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The role of lifetime anxiety history in the course of bipolar spectrum disorders

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ABSTRACT

Individuals with bipolar spectrum disorder (BSD) frequently meet criteria for comorbid anxiety disorders, and anxiety may be an important factor in the etiology and course of BSDs. The current study examined the association of lifetime anxiety disorders with prospective manic/hypomanic versus major depressive episodes. Participants were 244 young adults (aged 17–26) with milder forms of BSDs (i.e., bipolar-II, cyclothymia, BD-NOS). First, bivariate analyses assessed differences in baseline clinical characteristics between participants with and without *DSM-IV* anxiety diagnoses. Second, negative binomial regression analyses tested whether lifetime anxiety predicted number of manic/hypomanic or major depressive episodes developed during the study. Third, survival analyses evaluated whether lifetime anxiety predicted time to onset of manic/hypomanic and major depressive episodes. Results indicated that anxiety history was associated with greater illness severity at baseline. Over follow-up, anxiety history predicted fewer manic/hypomanic episodes, but did not predict number of major depressive episodes. Anxiety history also was associated with longer time to onset of manic/hypomanic episodes, but shorter time to onset of depressive episodes. Findings corroborate past studies implicating anxiety disorders as salient influences on the course of BSDs. Moreover, results extend prior research by indicating that anxiety disorders may be linked with reduced manic/hypomanic phases of illness.

1. Introduction

Bipolar disorder has long been recognized as an impairing clinical condition, but more recently, increased interest has emerged in exploring the concept of a bipolar disorder spectrum that incorporates milder bipolar conditions (e.g., cyclothymia and bipolar disorder not otherwise specified) along a continuum with bipolar II and bipolar I disorders (Dunner, 2003; Katzow et al., 2003). Research on these conditions indicates that bipolar spectrum disorders (BSDs) are chronic disorders characterized by high rates of relapse and recurrence (Harrow et al., 1990). Individuals with BSDs experience substantial functional impairment, even when receiving treatment (Judd et al., 2003; Judd et al., 2005). BSDs also carry great socioeconomic impact (Begley et al., 2001) and represent a leading cause of disability (Ferrari et al., 2016). Advancing knowledge of the potential factors influencing BSD course and persistence has the potential to curtail the adverse trajectories of these disorders, as well as to decrease the cost and burden to society.

One factor that may be important to consider is comorbidity. Individuals with BSDs frequently meet criteria for other, co-occurring psychiatric disorders, with anxiety disorders being among the most common (Merikangas et al., 2007). Epidemiological studies estimate that 46–75% of individuals with BSDs have had at least one lifetime anxiety diagnosis (Merikangas et al., 2007; Sala et al., 2012; Simon et al., 2004). Several conceptual models of comorbidity between anxiety disorders and BSDs have been proposed. One model suggests that anxiety disorders and BSDs are pathophysiologically distinct phenomena that overlap by chance due to their commonality; another suggests that they are separate disorders but have overlapping etiological mechanisms or risk factors (e.g., affective dysregulation, approach sensitivity, shared underlying affective temperaments) (Chen and Dilsaver, 1995; Freeman et al., 2002; McIntyre et al., 2006; Serafini et al., 2017). Yet another model suggests that anxiety is part of the etiology of BSDs, in that it serves as a reliable prodrome to developing

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BSDs and often manifests many years earlier than mood symptoms (Duffy et al., 2013). Indeed, research implicates anxiety as a frequent precursor to developing BSDs (Brückl et al., 2007; Goldstein and Levitt, 2007; Henin et al., 2007; Johnson et al., 2000; Jolin et al., 2008). Additionally, two independent prospective studies showed that childhood anxiety disorders were associated with an increased (2.1- to 2.6-fold) risk for later mood disorders in offspring of parents with BSDs (Duffy et al., 2013; Nurnberger et al., 2011).

Unfortunately, anxiety disorder comorbidity is also linked with greater BSD severity (e.g., suicide risk, mental health service use, and hospitalization), chronicity, poorer treatment outcomes, and impaired psychosocial functioning (Gaudiano and Miller, 2005; Goldstein and Levitt, 2008; Otto et al., 2006; Sala et al., 2014; Simon et al., 2004). In fact, anxiety disorders are shown to uniquely predict BSD severity independently of other common comorbidities such as substance use disorders (Goldstein and Levitt, 2008; Simon et al., 2004).

Taken together, the above research underscores the significance of anxiety in both the onset and course of BSDs. The strength of the anxiety/BSD relationship has led to the addition of a new "anxious distress" diagnostic specifier for bipolar disorder in the diagnostic and statistical manual (*DSM*), fifth edition (American Psychiatric Association, 2013). What is less clear is whether anxiety is associated more consistently with the persistence and severity of certain phases of the illness (Vazquez et al., 2014). Some research to date suggests more reliable links between anxiety and depressive phases (e.g., severity, persistence) than between anxiety and manic phases of BSDs (Coryell et al., 2012; Gaudiano and Miller, 2005; O'Garro-Moore et al., 2015; Otto et al., 2006). However, contrary evidence suggests that anxiety is associated similarly with both mood poles of BSDs (depression and mania/hypomania) (Sala et al., 2012). These discrepancies in the literature may be due to the fact that most studies have recruited participants from treatment facilities, which may represent a more severe population. In addition to the likelihood that such participants may not be representative of all individuals with bipolar conditions (e.g., those with bipolar II disorder or cyclothymia), it may be difficult to temporally disentangle risk mechanisms due to confounding effects of treatment. Past studies have been limited by cross-sectional or retrospective designs and have not examined progression of the illness. A better understanding of the relationship between anxiety comorbidity and the phases of BSDs might elucidate both the nosologic and clinical relationship between anxiety disorders and BSDs.

The current study examined cross-sectional and prospective associations of lifetime anxiety disorder history with BSD course among individuals with bipolar II disorder (BD-II), cyclothymia, and bipolar disorder not otherwise specified (BD-NOS). In the BSD sample, we first compared baseline differences in clinical characteristics among individuals with lifetime anxiety versus those without lifetime anxiety. Participants were judged to have lifetime anxiety if they met *DSM-IV* diagnostic criteria for an anxiety disorder (agoraphobia, panic disorder, PTSD, GAD, specific phobia, social phobia, or OCD) at baseline or at any previous time in their lives. We hypothesized that anxiety history would be associated with greater BSD severity (e.g., suicidal ideation, younger age of onset, etc.). Second, we examined the relationship between lifetime anxiety and BSD episodes over the course of the study. We expected that anxiety history would be associated with a greater number of prospective depressive but not manic/hypomanic episodes. Third, we examined the association between lifetime anxiety and time to episode onset, with the hypothesis that anxiety history would be associated with shorter time to prospective depressive but not manic/hypomanic episodes.

2. Methods

2.1. Participants and procedures

The study design was reviewed by an appropriate ethical committee (Temple University IRB); the study was carried out in accordance with the latest version of the declaration of Helsinki. All participants completed informed consent after the nature of the procedures had been fully explained. Participants were 244 undergraduate students enrolled in the longitudinal investigation of bipolar spectrum disorders (LIBS) Project at Temple University (48%) and the University of Wisconsin (52%) (Alloy et al., 2008; Alloy et al., 2012). For the LIBS Project, students were screened over the course of four years in two separate phases. Phase I encompassed screening of 20,543 students across the two sites utilizing a self-report measure of depressive and manic symptom severity, the general behavior inventory (GBI) (Depue et al., 1989). In Phase II, based on GBI cutoffs (see *Measures*), 1730 potentially eligible students completed the expanded SADS-L (see *Measures*) for screening. At a baseline visit following Phase I and II, participants eligible for the longitudinal study completed measures of depression symptom severity and hypo/manic symptom severity. All participants in the final sample met *DSM-IV* (American Psychiatric Association, 2000) and/or research diagnostic criteria (*RDC*) (Spitzer et al., 1978) criteria for BD-II disorder or cyclothymia, or met project-defined criteria for bipolar disorder not otherwise specified (BD-NOS).[4] A goal of the larger LIBS Project was to determine risk factors for bipolar I disorder (BD-I) onset, and therefore, individuals were excluded if they reported a *DSM-IV* or RDC manic episode at baseline (Alloy et al., 2012). However, individuals who eventually developed BD-I over the course of the study were not excluded, because one aim of the current study was to examine the effects of anxiety on time to onset of future hypo/mania episodes. Follow-up diagnostic assessments occurred approximately every 4 months (months in study = 43.45, *SD* = 32.24). The attrition rate in the LIBS Project was 10.71% of BSD and control participants across both sites (Alloy et al., 2012). Of the participants who attrited, 71.11% dropped out after the first or second follow-up timepoint, 22.22% dropped out after the third or fourth follow-up timepoint, and 6.67% dropped out following the fifth timepoint. The majority of participants who dropped out did so because they were unable to meet the required time commitment, and some participants (7.91%) also left the study because they dropped out, transferred, graduated from college, or moved out of the area.

The final sample (N = 244) was 58% female, aged 17–26 years (M = 20.49, SD = 1.74 years). At baseline, 66 participants had cyclothymia or BD-NOS (27.04%) and 178 participants had BD-II (72.96%). Almost half (47.2%) reported a history of outpatient psychiatric treatment (28.2% received medication, 42.3% received psychotherapy), and 1.8% reported psychiatric hospitalization. One hundred and eight (68.40%) participants in the sample had a positive family history of mood disorders among first-degree relatives.

2.2. Measures

2.2.1. The Beck Depression Inventory (BDI)

Participants completed the BDI (Beck et al., 1979), a measure of the presence and severity of current symptoms of depression. The BDI has been shown to be valid among student samples (Bumberry et al., 1978; Hammen, 1980). It was administered at baseline (α = 0.94).

2.2.2. The Halberstadt Mania Inventory (HMI)

Paricipants completed the HMI (Halberstadt and Abramson, 2008), a measure of current cognitive, motivational, affective and somatic symptoms associated with mania/hypomania. The HMI was modeled after the BDI and is administered and scored in a similar manner. In prior studies, the HMI has shown high internal consistency (α = 0.82), adequate convergent validity (r = 0.32) with the mania scale of the

[4] The BD-NOS group comprised individuals who had experienced three types of symptoms: (a) hypomanic episode(s) but no diagnosable depressive episodes, (b) a cyclothymic mood pattern with periods of affective disturbance that did not meet frequency/duration criteria for hypomanic and depressive episodes, or (c) hypomanic and depressive episodes not meeting frequency criteria for a diagnosis of cyclothymia.