Comparing anxiety disorders and anxiety-related traits in bipolar disorder and unipolar depression

Naomi M. Simon*, Jordan W. Smoller, Maurizio Fava, Gary Sachs, Stephanie R. Racette, Roy Perlis, Shamsah Sonawalla, Jerrold F. Rosenbaum

WACC 815, Massachusetts General Hospital, 15 Parkman Street, Boston, MA 02114, USA

Abstract

The frequent comorbidity of anxiety disorders and mood disorders has been documented in previous studies. However, it remains unclear whether specific anxiety traits or disorders are more closely associated with unipolar major depression (MDD) or bipolar disorder (BPD). We sought to examine whether MDD and BPD can be distinguished by their association with specific types of anxiety comorbidity. Individuals with a primary lifetime diagnosis of either bipolar disorder ($N = 122$) or major depressive disorder ($N = 114$) received diagnostic assessments of anxiety disorder comorbidity, and completed questionnaires assessing anxiety sensitivity and neuroticism. The differential association of these anxiety phenotypes with MDD versus BPD was examined with multivariate modeling. Panic disorder and generalized anxiety disorder (GAD) specifically emerged amongst all the anxiety disorders as significantly more common in patients with BPD than MDD. After controlling for current mood state, anxiety sensitivity and neuroticism did not differ by mood disorder type. This study supports prior research suggesting a specific panic disorder–bipolar disorder connection, and suggests GAD may also be differentially associated with BPD. Further research is needed to clarify the etiologic basis of anxiety disorder/BPD comorbidity and to optimize treatment strategies for patients with these co-occurring disorders.

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1. Introduction

The nosologic and clinical relationship between anxiety disorders and mood disorders has been the subject of considerable debate in the psychiatric literature. Comorbidity among these disorders is quite common (Kessler et al., 1994), particularly in tertiary care populations (Fava et al., 2000; Sanderson et al., 1990), and there is substantial overlap in their pharmacotherapy. Recent studies have suggested that the two major mood disorders, bipolar disorder (BPD) and unipolar major depressive disorder (MDD), may be distinguished by their relationship to specific anxiety disorders. For example, evidence from the population-based Epidemiologic Catchment Area study (Chen and Dilsaver,

1995) indicates that panic disorder (PD) comorbidity is significantly greater among individuals with bipolar disorder (20.8%) than those with unipolar depression (10%). A high prevalence of comorbid PD (33.1%) and panic attacks (35.1%) has also been observed among individuals with bipolar disorder in the National Comorbidity Survey (Goodwin and Hoven, 2002; Kessler et al., 1997). There have been conflicting results about the differential association between social phobia and mood disorders in epidemiologic studies, with some studies indicating a greater prevalence in BPD (Kessler et al., 1999), and others finding a greater prevalence in MDD (Rihmer et al., 2001). Family and genetic studies also suggest differential relationships between specific anxiety disorders and mood disorders. For example, evidence from twin studies indicates that the genes that predispose to major depression are essentially the same as those that influence generalized anxiety disorder (GAD), but are relatively distinct from those influencing

* Corresponding author. Tel.: +1-617-726-7913; fax: +1-617-726-7541.

E-mail address: nsimon@partners.org (N. M. Simon).

PD (Kendler et al., 1995). On the other hand, recent studies have pointed to a specific genetic relationship between bipolar disorder and PD (MacKinnon et al., 2002; Rotondo et al., 2002).

Further, there has been emerging interest in examining whether specific trait variables may be useful in discriminating mood disorders or familial subtypes of these disorders. Anxiety-related traits might underlie patterns of comorbidity between mood and anxiety disorders. Two well-studied traits that capture different aspects of anxiety proneness are neuroticism and anxiety sensitivity. Neuroticism refers to the predisposition to experience psychological distress and negative affects (Clark et al., 1994), and appears to be associated with the risk of both anxiety disorders and depression (i.e., "neurotic disorders") (Andrews et al., 1990; Bienvenu et al., 2001; Clark et al., 1994; Solomon et al., 1996). The genetic liability to major depression appears to overlap with that influencing neuroticism (Kendler et al., 2002). Although neuroticism scores on the NEO Five Factor Inventory were higher for patients with bipolar I disorder than seasonal affective disorder in one study (Jain et al., 1999), there is less evidence for familial transmission of this trait in BPD than MDD. For example, neuroticism has been reported to be elevated in first-degree relatives of individuals with MDD (Maier et al., 1992), but not in first-degree relatives of those with bipolar disorder (Maier et al., 1995). Further, neuroticism, as measured by scores on the neuroticism subscale of the Eysenck Personality Inventory, has been shown to be elevated in individuals with BPD who have a first-degree relative with BPD compared with individuals with BPD who have no first or second degree affected relatives (Moorhead and Scott, 2000).

Anxiety sensitivity (AS), which refers to the tendency to fear arousal and anxiety-related sensations because of the belief that such symptoms have catastrophic consequences (Reiss, 1991), has been shown to predict the development of PD (Schmidt et al., 1997). Much less is known about anxiety sensitivity and its association with BPD or MDD, although it has been shown that anxiety sensitivity may predict poor drug treatment adherence in depressed outpatients (Tedlow et al., 1996).

Using multivariate analyses, we examined the differential association of these anxiety phenotypes in a large clinical sample of patients with BPD or MDD. We sought to determine whether BPD and MDD are distinguished by a particular "anxiety profile" (i.e. specific patterns of anxiety disorder comorbidity and/or association with the anxiety-related traits of neuroticism and anxiety sensitivity). Identifying specific comorbid anxiety profiles should help refine phenotypic descriptions and subtyping of mood disorders; such results may inform genetic studies of mood disorders as well as clinical studies aimed at optimizing treatment strategies for specific mood disorder subtypes.

2. Method

2.1. Subjects and clinical assessments

Subjects were a convenience sample of 236 individuals with a primary lifetime diagnosis of either bipolar disorder ($N = 122$) or major depressive disorder ($N = 114$) recruited for a genetic study of mood disorders through the Bipolar Disorder or Depression Research Programs at Massachusetts General Hospital. All subjects received informed consent, and the protocol was approved by the IRB and in accordance with the Declaration of Helsinki. Subjects were recruited from (a) individuals inquiring about or enrolled in clinical trials of BPD or MDD treatments; (b) clinician referral; or (c) advertisement. Exclusion criteria for this study were limited to a primary diagnosis other than BPD or MDD, inability to provide informed consent, and age under 18 years. However, exclusion criterion for the studies from which some participants were recruited varied in level and type of comorbidity allowed.

Diagnoses were established using semi-structured clinical interviews [Structured Clinical Interview for DSM-IV; SCID-IV (First et al., 1996)] administered by highly trained doctoral-level clinicians who regularly use this instrument in clinical studies of BPD and MDD. Lifetime, rather than current diagnoses were examined, with the exception of GAD for which the SCID-IV diagnosis is based on the past 6 months. In addition to the clinical interview, subjects were asked to complete a packet of questionnaire measures, including demographic information and psychological rating scales. In the present study, we examined responses to two measures of anxiety-related traits. Anxiety sensitivity was assessed using the Reiss–Epstein–Gursky Anxiety Sensitivity Index (ASI), a 16-item questionnaire that measures the degree to which subjects are fearful of anxiety-related sensations (Reiss, 1991; Reiss and McNally, 1985). Neuroticism was assessed by the NEO Five Factor Inventory (Costa and McCrae, 1992).

2.2. Statistical methods

Univariate analyses were conducted to examine the association of bipolar disorder versus major depression with demographic variables (age and gender), the major anxiety disorder diagnoses (generalized anxiety disorder (GAD), panic disorder with or without agoraphobia (PD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), agoraphobia without panic, and specific phobia) and the anxiety-related traits (neuroticism and ASI) using the logistic function of STATA 7.0, with an alpha level of 0.05. To eliminate the potential effect of mood disorder symptoms (i.e. state effects) on the anxiety-related traits, the analysis of neuroticism and ASI was