



Research paper

Lifetime anxiety disorder and current anxiety symptoms associated with hastened depressive recurrence in bipolar disorder



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ABSTRACT

Aims: To assess differential relationships between lifetime anxiety disorder/current anxiety symptoms and longitudinal depressive severity in bipolar disorder (BD).

Methods: Stanford BD Clinic outpatients enrolled during 2000–2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation and followed with the STEP-BD Clinical Monitoring Form while receiving naturalistic treatment for up to two years. Baseline unfavorable illness characteristics/current mood symptoms and times to depressive recurrence/recovery were compared in patients with versus without lifetime anxiety disorder/current anxiety symptoms.

Results: Among 105 currently recovered patients, lifetime anxiety disorder was significantly associated with 10/27 (37.0%) demographic/other unfavorable illness characteristics/current mood symptoms/current psychotropics, hastened depressive recurrence (driven by earlier onset age), and a significantly (> two-fold) higher Kaplan-Meier estimated depressive recurrence rate, whereas current anxiety symptoms were significantly associated with 10/27 (37.0%) demographic/other unfavorable illness characteristics/current mood symptoms/current psychotropics and hastened depressive recurrence (driven by lifetime anxiety disorder), but only a numerically higher Kaplan-Meier estimated depressive recurrence rate. In contrast, among 153 currently depressed patients, lifetime anxiety disorder/current anxiety symptoms were not significantly associated with time to depressive recovery or depressive recovery rate.

Limitations: American tertiary BD clinic referral sample, open naturalistic treatment.

Conclusions: Research is needed regarding differential relationships between lifetime anxiety disorder and current anxiety symptoms and hastened/delayed depressive recurrence/recovery – specifically whether lifetime anxiety disorder versus current anxiety symptoms has marginally more robust association with hastened depressive recurrence, and whether both have marginally more robust associations with hastened depressive recurrence versus delayed depressive recovery, and related clinical implications.

1. Introduction

Bipolar disorder (BD) is a common, severe chronic mental illness, characterized by recurrent episodes of depression, mood elevation, and mixtures thereof (Miller et al., 2014). Lifetime prevalence of bipolar spectrum disorders in the United States is 4.4%, with the substantial heterogeneity of BD making diagnosis and treatment challenging,

resulting in substantial human, societal, and economic costs (Dilsaver, 2011; Merikangas et al., 2007). Accordingly, bipolar spectrum disorders have been associated with multi-dimensional impairment, challenging psychiatric comorbidities, compromised quality of life, and social stigma (Geddes and Miklowitz, 2013; Judd et al., 2005).

Despite preventive treatment, mood episode recurrence occurs in more than one-third of BD patients within one year, almost two-thirds

Abbreviations: BD, bipolar disorder; BD I, bipolar I disorder; BD II, bipolar II disorder; CGI-BP-OS, Clinical Global Impression for Bipolar Disorder-Overall Severity; CI, confidence interval; df, degrees of freedom; HR, hazard ratio; MINI, Mini International Neuropsychiatric Interview; SCID for DSM-IV, Structured Clinical Interview for the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders; SD, standard deviation; SPSS, Statistical Package for the Social Sciences; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder

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within two years (Perlis et al., 2006), and nearly three-quarters within five years (Gitlin et al., 1995). Accordingly, although slightly more than half of Systematic Treatment Enhancement Program for BD (STEP-BD) patients who had a syndromal mood episode at enrollment recovered (i.e., became euthymic for ≥ 8 weeks), approximately half of these had mood episode recurrence within two years, with twice as many depressive versus mood elevation (manic, hypomanic, or mixed) recurrences (Perlis et al., 2006). Thus, depressive episodes in BD are prevalent and highly recurrent, even while patients are receiving optimized measurement-, evidence-, and guideline-based treatment (Perlis et al., 2006). Depressive compared to mood elevation episodes not only have higher incidence, but also greater multi-dimensional impairment, highlighting the importance of delaying depressive recurrence and hastening depressive recovery (Di Marzo et al., 2006; Merikangas et al., 2011; Perlis et al., 2006). Thus, identification and mitigation of clinical variables associated with hastened depressive recurrence and delayed depressive recovery is crucial to effective BD management.

Anxiety in BD is highly prevalent (Pavlova et al., 2015), and associated with depression (Thompson et al., 2010; McIntyre et al., 2006), more intense psychiatric symptoms (McIntyre et al., 2006), and poorer affective (Tohen et al., 2007) and quality of life (Kauer-Sant'Anna et al., 2007) outcomes. Lifetime anxiety disorder in BD has been associated with multiple unfavorable illness characteristics including earlier BD onset age, less time euthymic (Zutshi et al., 2006), and more subsyndromal symptoms (MacQueen et al., 2003), mood episode accumulation (i.e., ≥ 10 prior mood episodes) (Tamam and Ozpoyraz, 2002), substance disorder comorbidity, suicidality (Simon et al., 2004), and mood stabilizer resistance (Zutshi et al., 2006). Current anxiety disorder comorbidity in BD has also been associated with multiple unfavorable illness characteristics including earlier BD onset age, less time euthymic (Simon et al., 2004), and more prior-year depressive episodes (Bauer et al., 2005), severe depression, impaired global functioning (Lee and Dunner, 2008), eating (MacQueen et al., 2003) and substance use (McIntyre et al., 2006) disorder comorbidity, suicidality (Lee and Dunner, 2008), and, treatment-resistance (Henry et al., 2003). Anxiety disorders in BD have been associated with worse longitudinal outcomes (Boylan et al., 2004), including longer time to remission (Feske et al., 2000) and lower likelihood of timely recovery from depression and hastened depressive recurrence (Otto et al., 2006). Accordingly, among National Institute of Mental Health (NIMH) STEP-BD patients, lifetime and current anxiety disorder(s)/symptoms were associated with significantly less time euthymic, whereas current (but not lifetime) anxiety disorder was associated with hastened depressive recurrence (Otto et al., 2006; Simon et al., 2004). Also, among NIMH Collaborative Depression Study BD (and unipolar depression) participants, number/severity of current anxiety symptoms (but not presence of pre-existing anxiety disorder) was associated with spending more time depressed (Coryell et al., 2012). Differential impacts of lifetime anxiety disorder and current anxiety symptoms upon delayed depressive recovery in BD remain to be established (Otto et al., 2006). We examined longitudinal relationships between lifetime anxiety disorder/current anxiety symptoms and BD course.

2. Methods

We included outpatients with bipolar I disorder (BD I) or bipolar II disorder (BD II) referred to the Stanford University BD Clinic between 2000 and 2011. Patients were assessed with the STEP-BD Affective Disorders Evaluation (Sachs et al., 2003), which included the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (First et al., 1996) mood disorders module, as well as the anxiety disorder screening questions from the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), and Clinical Global Impression for Bipolar Version-Overall Severity (CGI-BP-OS) score (Spearing et al., 1997). Bipolar and

comorbid (including lifetime anxiety disorder) psychiatric disorder diagnoses were determined by clinician consensus of results of the ADE and MINI (which was administered by trained research staff and assessed lifetime anxiety disorders) as well as available medical records. Clinical status at each follow-up visit was determined by the STEP-BD Clinical Monitoring Form (Sachs et al., 2002) while patients received naturalistic treatment (with monthly modal visit frequency) for up to 2 years. For this observational study that required only minimal patient effort (i.e., completing the STEP-BD ADE and MINI baseline assessments and the STEP-BD Clinical Monitoring Form longitudinal assessments), the base population and the recruited population were identical.

Presence or absence of lifetime anxiety disorder/current anxiety symptoms was determined from subjective report (as assessed by the STEP-BD Affective Disorders Evaluation and MINI), clinical assessment, and medical records. Current anxiety symptoms severity was assessed in relationship to baseline anxiety symptoms pervasiveness according to the STEP-BD ADE, and thus reflected any anxiety symptoms in the ten days prior to enrollment for the primary analysis, and anxiety symptoms thresholded for occurring on at least four or seven of the ten days prior to enrollment for secondary analyses. Other current mood symptoms (such as anhedonia) were similarly assessed according to the STEP-BD ADE and quantified (thresholded for any in the ten days prior to enrollment for the primary analysis, and occurring on at least four or seven of the ten days prior to enrollment for secondary analyses).

As described below, clinical characteristics of participants were evaluated and prospective clinical course of participants meeting diagnostic criteria for either a current major depressive episode or current recovery at enrollment were assessed. We used the STEP-BD definitions of recovery, which entailed sustained (≥ 8 weeks) euthymia/remission (fewer than three DSM-IV threshold-level symptoms of mood elevation or depression) and recurrence, which entailed development of a new DSM-IV syndromal mood elevation episode (hypomanic, manic, mixed) or major depressive episode, as assessed on the STEP-BD ADE and Clinical Monitoring Form, respectively. Thus, patients with subsyndromal mood symptoms (at least three DSM-IV threshold-level symptoms of mood elevation or depression but not meeting DSM-IV criteria for a syndromal mood elevation episode or major depressive episode, i.e. STEP-BD “continued symptoms” or “roughening” clinical status) were not included among recovered or syndromal episode patients. All patients were assessed with these STEP-BD instruments rather than symptom rating scales. The STEP-BD protocol and the subsequent similar Stanford-specific Assessment, Monitoring, and Centralized Database protocol were approved by the Stanford University Administrative Panel on Human Subjects, and patients provided verbal and written informed consent prior to participation.

Trained medical and research staff collected data on 6 demographic parameters and 22 illness characteristics/current mood symptoms/current psychotropic use. The demographic parameters assessed were: (A) Age (in years); (B) Gender; (C) Race/Ethnicity; (D) Education; (E) Marital status; and (F) Employment status. The illness characteristics/current mood symptoms/current psychotropic use assessed were: (1) Lifetime anxiety disorder; (2) Lifetime alcohol/substance use disorder; (3) Lifetime eating disorder; (4) Lifetime personality disorder; (5) BD II subtype; (5A) Lifetime psychosis (which is commonly associated with BD I); (5B) Lifetime prior psychiatric hospitalization (which is also commonly associated with BD I); (6) \geq One first-degree relative with mood disorder; (7) Onset age (in years); (8) Childhood (age < 13 years) onset; (9) Illness duration (in years); (10) Long Illness duration (≥ 15 years); (11) Episode accumulation (≥ 10 prior mood episodes); (12) Lifetime suicide attempt; (13) Rapid cycling in prior year; and (14) CGI-BP-OS; as well as current (i.e., in the prior 10 days) mood symptoms (15) Sadness; (16) Anhedonia; (17) Euphoria; (18) Irritability; (19) Anxiety, and psychotropic use (20) Mood stabilizers; (21) Antipsychotics; and (22) Antidepressants. In addition, DSM-5 depres-

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