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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.

Keywords

Bipolar disorder; Comorbidity; Anxiety disorders; Substance use disorders; Dimensional

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

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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, 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.

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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.

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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 randomly selected modules were re-administered. Dimensional measures of symptoms of alcohol abuse and dependence had excellent test-

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retest reliability (ICC = .76 – .89), and lifetime major depression, dysthymia, panic, mania and generalized anxiety disorder achieved good to excellent reliability (ICC = .57 – .86).

2.4. Statistical analysis

Symptom counts for each disorder were used to increase statistical power compared to dichotomous diagnostic classifications (Krueger et al., 2003; Markon, 2010). Lifetime amphetamine and cocaine dependence were collapsed into a single category. Opiates, hallucinogens, inhalants, and other drugs were collapsed into an 'other drugs' category because of their low prevalence rates. Symptom counts coded the number of DSM-IV symptom criteria met for each disorder; this meant that multiple AUDADIS items were sometimes combined into a single symptom score (i.e., for major depressive disorder a total of 9 symptoms were possible).

We used random assignment to divide the sample in two portions: one for exploratory factor analyses, and the other independent hold-out sample for confirmatory analyses. SPSS 15.0 estimated the exploratory factor analyses (EFA) with Promax rotation to allow factors to correlate. Initial factor extraction used principal components analysis; subsequent confirmatory analyses used maximum likelihood. The accepted configuration had to satisfy the scree test (Cattell, 1966), meet the requirement of Glorfeld's extension of parallel analysis (PA), and show the lowest minimum average partial correlation (MAP). MAP and PA methods are well-validated methods for determining the number of factors to accept (Glorfeld, 1995; Glutting et al., 2005; Velicer et al., 2000).

We used MPlus 5.2 to estimate the confirmatory factor analyses on the random cross-validation sample. Consistent with DSM-IV criteria, agoraphobia was only assessed if a person meets criteria for panic disorder. Similarly, antisocial personality disorder was only assessed if a person meets criteria for conduct disorder. Therefore, throughout each of the models, symptoms of panic disorder and panic disorder with agoraphobia and symptoms of antisocial personality disorder and conduct disorder were allowed to covary, respectively.

Six competing models were evaluated. These models were generated based on theory and prior work, and compared to simpler models, with a preference for parsimony when simple and complex models provide comparable fit. The first model was a one-factor model in which all comorbidities were loaded onto a single factor, representing an overall tendency toward having comorbid psychiatric disorders. Next, a two-factor Externalizing/Internalizing model was fit, drawing from research described above (Kendler et al., 2003; Krueger, 1999). In this model, internalizing disorders were represented by symptoms of major depressive disorder, dysthymia, generalized anxiety disorder, panic disorder, panic disorder with agoraphobia, specific phobia, and social phobia. An Externalizing factor was represented by symptoms of alcohol and substance dependence, conduct disorder, and antisocial personality disorder. Next, a three-factor model was fit. The Internalizing factor from the second model was split into two factors: Factor 1 (Mood) was represented by symptoms of depression and dysthymia while Factor 2 (Anxiety) was represented by symptoms of generalized anxiety disorder, panic disorder, panic disorder with agoraphobia, specific phobia, and social phobia. A four factor model was fit in which Mood and Anxiety factors were posited to load onto a higher order Internalizing factor. A fifth model examined whether the Externalizing factor

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was better characterized by two distinct factors: a Substance Dependence factor and an Antisocial Behavior factor. Lastly, a six factor model with a higher order Externalizing factor, composed of the Substance Dependence and Antisocial Behavior factors was examined. The Internalizing factor from the four factor model was maintained for the fifth and six models.

As recommended by Kline (2005), model fit was determined using the χ^2 test of model fit (cut off = $p < .05$), the Bentler Comparative Fit Index (CFI; cut off > .95), the Root Mean Square Error of Approximation (RMSEA; cut off < .06), the Standardized Root Mean Square Residual (SRMR, cut off < .10), and the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The χ^2 test of model fit is a test of the hypothesis that the model has perfect fit in the population. Failure to reject the null hypothesis provides support for the model; however, when sample sizes are large, the value of χ^2 might incorrectly lead to rejection of the model. The Comparative Fit Index assesses the proposed model against a baseline or null model in which the population covariances of observed variables are zero. The RMSEA is a "badness of fit measure" that assumes model fit in the population is not perfect and approximates a non-central chi-square distribution. The SRMR is a measure of the mean absolute value of the residuals of the covariance. Higher values of the SRMR indicate worse fit. The AIC and BIC are predictive fit indexes that assess model fit in hypothetical samples randomly drawn from the same population of the original sample. The AIC favors more parsimonious models, and the model with the smallest AIC is the one most likely to replicate. The BIC favors parsimonious models and penalizes complexity more so than the AIC. The goal was to identify the model with the smallest BIC value that still maintained good fit on other indices.

3. Results

3.1. Exploratory factor analysis

Mean symptom count levels in the sample selected for the exploratory factor analysis are presented in Table 1. Exploratory factor analysis revealed a three-factor solution that satisfied the three decision rules (Table 2). The first factor, Externalizing, explained 26% of the variance (unrotated eigenvalue = 3.68) and included lifetime alcohol and substance dependence disorders, conduct disorder, and antisocial personality disorder. The second factor, Anxiety, captured 18% of the variance (eigenvalue of 2.44) and included panic disorder, panic disorder with agoraphobia, generalized anxiety disorder, social phobia, and specific phobia. The third factor, Mood, had an eigenvalue of 1.14, and accounted for 8% of the variance. The Mood factor was defined by symptoms of major depressive disorder, dysthymic disorder, and generalized anxiety disorder. The three factors account for 52% of the total variance. Table 2 displays the rotated pattern matrix for the three factors. The rotation converged in 5 iterations. The Externalizing factor was relatively independent from the Anxiety (r =.17) and Mood factors (r = .16). The Anxiety and Mood factors were correlated (r =.26).

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3.2. Confirmatory factor analysis

Mean symptom count levels of the sample selected for the confirmatory factor analysis are presented in Table 1. Model fit for all CFA models is presented in Table 3. A single factor model was a poor fit to the data. The two-factor model was a significantly better fit than the one factor model. A three-factor model that paralleled the results of the EFA demonstrated an improvement in model fit over the two-factor model.

Given the results of the EFA and previous research that demonstrates GAD is more related to mood disorders, symptoms of GAD were allowed to load onto both the Anxiety and Mood factors. This cross loading was carried throughout all subsequent analyses. When the three-factor model was re-examined (not reported) it showed an improvement in fit over the original three-factor model and equivalent fit with the four factor model in which the Anxiety and Mood factors were indicators of a higher order Internalizing factor. The Internalizing and Externalizing factors were correlated ($r = .22$). This four-factor model is conceptually preferable to the three-factor model. This is also a higher-order model, with Internalizing as a second-order factor – a model that could not be tested directly via exploratory factor analytic methods.

A five factor model that examined whether separating Substance Dependence and Antisocial Behavior factors (rather than a general Externalizing factor) demonstrated poor fit. Lastly, when the Substance Dependence and Antisocial Behavior factors were loaded onto a higher order Externalizing factor, model fit improved significantly and the fit indices were similar to those in the four factor model. The four factor model yielded a lower BIC value than the six factor model. Thus, the more parsimonious four factor model is maintained (Fig. 1).

4. Discussion

Results of epidemiological studies indicate high rates of co-occurring psychopathology within bipolar disorder (Grant et al., 2005), and these comorbid conditions have been found to interfere with treatment (Krueger et al., 2003). The present study examined the factor structure of comorbid symptoms among people with mania in a general population sample. The findings of this study suggest that underlying major dimensions of internalizing and externalizing symptoms can capture the comorbid symptoms observed in BD, as has been observed in research outside of bipolar disorder. It is hoped that applying this dimensional lens organizes broad dimensions of comorbidity that can guide and improve treatment of BD (Krueger et al., 2003; Rodriguez-Seijas et al., 2015).

More specifically, EFA revealed an Externalizing factor, an Anxiety factor, and a Mood factor. The correlations between the Externalizing factor and the other factors were small, suggesting a high level of independence. The correlation between the Mood and Anxiety factors was greater, suggesting that these factors may be indicators of a higher order Internalizing factor. CFA confirmed that the Mood and Anxiety factors were indicators of a higher order Internalizing factor. This three-factor model, comprising Mood, Anxiety, and Externalizing factors, is a more parsimonious way to characterize the many symptoms often found to be comorbid with bipolar disorder.

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Before considering implications, it is important to describe the limitations of this study. Diagnostic interviews were completed by lay interviewers and relied on endorsement of symptoms, rather than interviewer observations. Test-retest reliability of mania diagnoses is not well established for the interview used in the NESARC study, although the probes have a similar content and format to other well-established diagnostic interviews for mania. In addition, several disorders known to be highly comorbid with bipolar disorder including posttraumatic stress disorder, obsessive-compulsive disorder, and attention deficit hyperactivity disorder were not assessed in the parent study and were thus not available for inclusion in analyses. Additional research is needed to determine if the presence of comorbid symptoms associated with these disorders would alter this factor structure. These models should also be examined in a clinical population (Krueger et al., 2003). Newer structural models of psychopathology have included a third dimension corresponding to thought disorders (Kotov et al., 2011), and future structural models should further consider the this dimension. Finally, these models reflect a structure specific to BD1 and may not generalize to other bipolar spectrum disorders.

Despite the methodological limitations, the current study provides a framework for more integrative studies of comorbid conditions in BD. Previous research has highlighted that a range of internalizing conditions could be tied to personality and cognitive variables; and many of those variables have been found to predict the course of bipolar depression. Future research would do well to examine whether those factors might more broadly explain both the high rates of anxiety and depression in BD. In the general psychopathology literature, considerable research suggests that deficits in cognitive control and impulsivity are central to the development of a broad range of externalizing conditions; given that cognitive control and impulsivity deficits are frequently observed in BD, it would be helpful to understand the range of comorbid conditions that might be explained by these trait-like tendencies in BD. Understanding central vulnerability factors that explain internalizing or externalizing conditions more broadly might provide parsimony in treatment targets (Rodriguez-Seijas et al., 2015). 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). Although the *Unified Protocol* has been studied in the context of treating principal emotional disorders (e.g. primary diagnosis of an anxiety disorder), it is possible that this intervention could help address the range of comorbid internalizing conditions observed within BD.

In sum, current findings suggest that comorbid symptoms in BD could be understood using a very parsimonious solution of Internalizing and Externalizing factors. This opens doors to future directions that may offer a simplified approach to studying the etiology and treatment of comorbid symptoms in BD.

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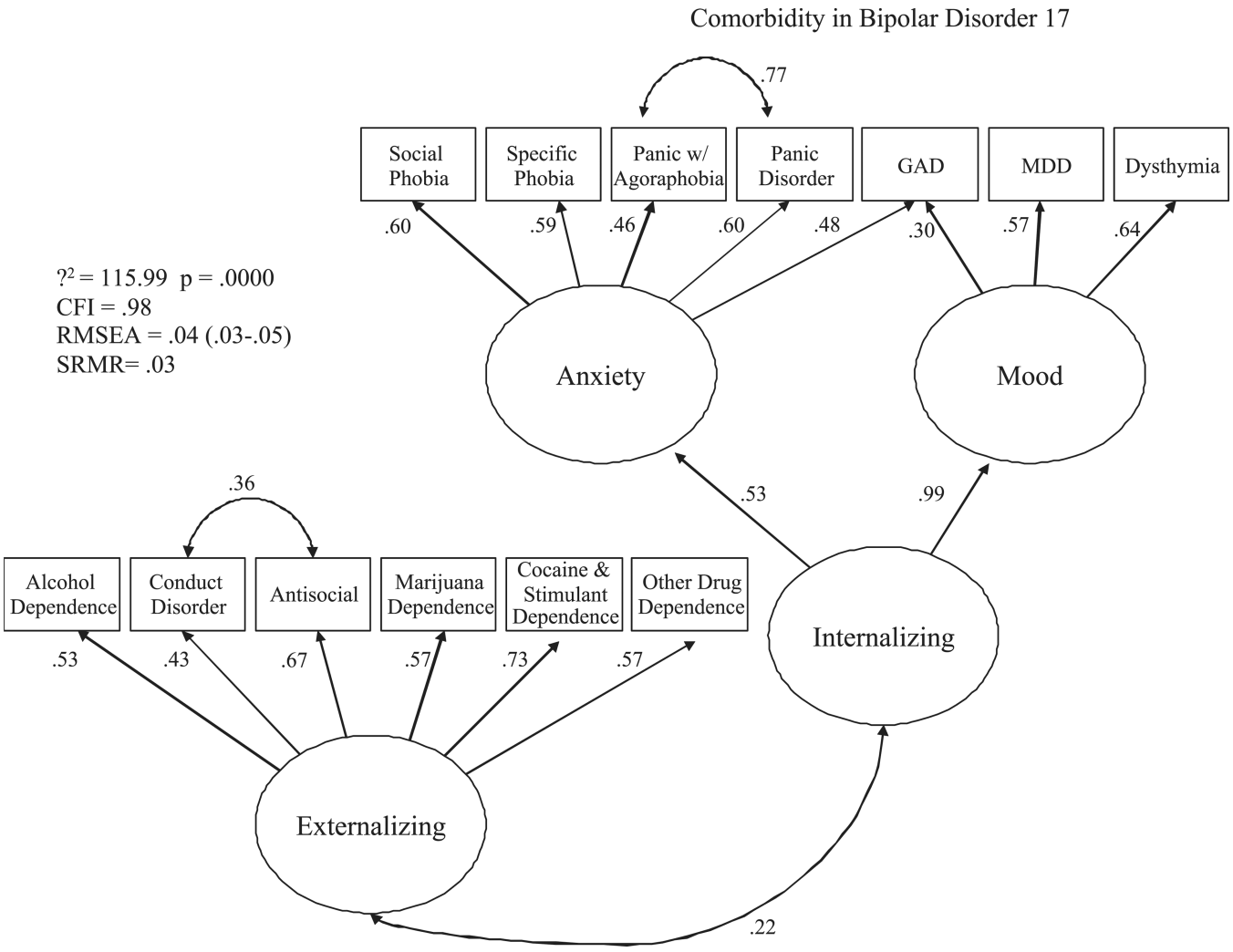

Fig. 1.
Confirmatory factor analysis of comorbid psychopathology in people with mania.

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Table 1

Means and standard deviations of symptom counts for DSM-IV psychiatric disorders.

	EFA Sample (n = 693)		CFA Sample (n = 718)	
	Mean	**SD**	**Mean**	**SD**
Antisocial Personality Disorder	3.73	3.68	3.68	3.62
Cocaine and Stimulant Dependence	.87	2.35	.81	2.12
Other Drugs Dependence	.50	1.37	.44	1.23
Marijuana Dependence	.77	1.52	.69	1.39
Alcohol Dependence	2.03	2.34	2.05	2.24
Conduct Disorder	3.76	2.62	3.59	2.30
Panic Disorder	.92	1.39	.93	1.4
Panic Disorder with Agoraphobia	1.07	2.33	1.17	2.46
Specific Phobia	1.09	1.05	1.15	1.06
Social Phobia	.99	1.41	1.04	1.44
Generalized Anxiety Disorder	1.75	2.96	1.99	3.12
Major Depressive Disorder	6.33	3.25	6.21	3.38
Dysthymic Disorder	1.92	3.01	1.94	3.03

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Table 2

Factor loadings for symptoms of psychiatric disorders (pattern matrix from Promax rotation of a principal axis factor analysis).

	Externalizing	Anxiety	Mood
Antisocial Personality Disorder	**.78**	−.03	.07
Cocaine and Stimulant Dependence	**.77**	.01	−.08
Other Drugs Dependence	**.73**	.09	−.04
Marijuana Dependence	**.74**	−.01	−.06
Alcohol Dependence	**.68**	.04	.06
Conduct Disorder	**.63**	−.11	.09
Panic Disorder	.02	**.90**	−.03
Panic Disorder with Agoraphobia	.03	**.89**	−.07
Specific Phobia	−.02	**.58**	.09
Social Phobia	−.04	**.58**	.04
Generalized Anxiety Disorder	−.07	**.26**	**.59**
Major Depressive Disorder	−.03	.02	**.78**
Dysthymic Disorder	.09	.09	**.78**

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Table 3

Fit Indices for confirmatory factor analysis models of comorbidity in bipolar disorder.

Model Name	# of Factors	χ^{2*}	df	CFI	RMSEA	AIC	BIC	SRMR
Psychopathology: General Comorbidity	1	762.68	63	.73	.12 (.11–.13)	37606.95	37794.01	.12
Internalizing & Externalizing	2	182.53	62	.95	.05 (.04–.06)	37029.09	37220.72	.04
Externalizing, Mood, Anxiety	3	137.40	60	.97	.04(.03–.05)	36987.97	37188.72	.03
**† Externalizing, Internalizing: Mood, Anxiety	4	115.99	59	.98	.04(.02–.05)	36968.56	37173.87	.03
† Drugs, Behavior Drugs with Behavior @0 Internalizing: Mood, Anxiety	5	398.91	59	.87	.09 (.082–.099)	37251.48	37456.79	.11
† Externalizing: Drugs, Behavior Internalizing: Mood & Anxiety	6	113.24	58	.98	.04 (.03–.05)	36967.81	37177.68	.03

*All p-values < .00005; Disturbance terms between conduct disorder and antisocial personality disorder and panic disorder with panic disorder with agoraphobia were allowed to correlate in all models.

**Illustrated in Fig. 1

†GAD symptoms cross load on Mood and Anxiety factor.