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Current irritability robustly related to current and prior anxiety in bipolar disorder

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ABSTRACT

Background: Although current irritability and current/prior anxiety have been associated in unipolar depression, these relationships are less well understood in bipolar disorder (BD). We investigated relationships between current irritability and current/prior anxiety as well as other current emotions and BD illness characteristics.

Methods: Outpatients referred to the Stanford Bipolar Disorders Clinic during 2000–2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation. Prevalence and clinical correlates of current irritability and current/prior anxiety and other illness characteristics were examined.

Results: Among 497 BD outpatients (239 Type I, 258 Type II; 58.1% female; mean ± SD age 35.6 ± 13.1 years), 301 (60.6%) had baseline current irritability. Patients with versus without current irritability had significantly higher rates of current anxiety (77.1% versus 42.9%, $p < 0.0001$) and history of anxiety disorder (73.1% versus 52.6%, $p < 0.0001$). Current irritability was more robustly related to current anxiety than to current anhedonia, sadness, or euphoria (all $p < 0.001$), and current irritability-current anxiety associations persisted across current predominant mood states. Current irritability was more robustly related to past anxiety than to all other assessed illness characteristics, including 1° family history of mood disorder, history of alcohol/substance use disorder, bipolar subtype, and current syndromal/subsyndromal depression (all $p < 0.05$).

Limitations: Limited generalizability beyond our predominately white, female, educated, insured American BD specialty clinic sample.

Conclusions: In BD, current irritability was robustly related to current/prior anxiety. Further studies are warranted to assess longitudinal clinical implications of relationships between irritability and anxiety in BD.

1. Introduction

Bipolar disorder (BD) is characterized as a spectrum of conditions involving recurrent episodes of depression and mood elevation (Ketter, 2010). BD is commonly complicated by high rates of other comorbid psychiatric disorders, with as many as 92% of BD patients having at least one other lifetime axis I disorder (Merikangas et al., 2007). Furthermore, the presence of at least one lifetime comorbid psychiatric disorder is associated with multiple unfavorable BD illness characteristics (McElroy et al., 2001). BD patients have particularly high rates of lifetime anxiety disorders (as high as 75%), which have been associated with a more severe illness course (Ketter et al., 2013; Merikangas et al., 2007; Simon et al., 2003). In addition to lifetime comorbid anxiety disorders, current anxiety symptoms are not only prevalent in BD but are also related to worse outcomes and other unfavorable illness characteristics (Otto et al., 2004, 2006).

Irritability has been observed in approximately three-quarters of manic (Goodwin and Jamison, 2007) and depressed (Winokur et al., 1969) bipolar disorder patients. Among bipolar depressed patients, current irritability has been associated with earlier bipolar disorder onset and higher rates of suicidal ideation, axis I comorbidity,

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atypical depressive features, and depressive mixed states (Balázs et al., 2006; Benazzi and Akiskal, 2005; Benazzi et al., 2004; Deckersbach et al., 2004). Otto et al. reported current anxiety comorbidity in 32% of BD outpatients (Otto et al., 2006). In BD, current anxiety comorbidity is associated with greater risk of relapse, fewer days of euthymia, lower quality of life, and reduced role function (Otto et al., 2006; Simon et al., 2004).

Both current irritability and current anxiety have been reported across mood states in BD, as well as in anxiety disorders and in (unipolar) major depressive disorder (MDD). Irritability in BD has been most often considered in relationship to mania or hypomania (Taylor and Abrams, 1977; Winokur and Tsuang, 1975). Although the fifth edition of the Diagnostic and Statistical Manual of Mood Disorders (DSM-5) (American Psychiatric Association, 2013) continued to acknowledge the importance of irritability in mood elevation, irritability has recently been studied in the context of mixed depressive episodes (Balázs et al., 2006; Benazzi, 2005, 2007; Benazzi and Akiskal, 2003; Goldberg et al., 2009), and is highly prevalent in mixed mania (Benazzi and Akiskal, 2003; Dayer et al., 2000; Dilsaver et al., 1999). Irritability has also been observed in BD patients between mood episodes (MacQueen et al., 2003). In addition to BD, irritability has been reported in adult (Fava et al., 1991; Judd et al., 2013; Perlis et al., 2009) and pediatric (American Psychiatric Association, 2013; Emslie et al., 2005; Kessler et al., 2001) depression, as well as in anxiety disorders (American Psychiatric Association, 2013; Brown, 1997; Marten et al., 1993).

Whereas irritability has been most often studied as a symptom of bipolar mania, current (Clayton et al., 1991) and prior (Andrade et al., 1994) anxiety have classically been associated with MDD. However, rates of lifetime comorbid anxiety in BD are not statistically different from those in MDD (Pini et al., 1997; Simon et al., 2003). Furthermore, prior anxiety has been reported across bipolar mood states (Young et al., 1993). Current and prior anxiety have also been examined in BD patients in remission (Feske et al., 2000; Vieta et al., 2008).

Relationships between irritability and anxiety might be expected, given the prevalence of current irritability and current and prior anxiety across BD, MDD, and anxiety disorders. Indeed, prior studies have found significant associations between current irritability and both current (Gullion and Rush, 1998; Perlis et al., 2005, 2009) and prior (Judd et al., 2013; Perlis et al., 2009) anxiety in MDD; however, whether these relationships are also present in BD remains to be established. Additionally, bipolar mixed states, of which some consider irritability to be a core feature, were found to be related to comorbid anxiety disorders, but direct relationships between irritability and anxiety in BD has remain to be examined (Balázs et al., 2006; Bauer et al., 2005).

Thus, the objective of the present study was to investigate relationships between current irritability and current and prior anxiety as well as other unfavorable bipolar disorder illness characteristics. We examined naturalistic, observational data from a sample of 503 patients with bipolar I disorder or bipolar II disorder.

2. Methods

Outpatients referred to the Stanford Bipolar Disorder Clinic from 2000 to 2011 were assessed using the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation (Sachs et al., 2002, 2003), which included the Structured Clinical Interview for DSM (First et al., 1997) mood disorders module and the Clinical Global Impression for Bipolar Disorder-Overall Severity (CGI-BP-OS) score (Spearing et al., 1997). The Stanford University Administrative Panel on Human Subjects approved the STEP-BD protocol, as well as the subsequent similar Assessment, Monitoring, and Centralized Database protocol specific to Stanford University. Both protocols conformed to the standards of the Helsinki Declaration of 1975, and all subjects provided verbal and written informed consent before participating in the study.

Trained medical and research staff collected data on 6 demographic parameters and 23 illness characteristics/current mood symptoms/medications. 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/medications/current mood symptoms assessed were: (1) Lifetime anxiety disorder; (2) Lifetime alcohol/substance use disorder; (3) Lifetime eating disorder; (4) Lifetime personality disorder; (5) Bipolar II Disorder; (5A) Lifetime psychosis (which is very commonly associated with Bipolar I Disorder); (5B) Lifetime prior psychiatric hospitalization (which is also very commonly associated with Bipolar I Disorder); (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) Lifetime suicide attempt; (11) Rapid cycling in prior year; (12) CGI-BP-OS; (13) Current antipsychotic use; (14) Current mood stabilizer use; (15) Current antidepressant use; (16) Complex pharmacotherapy ($\geq$4 psychotropics, not including benzodiazepines); (17) Number of psychotropics (not including benzodiazepines); (18) S/SS Depression; (19) and S/SS Mood Elevation; as well as current (i.e., any in the prior 10 days) (20) Anxiety; (21) Anhedonia; (22) Sadness; and (23) Euphoria.

Current mood symptoms were directly assessed with the STEP-BD Affective Disorders Evaluation, based on patient recall of the number of days among the ten days prior to enrollment during which they experienced abnormal irritability, anxiety, anhedonia, sadness, and euphoria. For the primary analysis, we examined current irritability dichotomized according to the presence or absence of any irritability. For secondary analyses, we examined current irritability dichotomized according to the presence or absence of irritability for at least four, five, and at least seven of the prior ten days.

The parameter "lifetime anxiety disorder" included all DSM-IV-TR anxiety disorders: panic disorder, agoraphobia, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder, and obsessive-compulsive disorder.

Current predominant mood state was evaluated according to criteria in the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mood Disorders (DSM-IV-TR) (American Psychiatric Association, 2000) and was categorized into one of three mutually exclusive subgroups: euthymia, syndromal or subsyndromal (S/SS) depression, and S/SS mood elevation. Syndromal mood elevation consisted of DSM-IV-TR manic, mixed (concurrent syndromal mania and depression), and hypomanic (without concurrent syndromal depression) episodes. Patients with concurrent syndromal depression and hypomania were included in S/SS depression. Subsyndromal depression and mood elevation consisted in having more than 2 threshold-level depressive or mood elevation symptoms, but not a syndromal depressive or mood elevation episode (Sachs et al., 2002).

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 23.0 software (IBM Corp.; Armonk, NY) on an Apple MacBook Air computer (Apple Corporation, Cupertino, CA). Descriptive statistics were used to characterize the sample. Analytical statistics included Chi-Square test comparisons of unpaired categorical data and independent-sample *t*-test comparisons of continuous variables. For paired categorical data, McNemar's tests were performed. In addition, binary logistic regression was used to adjust for potential confounding variables. Statistical significance was defined as $p < 0.05$, with no correction for multiple comparisons.