, we only included the data from bipolar I studies in order to minimise selection bias, as previous studies suggested different prevalence of comorbidity between bipolar I and II with anxiety disorders. Otherwise, we used the data of those studies, which had clearly reported no significant differences in their findings regarding the type of bipolar disorder. Hence, the term of 'bipolar affective disorder' in this paper mainly indicates bipolar disorder type I. The included studies were stratified into those comorbidities with all anxiety disorders and those with a specific subtype of anxiety disorder, including GAD, panic disorder, OCD, PTSD, SAD, specific phobia and agoraphobia. We excluded the data from any diagnoses of cyclothymia. In order to minimise selection bias, we also excluded the community-based studies, as well as the data from child and adolescent studies. We took extra care to exclude duplicate publications (i.e. two or more studies investigating the same sample) in order to avoid multiple or duplication bias (Fig. 1).

3. Validity Assessment

3.1. Data Abstraction and Classification

We extracted the primary data independently, which was reviewed systematically. Based on the Cochrane Bias Method Group recommendations, a four-point quality rating and a five-point bias risk were applied to each study. The quality rating score was used to assess the study sample size, design, attrition, criterion method and method of dealing with possible confounders using the following scale: 1 = low quality; 2 = low-to-medium quality; 3 = medium-to-high quality; and 4 = high quality. The bias rating score was similarly used to assess possible bias in assessments of age, clinical setting with the following score: 1 = low bias risk; 2 = low-to-medium bias risk; 3 = medium-to-high bias risk; and 4 = high bias risk. Finally the sampling method was assessed for each study, because this could affect the interpretation of the comorbidity data. Any area of disagreement was resolved by BN and AJM.

3.2. Outcome Measures

We defined the main outcomes of interests as the lifetime prevalence of comorbidity between bipolar affective disorder type I and anxiety disorders, as well as any specific type of anxiety disorders, defined by the DSM-III, DSM-III-R and DSM-IV, ICD-9 and ICD-10 criteria.

3.3. Statistical Analysis

Overall effects estimates were calculated using the DerSimonian–Laird meta-analysis. Heterogeneity was invariably moderate to high. Therefore, a random effects meta-analysis was chosen over a fixed effects model with StatsDirect (version 2.7.7). For comparative and sub-analyses, we needed a minimum of three independent studies to justify analysis according to convention. The impact of heterogeneity on the pooled estimates of the individual outcomes of the meta-analysis was assessed using Cochran's Q, a χ^2 statistic. This was used to test whether the differences between studies was due to chance. A P value close to 1 suggests a high probability that the observed heterogeneity was due to sampling error. We also used the I^2 test to assess heterogeneity (thresholds were ≥80% = moderate and ≥90% = high).

We examined the presence of publication bias with the Begg funnel plot (Dear and Begg, 1992). In addition, we used the following three tests to see if asymmetry in the funnel plot is caused by publication bias. 1) Begg–Mazumdar test (Begg and Mazumdar, 1994), which tests the inter-dependence of variance and effect size with a rank correlation method. B) The Egger test (Egger et al., 1997), which tests for asymmetry of the funnel plot. C) The Harbord test (Harbord et al., 2006), which is similar to the Egger test but uses a modified linear regression method to reduce the false-positive rates. We also used Spearman correlation with adjusted r^2 to assess the association between linear variables.