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Simplifying profiles of comorbidity in bipolar disorder

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ABSTRACT

Background: Comorbid psychiatric symptoms in bipolar disorder (BD) predict poorer course of illness and treatment outcome. The sheer number of comorbid symptoms has thwarted developing treatments to address these comorbid concerns. The goal of this study was to develop a more parsimonious approach to understanding clusters of comorbid symptoms within BD.

Method: Data were collected as part of the National Epidemiologic Survey on Alcohol and Related Conditions. Structured diagnostic interviews were conducted with 43,093 participants using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV (AUDADIS-IV). Analyses were conducted on lifetime symptom counts for the most common 14 comorbid disorders among the 1411 persons who met lifetime criteria for bipolar I disorder.

Results: An exploratory factor analysis with promax rotation as well as confirmatory factor analyses revealed a three-factor solution of Externalizing, Anxiety, and Mood syndromes, with a higher order Internalizing factor comprised of the Mood and Anxiety factors. *Limitations:* Further research is needed in a clinical sample.

Conclusions: Comorbid symptoms in BD tend to cohere into Internalizing and Externalizing disorders, which could simplify research and treatment on comorbidity in BD.

1. Introduction

Although more than 300 diagnoses have been codified in the DSM, a growing body of research suggests that many of these syndromes show substantive overlap. That is, individuals who experience one externalizing disorder are at high risk for a range of externalizing disorders, and many of the externalizing disorders show parallels in genetic and other aspects of etiology. Similarly, this pattern emerges in internalizing disorders, such that having one internalizing disorder increases risk for other internalizing disorders and many of the internalizing disorders show parallels in genetic and other aspects of etiology. Recognizing this overlap, the Research Domain Criteria (RDOC) initiative at NIMH focuses on the study of risk factors that are relevant to a broad range of psychopathologies (Kozak and Cuthbert, 2016). Despite the considerable advances in recognition of this overlap among conditions, much of the research in bipolar disorder continues to follow traditional diagnostic approaches. In the current paper, we consider how to conceptualize commonalities across the many comorbid symptoms observed in bipolar disorder.

Bipolar disorder is highly comorbid with other psychiatric disorders in both clinical and community samples (Bauer et al., 2005; Grant et al., 2005), with as many as two-thirds to 99% who will meet diagnostic criteria for comorbid conditions (Kessler et al., 2005). Adding to the complexity, among those who meet criteria for a comorbid condition, many will meet criteria for 2 or more comorbid conditions (Bauer et al., 2005).

Comorbid diagnoses in bipolar disorder are strongly associated with a more severe course of illness (Soreca et al., 2009), poorer response to treatment (Feske et al., 2000), as well as impairment and earlier age of onset (Perlis et al., 2004). Indeed, some have argued that the high treatment costs for bipolar disorder might be largely accounted for by those with psychiatric comorbidity (Guo et al., 2007). As an example, comorbid anxiety disorders are related to younger age of onset (Simon et al., 2004), greater severity of bipolar disorder (Otto et al., 2006), including fewer days well, longer time to recovery (Simon et al., 2004), poorer quality of life (Otto et al., 2006), greater suicidality (Simon et al., 2004), higher risk of substance abuse (Goodwin and Hoven, 2002), and lower lithium responsivity (Young et al., 1993). Similarly, comorbid substance use is related to an earlier onset of more comorbid diagnoses, more hospitalizations, more dysphoric and irritable mood states, and more frequent mood swings in BD (Sonne et al., 1994). Given the significant impact on functional impairment, illness course,

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and treatment response, it is critically important to develop models to better understand comorbidity in bipolar disorder. With the complexity of these profiles, researchers have made relatively few gains in developing treatment models that take into account the rich array of conditions to be addressed within BD.

Some researchers have examined the range of clinical presentations observed in BD. Much of this work, however, focuses on the diversity of manic symptoms of mania (Cassidy, Yatham, Berk, and Grof, 2008), rather than the conditions that are comorbid with BD (Karam et al., 2010) or to specific profiles within BD (Angst et al., 2010).

Within the broader psychopathology literature, results of several large-scale epidemiological studies indicate that a two-factor model (Kendler et al., 2003; Krueger, 1999) may explain patterns of psychiatric diagnoses. Relationships among comorbid disorders follow a replicable pattern in factor analyses of epidemiological samples (Krueger, 1999; Kessler et al., 2005; Krueger et al., 2003; Kendler et al., 1995) and are characterized by two broad dimensions: an internalizing dimension defined by unipolar depression and anxiety disorders and an externalizing dimension indicated by substance use and antisocial behavior disorders. This model appears to generalize across genders as well as samples.

These more parsimonious models have shown excellent validity, in that there is growing evidence that many risk factors broadly operate to increase risk of internalizing or externalizing conditions rather than more specific diagnoses. This has been particularly evident in genetic models (Kendler et al., 2003; Krueger, 1999). Among internalizing disorders, shared genetic variance has been found among major depression and generalized anxiety disorder, panic disorder and phobias, and to a lesser degree major depression and phobias (Kendler et al., 1995). Among externalizing disorders, shared genetic variance has been found among substance use disorders and antisocial personality disorder (Slutske et al., 1998). Findings of genetic studies validate the factor analytically derived dimensions of internalizing and externalizing disorders. Across mental health disorders, two-factor models have also achieved substantive support in pharmacological and psychological treatments. For example, high rates of comorbidity and shared etiologies across internalizing disorders have led to the development of a transdiagnostic treatment for emotional disorders, *The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders* (Barlow et al., 2011), providing evidence for the utility of classifying comorbidities into higher-order factors. Taken together, epidemiological, genetic, and treatment studies provide compelling evidence to support the classification of a two-factor Internalizing and Externalizing model derived from factor analytic studies.

In sum, comorbid conditions are all too common in BD and are important correlates of course and treatment outcome. The bewildering complexity of conditions, though, has served as a deterrent for developing personalized medical approaches to the treatment of BD. In the more general literature on psychopathology, internalizing and externalizing dimensions have been extremely well validated, and provide a much simpler way to understand patterns of overlap in disorder occurrence, etiology, and treatment. These dimensional models have not been applied to comorbidities in bipolar disorder. This study aims to understand whether models of internalizing and externalizing symptoms can be applied within the context of BD to describe comorbidity more parsimoniously. Our goal is to consider whether symptoms comorbid with BD may be better characterized using a dimensional model rather than discrete diagnoses.

To examine this, the current study uses exploratory and confirmatory factor analysis to assess the structure of comorbid psychiatric symptoms among people with a history of mania, the defining feature of bipolar I disorder. In planning this study, we were influenced by findings that a substantial percentage (with estimates ranging 5–33%) of people with lifetime manic episodes does not experience major depressive episodes (Baek, Eisner and Nierenberg, 2014; Cuellar, Johnson, and Winters, 2005; Yazici et al., 2002). One study has determined that mania and depression do not serve as opposite poles of the same disorder, and instead fluctuate independently (Johnson et al., 2011). Given this, we were interested in understanding the structure of lifetime symptoms of depression and dysthymia, as well as other syndromes that are typically considered to be comorbid with mania. This is the first study to our knowledge to examine the factor structure of comorbidity among people with mania in a general population-based sample. Determining the factor structure of syndromes that co-occur with mania may simplify assessment and improve treatment of comorbid disorders.

2. Method

2.1. Design

Data for this study were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Grant et al., 2003; Grant and Dawson, 2006). The survey was approved by the U.S. Census Bureau and the U.S. Office of Management and Budget. Interviews were conducted from 2001 through 2002. The NESARC sample was comprised of 43, 093 non-institutionalized adults in the United States, including Alaska, Hawaii, and Washington DC. For additional details on how the study sample was selected see Grant et al. (2003). All respondents were administered the Alcohol Use Disorder and Associated Disability Interview Schedule DSM-IV Version (AUDADIS-IV). Data were collected in face-to face, computer assisted interviews conducted in participant homes.

2.2. Sample

The sample for this study included respondents who met criteria for bipolar I disorder (n = 1411), defined by NESARC as having at least 1 manic or mixed episode (with or without one or more major depressive or hypomanic episodes) over the course of a lifetime (Grant et al., 2005). Respondents were included if their manic or mixed episode was not substance-induced or due to medication or another medical condition. The sample for this study was 59% female, 58% White, non-Hispanic, 19% Black, non-Hispanic, 3% American Indian / Alaskan native, 2% Asian / Native Hawaiian / Pacific Islander, and 18% were Hispanic or Latino. The mean age of the sample was 39 years (SD = 14.81). Most of the sample (88%) was born in the United States. Forty-two percent were married or living as married, 23% were divorced or separated, 31% never married, and 5% were widowed. Thirty-one percent had completed high school or GED, 25% attended some college, 10% obtained an associates degree, and 14% completed college. Forty-five percent of the sample was employed full time. Thirty-four percent of the bipolar I sample reported seeking help from a counselor, doctor, therapist, or other person specifically for mania.

2.3. Measures

The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV; Grant et al., 2000) is a structured diagnostic interview designed to be administered by either lay interviewers or clinicians. The AUDADIS-IV captures a broad range of information through its assessment of alcohol, tobacco, and drug use, as well as mood disorders, anxiety disorders, and personality disorders. The AUDADIS-IV interview covers current (past 12 months) and past disorders (prior to the past 12 months). The interview takes about one hour to administer, but varies depending on the symptoms endorsed.

Reliability studies have been conducted in clinical and general population samples within the United States and in other countries with good to excellent results (Grant et al., 2003; Hasin et al., 1997). Reliability of the most recent version was examined in a subsample of 400 respondents who completed the AUDADIS-IV interview (Grant et al., 2003). Respondents were randomly chosen to participate in a retest interview two to three months after their initial interview. One to three