NATURE OF AND RISK FOR EXPERIENCING MIXED STATES
IN RECENT-ONSET BIPOLAR SPECTRUM SAMPLE

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ABSTRACT

Clinicians and researchers have identified a pattern of “mixed” symptoms that are sometimes exhibited by individuals with bipolar spectrum disorders (BSDs). However, the criteria for these mixed states as outlined by the American Psychological Association have been criticized for being too stringent for most individuals that experience impairing episodes of mixed symptomatology (e.g., Akiskal, 1996). Mixed states are associated with a more impairing course of illness and suicidality. More research is needed on mixed states, and there is particularly little evidence for risk factors in recent-onset samples. The aims of this study were to 1) examine the prevalence of mixed states in a sample of individuals with recent-onset bipolar spectrum disorders, 2) examine the symptom structure of hypomanic and depressive episodes, and 3) examine some of the risk factors associated with mixed states. Participants in sample 1 were adolescents, initially aged 14-19, selected for exhibiting either moderate or high Behavioral Approach System (BAS) risk for first onset of BSDs. Participants in sample 2 were 18-24 year old undergraduates from Temple University recruited for having a bipolar spectrum diagnosis. Mixed states captured 37.10% of all episodes examined in sample 1, yet only 13 (10.48%) of these episodes met available research criteria for mixed mood episodes. Factor analysis yielded two adequate models that fit the data; one model had two factors that aligned with traditional depressive and hypomanic symptomatology, and another model had three factors that aligned with hypothesized overactivity, inhibited depression, and irritable risk taking components of bipolar disorder. Latent class analysis allowed for examining observed patterns of responses within individuals, and then grouping

heterogeneous groups of individuals into classes based on similarities on dimensions of interest, performance within dimensions, or both (Nylund, Bellmore, Nishina, & Graham, 2007). The latent class analysis showed that three classes best defined bipolar spectrum individuals in sample 1: low impulsivity, aggressive, and substance problems classes were obtained. The ‘aggressive’ class was significantly more likely than the ‘low impulsivity’ class to experience any mixed symptomatology, although a continuous measure of mixed symptoms did not yield significant differences between classes.

Overall, the results from the current study support findings suggesting that mixed mood states are more commonly experienced than originally believed. These results extend previous studies to include individuals with bipolar spectrum disorders, not solely bipolar I and II disorders. These findings also suggest that non-treatment-seeking samples may have different types of mixed mood states than those seeking treatment. These findings add support to the literature that individuals with BSDs and comorbid substance use diagnoses are at increased risk for chronic illness, and show that these individuals are also more likely to experience mixed mood states than those without comorbid substance use diagnosis. Treatment providers should be aware of the complications that are inherent in bipolar individuals with comorbid substance diagnoses, as they are more likely to experience more episodes as well as mixed symptoms.

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CHAPTER 1

INTRODUCTION

Classic definitions of bipolar spectrum disorders (BSDs) give a picture of discrete episodes of either hypo/mania or depression, interspersed with long periods of euthymia (see Court, 1968, for review). Many researchers have discussed the moods as being on a continuum, with mania and depression at separate poles (see Murphy & Beigel, 1974, for review). However, more recently, researchers have begun to call for a dimensional conceptualization of moods, as symptoms of mania and symptoms of depression sometimes co-occur. Clinicians and researchers have identified a pattern of "mixed" symptoms that are sometimes exhibited by individuals with BSDs. Mixed states are defined in many different ways, but the overarching concept is the presence of hypo/manic and depressive symptoms occurring concurrently (American Psychological Association, 2013), or at least fluctuating between these symptoms at a rapid rate (World Health Organization, 1992). However, because mixed states have been defined in various ways by different research groups, it is difficult to draw conclusions from the extant literature, as very few replications have been conducted because the operationalization of so-called mixed states varies so widely.

Definitions of Mixed States

In the penultimate edition of the Diagnostic and Statistical Manual for Mental Disorders, fourth version text revision (DSM-IV-TR), there were diagnostic criteria for one type of mood episode that contains both manic and depressive features (APA, 2000). A mixed episode was defined as at least one week of meeting full criteria for both a manic and major depressive episode (MDE), which causes impairment (see Table 1).

Since these criteria were first published in the DSM-IV in 1994, many researchers have criticized the operationalization, stating that it was too stringent to be employed for most individuals that experience impairing episodes of mixed symptomatology (Akiskal, 1996; Akiskal et al., 1998; Swann et al., 2007; McElroy et al., 1992). The World Health Organization's (WHO) International Classification of Diseases (ICD-10; 1992) has a slightly different definition for bipolar mixed episode. ICD-10 defines mixed episode as a mixture or rapid shifting between hypo/manic and depressive symptoms during a period lasting at least two weeks (World Health Organization, 1992). Contrary to DSM criteria, ICD criteria are generally thought to be too vague by researchers in the field (see Cassidy et al., 2008, for review). The American Psychiatric Association took steps towards a more dimensional categorization of mood episodes in bipolar spectrum disorders with the publication of the Diagnostic and Statistical Manual for Mental Disorders, fifth version (DSM-5; APA, 2013). In the DSM-5, there is an optional "mixed features" specifier for bipolar mood episodes, and the criteria for mixed episode were removed completely. Whereas the dimensional nature of these new criteria is a step forward, there is cause for concern with regard to how this will be examined in investigations, as it may be too vague to be operationalized in research, similar to criticisms of ICD criteria (Cassidy et al., 2008). There are also other changes to manic and hypomanic episodes that may pose other diagnostic concerns (for review, see Angst, 2013), although that is beyond the scope of the current dissertation.

Table 1. Criteria for DSM-IV-TR mixed episode

five or more of following
*depressed mood
*diminished interest or pleasure
weight loss or gain, or change in appetite
insomnia or hypersomnia
psychomotor agitation or retardation
fatigue or loss of energy
feelings of worthlessness or excessive guilt
diminished ability to think or concentrate, or indecisiveness
suicidality
AND elevated, expansive, or irritable mood
plus 3 or more of following (4 if mood is irritable)
inflated self-esteem or grandiosity
decreased need for sleep
more talkative than usual or pressure to keep talking
flight of ideas or racing thoughts
distractibility (external stimuli)
increase in goal directed activity or psychomotor agitation
risky behavior

* One of these two symptoms must be included

Given the lack of acceptable criteria laid out by the APA and WHO for many years, researchers began defining mixed states in their own terms. Apart from DSM and ICD, there are five different criteria for mixed mood states that researchers use when operationalizing their investigations. These are explained in detail below (see Tables 2 and 3 for reference). Mixed depression and agitated depression are terms used for criteria defining mixed mood states predominantly characterized by depressive symptoms, whereas mixed hypo/mania and dysphoric hypo/mania are terms used for criteria defining mixed mood states predominantly characterized by hypo/manic symptoms. Few researchers examine mixed depression and mixed mania in the same investigation, as these are thought to be theoretically and epidemiologically separate constructs (e.g., Benazzi, 2001).

Table 2. Research criteria for mixed mania

Cassidy et al., 2000	**Akiskal et al., 1998**
mixed mania	**dysphoric mania**
elevated, expansive, or irritable mood	elevated, expansive, or irritable mood
plus 3 or more of following (4 if mood is irritable)	*plus 3 or more of following (4 if mood is irritable)*
inflated self-esteem or grandiosity	inflated self-esteem or grandiosity
decreased need for sleep	decreased need for sleep
more talkative than usual or pressure to keep talking	more talkative than usual or pressure to keep talking
flight of ideas or racing thoughts	flight of ideas or racing thoughts
distractibility (external stimuli)	distractibility (external stimuli)
increase in goal directed activity or psychomotor agitation	increase in goal directed activity or psychomotor agitation
risky behavior	risky behavior
plus 2or more of	*plus 2 or more of*
depressed mood	depressed mood
anxiety	diminished interest or pleasure
guilt	weight gain or increase in appetite
fatigue	hypersomnia
diminished interest or pleasure	psychomotor retardation
	fatigue
	worthlessness or guilt
	helplessness or hopelessness
	suicidality
Bauer et al., 1994	**McElroy et al., 1992**
mixed mania	**dysphoric mania**
elevated, expansive, or irritable mood	elevated, expansive, or irritable mood
plus 3 or more of following (4 if mood is irritable)	*plus 3 or more of following (4 if mood is irritable)*
inflated self-esteem or grandiosity	inflated self-esteem or grandiosity
decreased need for sleep	decreased need for sleep
more talkative than usual or pressure to keep talking	more talkative than usual or pressure to keep talking
flight of ideas or racing thoughts	flight of ideas or racing thoughts
distractibility (external stimuli)	distractibility (external stimuli)
increase in goal directed activity or psychomotor agitation	increase in goal directed activity or psychomotor agitation
risky behavior	risky behavior
*plus**2** or more of*	*plus**3** or more of*
depressed mood	depressed mood
diminshed interest	diminished interest or pleasure
weight loss	weight gain or increase in appetite
loss of interest in sex	hypersomnia
psychomotor retardation	psychomotor retardation
overpreoccupation with health	fatigue
guilt	worthlessness or guilt
anxiety (psychic)	helplessness or hopelessness
suicidality	suicidality
anxiety (somatic)	
gastrointestinal symptoms	
general somatic symtpoms	

Table 3. Research criteria for mixed depression

Research Diagnostic Criteria (Spitzer et al., 1975)	Benazzi, 2000
Agitated depression	**Mixed depression (DMX)**
five or more of following	*five or more of following*
*depressed mood	*depressed mood
*diminished interest or pleasure	*diminished interest or pleasure
weight loss or gain, or change in appetite	weight loss or gain, or change in appetite
insomnia or hypersomnia	insomnia or hypersomnia
psyhomotor agitation or retardation	psyhomotor agitation or retardation
fatigue or loss of energy	fatigue or loss of energy
feelings of worthlessness or excessive guilt	feelings of worthlessness or excessive guilt
diminished ability to think or concentrate, or indecisiveness	diminished ability to think, concentrate, or indecisiveness
suicidality	suicidality
plus 2 or more of	*plus 2-3 of*
psychomotor agitation	elevated, expansive, or irritable mood
psychic agitation or intense inner tension	inflated self-esteem or grandiosity
racing or crowded thoughts	decreased need for sleep
	more talkative than usual or pressure to keep talking
	flight of ideas or racing thoughts
	distractibility (external stimuli)
	increase in goal directed activity or psychomotor agitation
	risky behavior

* One of these two symptoms must be included

One study conducted by Swann and colleagues (1993) using symptom ratings of inpatients found that mixed mania appears to be more severe than “pure” mania or agitated depression. Mixed depression as defined by Benazzi (2000, 2008) is the presence of a major depressive episode with two to three co-occurring hypomanic or manic symptoms, lasting at least one week in duration. Benazzi (2008) has stated that these criteria best fit the clinical conceptualization of a predominantly depressive episode with co-occurring hypomanic symptoms. Furthermore, Benazzi published articles detailing why he chose these cutoffs (2001, 2008a). Similarly, Spitzer and colleagues described “agitated depression” as the presence of a major depressive episode, as well as two or more of the following: psychomotor agitation, psychic agitation or intense inner tension, and racing or crowded thoughts (Spitzer, Endicott, & Robins, 1975). Agitated depression is thought to be a specific type of major depressive episode. By definition, mixed depression (Benazzi, 2000) and agitated depression (Spitzer et al., 1975) are both characterized by more depressive than manic symptoms (see Table 3). Significantly, the manic symptoms required to meet criteria for an agitated depressive episode are much more specific, and therefore restrictive, than those required to meet criteria for Benazzi’s mixed depressive episode.

There are three widely used definitions in the literature that are thought to describe a manic episode with concurrent depressive features. McElroy, Hudson, Faedda and Swan (1992) published a thorough review of the mixed mania phenomenon, and suggested that “dysphoric mania” be defined as the presence of a manic episode and three or more symptoms of major depression. However, the authors noted that several DSM depressive symptoms overlap with mania, so the following were deemed ‘eligible’ depressive symptoms for dysphoric mania: depressed mood, diminished interest or pleasure in activities, weight gain or increase in appetite, hypersomnia, psychomotor retardation, fatigue or loss of energy, worthlessness or guilt, helplessness or hopelessness, and suicidality (see Table 2). The authors also suggested that dysphoric hypomania be defined as full criteria for DSM hypomania with three or more of these same depressive symptoms. In conducting a replication study for McElroy and colleagues' (1992) criteria, Akiskal and colleagues (1998) suggested that the criteria for mixed mania require two rather than three depressive symptoms, as they stated this better captured the concept and clinical picture of mixed mania.

To our knowledge, the only empirically derived criteria for mixed mania come from Cassidy and colleagues (1998; 2000; 2001). In the study that finalized the criteria (Cassidy et al., 2000), 237 patients with bipolar I disorder (BD I) currently in a manic episode were assessed for DSM mood episodes and symptoms. By using receiver operator curve (ROC) analyses, the authors found that many of the DSM depressive symptoms performed weakly in differentiating between manic and mixed episodes. The authors proposed that mixed mania be defined as a manic episode with at least two of the following symptoms in co-occurrence: depressed mood, anhedonia, guilt, suicidality, fatigue, and anxiety (Cassidy et al., 2000). Finally, Bauer, Whybrow, Gyulai, Gonnel and Yeh (1994) also suggested their own criteria for a mixed manic state. They stated that mixed mania should be defined as a full manic episode, plus two or more out of nine possible depressive symptoms (see Table 2).

Importantly, of the three aforementioned widely used definitions of mixed mania in the literature, neither McElroy and colleagues (1992), nor Bauer and colleagues (1994), nor Cassidy and colleagues (2000) stated any cutoffs for maximum amount of depressive symptoms during a manic episode. Whereas Cassidy and colleagues (2000) have an automatic limit of five depressive symptoms, as they restricted their possible number due to their factor analysis, McElroy and colleagues (1992) have a maximum of nine depressive symptoms, and for Bauer and colleagues (1994) it is possible to have nine depressive symptoms. In addition, the possible depressive symptoms for these three mixed manic criteria are very dissimilar (see Table 2 for comparison). These various criteria for mixed mania lend themselves to describing very different states (see Table 4), and it remains unclear whether these criteria are capturing the same type of mood episode.

Table 4. Differences between theoretical mixed manic episodes.

Cassidy mixed mania		**McElroy dysphoric mania**	
depressive	*manic*	*depressive*	*manic*
depressed mood	irritable mood	hypersomnia	elevated mood
anxiety	distractibility	anhedonia	talkativeness
	decreased need for sleep	suicidality	flight of ideas
	grandiosity	weight gain	risky behavior
		guilt	

Few studies have focused on whether there are clinical distinctions between mixed states with predominant manic versus depressed mood. Benazzi (2001) reported that a major depressive episode with three or more manic symptoms (rather than two) was the best predictor of a diagnosis of bipolar disorder II (BDII) rather than MDD, highlighting other findings that mixed depression is more common in bipolar than unipolar mood disorders (Benazzi & Akiskal, 2005). Swann and colleagues reported significant differences in the symptoms exhibited between “pure” mania, mixed mania, and agitated depressed patients (Swann et al., 1993). Furthermore, given the wide variety of possible symptom clusters, mixed depression and mixed mania are very nearly overlapping entirely. Theoretically, a dysphoric manic episode (McElroy et al., 1992) and a mixed depressive episode (Benazzi, 2008) could differ by only one manic symptom (see Table 5 for illustration). It is not clear if these two hypothetical episodes could or should be considered theoretically different in nature. However, McElroy and colleagues (1995) also pointed out that rather than examining mood states categorically (i.e., with cutoffs), it may be more meaningful to examine mood states dimensionally (i.e., mania with mild, moderate, or severe depressive symptoms). This has yet to be operationalized in the literature.

Table 5. Similarities between theoretical dysphoric mania and mixed depression

McElroy dysphoric mania		**Benazzi mixed depression**	
depressive	*manic*	*depressive*	*manic*
hypersomnia	elevated mood	hypersomnia	elevated mood
anhedonia	talkativeness	anhedonia	talkativeness
suicidality	flight of ideas	suicidality	flight of ideas
guilt	risky behavior	guilt	
weight gain		weight gain	

It is clear that in order for the field to progress towards a coherent definition of mixed states, research must be conducted examining differences in existing definitions, and making informed decisions as to which definition best operationalizes the experience being described. More research should be conducted on the symptom clusters that individuals with BSDs exhibit, and deriving clinical distinctions from those investigations. Most researchers can agree that mixed states are an impairing and significant part of BSDs, so being able to make more definitive distinctions will help further progress in finding effective treatments. Furthermore, having fewer definitions and more agreement about what these states are and how they present will allow for a more streamlined literature that clinicians can eventually use in assessment and treatment methods.

Factor Analyses of Mood Episodes

Investigation into which symptoms are occurring at what frequencies is also necessary to further this line of research on mixed states. Multiple research groups have performed factor analyses on samples in manic episodes. This research is important, as a variable-centered approach can examine more closely which symptoms commonly co-occur and can help us better understand the phenomenon (see Murphy & Beigel, 1974, for review). These investigations nearly always find classically dysphoric symptoms as separate factors within mania. The first factor analytic study was conducted by Murphy and Beigel (1974), using the clinician-administered Mania State Rating Scale (MSRS; Beigel, Murphy, & Bunney, 1971). They reported two factors arising from their sample of 31 manic patients: global mania (e.g., elation, grandiosity) and paranoid-destructive (including some depressive symptoms). Akiskal, Azorin, and Hantouche (2003) analyzed the symptom structure of the French inpatient sample presented above by Akiskal and colleagues (1998), also using the MSRS. They found seven orthogonal factors in a principal component analysis (PCA): disinhibition-instability, paranoia-hostility, deficit, grandiosity-psychosis, elation-euphoria, depression, and hypersexuality. Furthermore, after grouping individuals based on symptom presence, the authors reported that the pure mania group was significantly more likely to exhibit symptoms of deficit (e.g., distractibility, poor judgment, inappropriate dress), elation/euphoria, and hypersexuality. The dysphoric group (i.e., with two or more concurrent depressive symptoms) had significantly higher scores on items of depression. However, the groups did not differ with regard to symptoms of disinhibition, hostility, or psychosis, or overall severity of manic episode.

Other researchers have criticized the use of the MSRS, as it was validated many decades ago, and does not take into consideration anxiety and mood lability, which have been considered significant aspects of mania (e.g., Gupta, Sinha, Praharaj, & Gandotra, 2009). Cassidy, Murry, Forest, and Carroll (1998) created and validated a new measure entitled the Scale for Manic States (SMS). These researchers also conducted a PCA using this scale to assess symptomatology in 237 patients hospitalized for DSM-III-R manic or mixed episode (Cassidy et al., 1998). The authors reported that while adhering to DSM-III-R definitions, 86.1% of the patients met criteria for manic episode and only 13.9% met criteria for mixed episode. These authors reported five factors, the strongest (most variance accounted for) of which was dysphoria, characterized by depressed mood, lability, guilt, anxiety, suicidality, and a negative loading for euphoria. The other factors reported were psychomotor agitation, psychosis, increased hedonic function with euphoric mood, and irritable aggression. Surprisingly, the authors also conducted a separate PCA with just the DSM-III-R manic (not mixed) patients' symptoms, and found only minor changes in the loading of the aforementioned seven factors. This is a significant finding, showing that even in "pure" manic episodes, there is much more dysphoria than described in the DSM, at least among hospitalized individuals.

There is a wide variety of methodology in factor analytic studies in the literature on mixed mania. Swann and colleagues (2001) examined symptomatology in 162 patients hospitalized for manic episodes using the Schedule for Affective Disorders – Change version (SADS-C; Endicott & Spitzer, 1978) and the Affective Disorders Rating Scale (ADRS; Murphy et al., 1982) using PCA. The authors found six factors: impulsivity, hyperactivity, anxious pessimism, distressed appearance, hostility, and psychosis. Sato, Bottlender, Kleindienst, and Möller (2002) examined symptoms using another rating scale (Association for Methodology and Documentation in Psychiatry) in 576 consecutively admitted patients with DSM IV manic or mixed episodes. They performed a confirmatory PCA and found seven factors: depressive mood, irritable aggression, insomnia, depressive inhibition, pure manic symptoms, emotional lability/agitation, and psychosis. Even though these research groups used widely different measures to assess mood, negative or dysphoric factors are still omnipresent in the results.

Although factor analytic studies of patients in manic episodes have varied widely in their methodology, there are many findings that remained consistent across studies. Even when examining symptoms of “pure” mania (i.e., according to DSM or ICD), factors related to dysphoria have been obtained. In most studies, researchers found more than one negatively valenced factor of mania (e.g., Akiskal et al., 2003; Gupta et al., 2009; Swann et al., 2001; Cassidy, et al., 1998). Also of note, many of these factors have included symptoms of depressed mood, anxiety, and irritable aggression (e.g., Cassidy, et al., 1998; Gupta et al., 2009; Swann et al., 2001). Whereas the endorsed symptoms themselves may change in different samples and methodologies, this line of research has consistently shown that there is quite a wide variety of symptoms seen in manic episodes, often going beyond the DSM list of symptoms and including dysphoria in various forms.

Far fewer investigations have examined the factors present in hypomanic episodes. Hantouche, Angst, and Akiskal (2003) reported factor analytic results from a sample of bipolar II outpatients in France. Using two interviewer-rated scales, they reported that this sample had two factors, one characterized by drive and euphoria, and the other by irritability and risk-taking (Hantouche et al., 2003). Benazzi and Akiskal (2003) examined self-reported past hypomanic symptoms in a sample of depressed outpatients. The scale used was the Mood Disorder Questionnaire (MDQ; Hirschfield et al., 2000), which gathers yes or no answers for all DSM mood symptoms. Benazzi and

Akiskal (2003) reported two factors of hypomania: energized-activity and irritability-racing thoughts. The authors concluded that euphoria or elevated mood is not very indicative of hypomania, and dysphoria is common. In another study, Benazzi (2004) conducted a factor analysis on interviewer-assessed past hypomanic episodes in a sample of remitted bipolar II outpatients and found three factors: mental activation, also characterized by irritability, high mood, also characterized by talkativeness, and behavioral activation, also characterized by risky behavior. Benazzi (2004) reported that elevated mood was less relevant than outlined in the DSM, and overactivation may be more characteristic of hypomania. Much more investigation is needed into mixed hypomania, particularly from other research groups, but these studies highlight the finding that mixed symptoms are common in hypomania.

Few studies have examined the factors present in mixed depressive episodes. Several studies propose criteria to outline these mixed depressive episodes (e.g., Benazzi, 2003; Perugi, Akiskal, Micheli, Toni, & Madaro, 2001), yet the researchers have not employed factor analysis but rather *a priori* definitions according to long-standing theoretical views. To our knowledge, three studies were published regarding results of factor analysis on depressive mixed states. Benazzi and Akiskal (2005) examined mixed depression in individuals with bipolar II disorder and reported that there are two factors, which they deemed psychomotor agitation, also characterized by irritability and talkativeness, and mental agitation, which included racing thoughts, irritability, and distractibility. Unfortunately, this investigation did not include depressive symptoms in the factor analysis. Sato, Bottlender, Kleindienst, and Moller (2005) examined the factors present in a large sample of depressed inpatients. These authors extracted the following factors: vegetative symptoms, depressive retardation/loss of feeling, hypomanic syndrome, anxiety, psychosis, and depressive mood/hopelessness. They also reported that BSD diagnosis was associated with higher scores on depressive retardation and hypomanic symptoms, and lower scores on anxiety. However, those with unipolar diagnoses did exhibit some hypomanic symptoms in this sample, suggesting that mixed depression is a predictor of BSD, but does not exclusively occur in BSDs (Sato et al., 2005).

Hantouche and Akiskal (2005) reported factor analytic results detailing mixed depression from the same bipolar II sample employed by Hantouche and colleagues (2003), combined with samples of individuals with unipolar depression and bipolar I disorder. Depressive symptoms were rated by clinicians, and principal component analysis yielded nine factors: weight change, sleep disturbance, sadness-guilt, retardation-fatigue, somatic, diurnal variation, insight-delusion. When depressive symptoms were self-reported via visual analog scales, the principal component analysis yielded eight factors: psychomotor retardation, central pain, somatic, social contact, worry, loss of interest, guilt, and anger. The authors noted that although clinician and patient agreement was lowest in the bipolar II group, depression experienced by that group seemed to be characterized by psychomotor activation. Further research into the factors present in mixed depression is needed, as there are limitations on whether we can generalize these studies' results to other samples. Again, replication is needed from alternate research groups.

The strongest studies use experienced interviewers to gather symptom data, as self report measures of symptoms are inherently more subjective. These studies also should employ EFA, as it is the best way to assess the underlying factors of mood episodes as the assumptions are that responses are based on underlying factors, whereas PCA is data reduction that is specific to responses but not any underlying factors. CFA only should be used when a strong theory is being tested, and it is clear that more research is needed before a strong theory is developed.

All studies reviewed here analyzed data from one episode per person; because individuals do not exhibit the same symptoms during every episode (see Kessing, 2008), multilevel factor analysis should be considered. In this way, the between-level factor analysis would examine underlying factor structure of episodes in multiple episodes captured per person without confounding between- and within-level variance.

Diagnostic Considerations

BD I long has been considered the most “severe” bipolar spectrum disorder, possibly due to the criteria of at least one manic episode, which requires impairment (APA, 2000). However, recent research has highlighted the finding that those with “lesser” diagnoses (e.g., BD II and cyclothymia) experience a chronic course of the disorder and should not be forgotten or cast aside (e.g., Judd, Schettler, et al., 2003). The DSM criteria for BD II are history of at least one hypomanic episode and one major depressive episode. DSM criteria for cyclothymia are history of at least two years of numerous episodes of hypomania and subthreshold depression. Whereas bipolar not otherwise specified (BNOS) is often considered the least severe on the spectrum, as it is a catchall diagnosis, individuals with histories of only hypomanic episodes do meet criteria.

Diagnostic differences in the presence of mixed symptoms have varied across studies. Judd, Schettler, and colleagues (2003) prospectively followed a sample of BD I and BD II outpatients and reported that those with BD I had more weeks of mixed polarity (not necessarily episodes). Another report from the same sample found that BD I patients had more DSM mixed episodes (Judd, Akiskal, et al., 2003). Goldberg and colleagues (2009) reported on index episodes of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) project, and found that DSM mixed episodes were more common in those with BD II. Seretti and Olgiati (2005) reported on a large sample's retrospective symptom histories and found that those with BD I had higher levels of irritability in their past.

Few studies have examined the diagnostic differences seen in mixed mood episodes; further complicating our assessment, methodology and operationalization of episodes varies widely between studies. While following a sample of BSD patients for 20 years, Judd, Akiskal, and colleagues (2003) found that episodes with mixed hypomania and depressive symptoms were significantly more common in those with bipolar I disorder versus bipolar II disorder. However, the same sample showed that those with BD II spent three times longer in depressive episodes. Another analysis of this sample showed that those with BD II also spent significantly more time experiencing subthreshold depressive symptoms (Judd, Schettler, et al., 2003), whereas those with BD I experienced more subthreshold symptoms of cycling, mixed, and hypomania. From the research conducted with this spectrum sample, we can conclude that those with BD I experience more mixed episodes as well as subthreshold cycling, mixed, and hypomanic symptoms, whereas those with BD II experience significantly more depressive episodes and subthreshold depressive symptoms. Goldberg and colleagues (2009) conducted similar analyses in a sample from the STEP-BD project, using episode data reported at study baseline. Goldberg and colleagues (2009) reported that depressive episodes with subthreshold manic symptoms and/or mixed symptoms were recorded more often in those diagnosed with BD II rather than BD I. This contradicts the longitudinal findings of Judd, Schettler, and colleagues (2003).

Serretti and Olgiati (2005) reported on a sample of 158 patients with BD I and 122 patients with BD II, all hospitalized for mood episodes. The researchers conducted interviews to gather histories of manic symptoms across disorder course. They reported that compared to those with BD II, patients with BD I had higher instances of distractibility, psychomotor agitation, irritable mood, elevated self-esteem, and reckless activity. Of note, reckless activity in and of itself may be enough for a hypomanic episode to reach criteria for manic episode, as reckless activity may lead to impairment or hospitalization by its nature. However, the authors noted that those five symptoms performed very well in a discriminant analysis differentiating BD I and BD II. Only irritability reported here may lend itself to presence of mixed manic state, as this study did not seek to examine mixed states. Yet, this report would suggest that those with BD I may display more dysphoric manic symptoms.

Future research should continue to examine diagnostic differences in the presentation of symptoms and episodes, as Goldberg and colleagues (2009) reported evidence contradicting that of Judd, Schettler, and colleagues (2003) and Judd, Akiskal, and colleagues (2003). Seretti and Olgliati (2005) examined the phenomenon differently, and found that irritability during mania was one of a few symptoms that accurately discriminated BD I from BD II. Future research should examine all mood symptoms and concurrent anxiety in longitudinal paradigms, especially considering the evidence for increases in mixed episodes over illness course (e.g., Kessing, 2008).

Associated Demographic Characteristics

Many studies of dysphoric mania have shown that females with bipolar spectrum disorders are more likely to experience mixed mania or hypomania than males (e.g., Akiskal & Benazzi, 2005; Kessing, 2008; Akiskal et al., 1998; Suppes et al., 2005). However, the methodology and criteria employed vary between studies. In one study of 104 acutely manic inpatients, dysphoric mania (defined as DSM manic episode with two or more concurrent depressive symptoms) was significantly more likely to be experienced by females (Akiskal & Benazzi, 1998). However, Goldberg and colleagues (2009) reported from one time-point that males were more likely to have DSM mixed episodes. One group of researchers found that females are more likely to experience dysphoric hypomania depending on the criteria used (Bauer et al., 1994); these authors reported that females were more likely to have mixed episodes when defined by mania plus one depressed mood item or more than four depressive mood or somatic items. Indeed, definitions are extremely important. Hantouche and colleagues (2001) reported higher anxious and depressed symptoms in manic females than males. Akiskal and Benazzi (2005) examined dysphoric hypomania in an outpatient sample of bipolar II patients, defined as concurrent DSM hypomanic and major depressive episodes. Akiskal and Benazzi (2005) reported that compared to major depressive episodes, those with dysphoric hypomania were much more likely to be females. Another previously mentioned study (Kessing, 2008) found that mixed episodes (using ICD-10 criteria) increase in frequency over time for females, but remain stable in males. Furthermore, Kessing (2008) reported that the presence of mixed episode increased risk for future episodes, highlighting the point that more longitudinal studies are needed to examine this phenomenon.

Some research has suggested that age of onset predicts mixed states; this is particularly clear in the research on pediatric bipolar disorder, as irritability is a core feature (e.g., Geller, Tillman, Craney, & Bolhofner, 2004). However, others have reported that increased time since onset of disorder predicts mixed symptoms (e.g., Kessing, 2008). Unfortunately, many studies have not examined individuals with recent-onset BSDs, and few studies are prospective in nature, as many researchers collect retrospective episode and symptom data over illness course (e.g., Seretti & Olgiati, 2005; Benazzi, 2004; Benazzi & Akiskal, 2003). Future research should focus on individuals with a recent onset, as it is unclear whether mixed states occur early in course. Furthermore, definitions of mixed states vary across studies. The literature will not provide a clear picture of the demographic characteristics of mixed mood states until these definitional issues are addressed.

Clinical Implications

Suicidality

Risk for suicidal ideation and suicide attempts has been shown to be higher in bipolar disorders than any other mental disorder (Nock, Hwang, Sampson, & Kessler, 2010). Many studies have found that mixed states are associated with greater risk of suicidality (Goldberg, Wankmuller, & Sutherland, 2004; Strakowski, McElroy, Keck, & West, 1996; Maj, Pirozzi, Magliano, & Bartoli, 2003). These authors have theorized that since “pure” manic episodes are characterized by elation, these individuals are less likely to experience suicidality. Conversely, those with “pure” depressive episodes may not have the energy or capacity to follow through with suicidal plans. However, the mixing of depression and impulsivity is especially likely to lead to suicidality and suicide attempts (Swann et al., 2007). This fits with research in the larger field of suicidality, which has shown that individuals with mental disorders characterized by severe agitation and poor impulse control are most likely to make plans and/or attempt suicide (e.g., Nock et al., 2010).

One study of adolescents found that although there was no gender difference in prevalence of mixed hypo/mania, females with these mixed states were four times more likely to have a history of suicide attempts (Dilsaver, Benazzi, Rihmer, Akiskal, & Akiskal, 2005). This association was not found in males in the study. Although the exact findings differ between studies, it is clear that mixed states are associated with increased risk for suicidality.

Comorbid Alcohol Abuse/Dependence

Mixed states in BSDs long have been associated with alcohol use disorders (e.g., Himmelhoch et al., 1976; Keller et al., 1986). Some investigators have found that bipolar II disorder particularly is associated with both mixed episodes as well as alcohol use disorders (e.g., Akiskal, Akiskal, Lancrenon, & Hantouche, 2006). In unipolar depressed individuals, concurrent manic symptoms also have been shown to be associated with alcohol use disorders (Ducrey et al., 2003). Swann and colleagues (2007) examined symptoms of mixed depression in individuals with BSDs and found that even modest concurrent manic symptoms were associated with alcohol abuse.

Unfortunately, comorbid alcohol use disorders have been shown to aggravate the course of BSDs (see Salloum & Thase, 2000, for review), by shortening time to episode recurrence and maintaining subthreshold symptoms. Furthermore, alcohol use disorders have been shown to lead to high levels of irritability and anxiety due to intoxication as well as withdrawal (Salloum & Thase, 2000). For these reasons, several researchers have speculated whether alcohol abuse predates bipolar disorder onset (e.g., Keller et al., 1986; Himmelhoch, Mulla, Neil, Detre, & Kupfer, 1976).

Course and Correlates

The course of BSDs is usually complex. Without proper treatment, individuals with BSDs experience many mood episodes as well as subsyndromal mood symptoms throughout their lives (Kessler, Merikangas, & Wang, 2007). Furthermore, many studies have shown that there are global impairments that occur around illness onset and usually worsen over time (Johnson & Magaro, 1987; Merikangas et al., 2007). Generally, earlier age of onset has been shown to predict longer and more chronic course of disorder (Birmaher et al., 2006; Mick, Biederman, Faraone, Murray, & Wozniak, 2003). Increased levels of stressful life events and stress generation have been studied as indicators of impairment in BSDs (e.g., Molz et al., 2013).

Several studies have shown that mixed or dysphoric mania is associated with a poorer course of disorder. Akiskal and colleagues (1998) examined 104 manic inpatients and found that those with dysphoric mania (i.e., two or more depressive symptoms) had more psychotic features during episodes, higher rates of suicidal ideation, and more complex temperamental dysregulation outside of episodes as compared to those with a more “pure” manic episode. Similarly Goldberg (2009) reported on participants in the

STEP-BD project, and found that those with mixed depression had higher instances of suicide attempts, earlier illness onset, and higher subthreshold levels of irritable mood in the previous year than those with “pure” depressed episodes. However, Kassem and colleagues (2006) reported that a later age of onset was associated with an index mixed episode (mean age 21, versus 17 for depression and 20 for mania). Swann, Steinberg, Lijffit, and Moeller (2009) reported that both mixed mania and mixed depression were associated with early age of onset.

Although age of onset and poor course of illness are often both associated with mixed states, few prospective investigations have examined whether time since onset predicts mixed states. Research in pediatric bipolar disorder may suggest that early age of onset does predict mixed states, as irritability is a core feature (e.g., Geller et al., 2004). However, others have reported that longer time since onset of disorder predicts increasingly mixed symptoms (e.g., Kessing, 2008). Unfortunately, many studies have not examined individuals with recent-onset BSDs, and few studies are prospective in nature, as many researchers collect retrospective episode and symptom data over illness course (e.g., Seretti & Olgiati, 2005; Benazzi, 2004; Benazzi & Akiskal, 2003). Future research should focus on individuals with a recent onset, as it is unclear whether mixed states occur early in the course of bipolar disorders.

Another study examined BD II depressive episodes with and without irritability, assessed by Benazzi and Akiskal (2005), and found that those with irritable-hostile depression were significantly younger at illness onset, had a longer history of depressive mixed episodes, and higher rates of axis I comorbidity.

Delbello, Hanseman, Adler, Fleck, and Strakowski (2007) examined a first-onset adolescent inpatient sample and found that over half of the patients were admitted for a mixed, rather than manic, episode. Those with mixed episodes had significantly slower symptom and functional recovery than those with manic episodes. Furthermore, girls had significantly slower symptom recovery. Several studies have shown associations between early age of onset and mixed states, as well as poorer course of illness. It is unclear which association best explains poor course of illness. Clearly mixed states present a difficulty for clinicians and researchers.

Theories of Mixed States

Behavioral Approach System

One of the prevailing biopsychosocial theories of BSDs is the Behavioral Approach System (BAS) model. The BAS is a neurobiological system theorized to facilitate goal-seeking in response to incentives and cues for reward (see Alloy et al., 2012 for review). The BAS model of bipolar spectrum disorders holds that individuals with an overly sensitive BAS are more likely to experience elation and excessive goal-seeking in response to reward cues, as well as experience depressive withdrawal in response to cues of failure (Depue & Iacono, 1989). Bowins (2008) theorized that hypomania evolved as a defense mechanism, via the BAS. This evolutionary psychological theory holds that depression and the associated inhibition arise as a function of the Behavioral Inhibition System (BIS), a system theorized to respond to aversive cues in the environment, so the individual will move away from such stimuli. Bowins (2008) theorized that as human intelligence evolved, cognitions that activate BIS became amplified, resulting in more depressive inhibition, which is not adaptive. Given that depressive inhibition puts the individual in a low-fitness state, Bowins (2008) hypothesizes that hypomania evolved as a mechanism to override depression, to restore physical and mental activity to sustain or enhance levels of fitness. Therefore, Bowins (2008) theorized that overactivity is the core feature of hypomania, rather than elevated mood. Bowins (2008) also theorized that mixed states occur when hypomania is in the process of overriding depressive inhibition, which he states could occur during the entirety of the hypomanic episode. In this way, Bowins (2008) lays out an evolutionary psychological theory including the BAS that explains the occurrence of mixed states.

Other researchers discussing BAS models (see Carver, 2004; Fowles, 1988; Urosević, Abramson, Harmon-Jones, & Alloy, 2008; for review) have theorized that irritability could be explained by BAS overactivation, because anger has been found to be an approach-related emotion (Carver & Harmon-Jones, 2009; Eddie Harmon-Jones, Sigelman, Bohlig, & Harmon-Jones, 2003; Eddie Harmon-Jones & Sigelman, 2001). In this way, manic episodes characterized by irritability may be explained by the BAS model. Specifically, Fowles (1988) hypothesized that hypo/mania characterized by euphoria and/or overactivity could be explained by environmental cues of reward and goal-striving, whereas hypo/mania characterized by irritability could be explained by an obstructed reward, leading to frustration. Evidence for this theory includes the finding that people with BD and at risk for BD are more psychophysiologically reactive to thwarting of a goal (Eddie Harmon-Jones et al., 2002). However, to our knowledge, Bowins' (2008) evolutionary theory is the only one that specifically attempts to explain the co-occurrence of manic and depressive symptoms like anhedonia and depressed mood.

Temperament

Another psychological theory holds that temperament, or the innate aspects of personality, leads to BSDs (Akiskal, 1992). Akiskal wrote that temperament is present in individuals long before the illness manifests, and the sanguine-hyperthymic and irritable temperaments are both strongly associated with BSDs. Akiskal's theory (1992) does speak to the causes of mixed states, as he believes that the irritable temperament is more associated with "hot temper" and "dysphoric overactivity" in cyclothynmic disorder, whereas the sanguine-hyperthymic temperament is associated with the high energy and sleeplessness of hypomania. Akiskal and colleagues went on to provide evidence for this theory (1998, 2006), showing that those with mixed states and mood cycling are more likely to have irritable temperament.

More recently, Akiskal has broadened this theory of temperament to account for most mental illnesses (see Lara, Pinto, Akiskal, & Akiskal, 2006). Lara and colleagues (2006) propose that nearly all mental illnesses can be explained by evolutionary drives of fear (ranging from cautious, dependent, to pessimistic) and anger (ranging from attentive, goal-directed, to irritable). In this model, the authors explicitly state that mixed states can be explained by high levels of both fear (anxiety and agitation) and anger (irritability and goal-driven behavior). However, this model seems to be conceptually very similar to the BIS/BAS model of behavior and emotion (Carver & Scheier, 1999).

Integrative Theory

One possible integrative theory of BIS/BAS and temperament could help to explain a preponderance of mixed states. Whereas overactivation of the BAS could lead to irritable mania (Urosevic et al., 2008), perhaps this combination is more likely in individuals with high trait levels of anger or impulsivity. Since anger is an approach emotion (Eddie Harmon-Jones et al., 2003), and impulsivity and anger are considered to be closely linked to mania (Lara et al., 2006), I propose the following: if an individual with high BAS sensitivity and trait anger were to develop a bipolar spectrum disorder, it is plausible that rather than an illness course characterized by euphoric hypo/mania and psychomotor retarded depression, episodes could be fraught with activation and therefore mixed symptoms (i.e., irritable hypo/mania and agitated depression). Much research is needed to support this model of mixed symptom etiology, although different research groups have examined parts of this theory in the past (e.g., Akiskal et al., 2006; Alloy et al., 2012).

The Current Study

The current study sought to examine the nature of mixed mood states in individuals with bipolar spectrum disorders, the underlying factor structure of bipolar mood episodes, and whether trait level variables predicted mixed mood symptoms. Of note, most analyses performed towards this end have employed variable-centered approaches (e.g. regression, factor analysis, etc.), which focus on the relationship between variables across individuals. However, many researchers have suggested that focusing entirely on variable-centered approaches could lead to over-looking important details. For this reason, the current study also employed the person-centered approach of latent class analysis, which focuses the analysis on relationships among individuals after grouping them into categories due to similar characteristics. To our knowledge, no study to date has examined mixed mood states by first grouping individuals into latent classes.

The current study was conducted in a variety of ways employing two separate samples, so as to best test the hypotheses laid forth here. Analyses employed included multilevel exploratory factor analysis, latent class analysis, and linear regressions and tests for interactions. Specifically, it was hypothesized that the DSM-IV-TR definition of mixed state would be exceedingly rare in this sample, and that hypomania without concurrent depressive symptoms (and conversely, depression without concurrent hypomanic symptoms) would capture less than 40% of the respective samples of episodes. Furthermore, it was hypothesized that Benazzi and Akiskal's (2005) definition of dysphoric hypomania and Benazzi's definition of mixed depression (2008) would adequately capture the mixed symptomatology seen in this sample, and that these criteria would be more prevalent than Cassidy and colleagues' (2000) criteria for mixed mania and Spitzer and colleagues' (1975) criteria for RDC agitated depression, respectively.

Examination of underlying factors focused on mood episode data from individuals who were not generally treatment seeking. Previous research has established that mania is characterized by psychosis, irritable aggression, dysphoria, accelerated thought, hedonia, and hyperactivity (e.g., Gupta et al., 2009). Several studies examining factors of hypomania have shown results similar to overactivity and irritable risk taking (e.g., Hantouche et al., 2003). Several studies that examined symptoms in bipolar depression have yielded at least one hypomanic factor (e.g., Sato et al., 2005). A previous study combined manic and depressive episodes (Pacchiarotti et al., 2013) and found factors related to euphoria, "mixity," (suicidality, excitement, motor hyperactivity, and anxiety), inhibited depression, and psychosis. For this reason, it was hypothesized that the mood episodes in sample 2 would be characterized by overactivity, irritable risk taking, and inhibited depression.

Previous research has shown that female gender is associated with risk for experiencing mixed symptoms throughout the course of illness (see Akiskal & Benazzi, 2005). Research is inconsistent on whether bipolar I or II diagnosis is more associated with mixed states (see Goldberg et al., 2009, also Judd, Schettler, et al., 2003), although rapid cycling has been reliably associated with mixed states (e.g., Goldberg et al., 2004). Research on the behavioral activation system has shown that aggression and impulsive aggression are highly related to activation as well as irritability. For these reasons, it was hypothesized that females and individuals with high trait levels of aggression and impulsivity would have a higher risk of experiencing mixed mood symptoms. Latent class analysis was used to define groups based on these variables and test whether these groups differed in their levels of mixed mood symptoms. Sample 1 is comprised mostly of individuals with bipolar II, cyclothymia, or bipolar NOS, so there was not enough power to examine differences between bipolar I and II groups in mixed mood symptoms.

Previous research consistently has shown that mixed episodes are associated with suicidality and more chronic illness course. For this reason, it was hypothesized that history of mixed mood symptoms would be associated with increased history of suicidality and more chronic course of illness, operationalized by number of mood episodes experienced during follow-up.

CHAPTER 2

METHODS

Participants

Sample 1

Participants in sample 1 are adolescents, initially ages 14-19, who are participating in a larger, prospective longitudinal study of the risk factors for first onset of BSDs (Project TEAM). Detailed recruitment and selection procedures are described elsewhere (Alloy et al., 2012). Briefly, participants were selected based on a two-phase screening procedure. In Phase I, high school students (aged 14-18), as well as college students (aged 17-19), were screened on demographics and two self-report BAS sensitivity measures, the Behavioral Inhibition System/Behavioral Activation System Scales (BIS/BAS; Carver & White, 1994) and the Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSRQ; Torrubia, Avila, Molto, & Caseras, 2001). Students scoring in the highest 15^{th} percentile on both the BAS-Total score of the BIS/BAS Scales (high BAS-T score cutpoint $\geq$ 43) and the Sensitivity to Reward (SR) scale of the SPSRQ (high SR cutpoint $\geq$ 16) were categorized as High BAS (HBAS; see Alloy et al., 2012, for details on cutpoints). Participants were classified as Moderate BAS (MBAS) if they scored between the 40^{th} and 60^{th} percentiles on both the BAS-T (cutpoints $\geq$ 37 and $\leq$ 39) and SR (cutpoints $\geq$ 10.4 and $\leq$ 12.6) subscales. Of 9991 students screened at Phase I, 7.77% (n = 776) qualified for HBAS and 4.04% (n = 404) for MBAS status.

Given that the goal of the larger project was to predict first onset of BSDs (see Alloy et al., 2012), a moderate BAS group, rather than a low BAS group, was included as the comparison group for the at risk high BAS participants. Interpretation of differences in BSD onset rates between high vs. low BAS groups would be unclear, because such differences could be due to increased risk in the high BAS group or decreased risk in the low BAS group. Comparison of the HBAS group to the MBAS group resolves this ambiguity. In addition, the MBAS group is closer to the mean on the BAS sensitivity dimension and, thus, is more normative from a statistical perspective.

A subset of the HBAS and MBAS participants from Phase I was invited for Phase II screening. In Phase II, participants were administered the mood and psychosis disorder sections of an expanded Schedule for Affective Disorders and Schizophrenia – Lifetime (exp-SADS-L) diagnostic interview, the Altman Self-Rating Mania Scale (ASRM; Altman, Hedeker, Peterson, & Davis, 1997) to assess hypomanic/manic symptoms, and the Beck Depression Inventory (BDI; Beck, Steer, Ball, & Ranieri, 1996) to assess depressive symptoms. Diagnostic interviews were administered by clinical psychology postdoctoral fellows, Ph.D. and Masters students, and post-BA psychology research assistants, who were all blind to participants' BAS risk group status. At Phase II, written parental consent and adolescent assent were obtained for participants aged < 18, whereas participants ≥ 18 provided their own written consent.

Participants were excluded from the final sample if they met *DSM-IV-TR* (American Psychiatric Association, 2000) or Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) diagnoses for any bipolar spectrum disorder prior to the date of the Phase I screening, any lifetime psychotic disorder, or if they lacked fluency in written or spoken English. Of 443 participants interviewed in Phase II, 382 participants completed Time 1; 7 were excluded because they met criteria for a psychotic disorder, 5 were excluded due to poor fluency in English, and 12 were excluded from the main project due to onset of BSD prior to Phase I. These individuals with prior onset of BSDs were asked to participate as extras. After Time 1, participants were followed for up to four years, and were assessed in follow up visits about every 6 months. This sample varied in the amount of time they participated, with a range of 0 to 39 months of follow-up (*M* = 13.11, *SD* = 12.62).

The sample for the current study is composed of all participants (N = 72) who met criteria for a bipolar spectrum diagnosis, including those who experienced onset prior to Phase I of the larger study. See Table 6 for sample statistics. This sample consisted of 9.70% with DSM or RDC bipolar I disorder, 59.70% with bipolar II disorder (DSM or RDC), 27.80% with bipolar NOS (DSM or RDC, signifying a hypomanic but no depressive episode), and 2.80% with DSM or project-criteria cyclothymia.

Table 6. Demographic characteristics of sample 1

Variable	*N*	*M (SD)*	%
Female	52		72.22
Racial			
Caucasian	40		55.60
African-American	17		23.60
Asian-American	3		4.20
Native Hawaiian or Pacific Islander	1		1.40
Biracial or multiracial	8		10.12
Declined to respond	3		3.20
Ethnicity			
Hispanic or latino	10		13.90
Bipolar diagnosis			
Bipolar I disorder	7		9.70
Bipolar II disorder	43		59.70
Bipolar not otherwise specified	20		27.80
Cyclothymia	2		2.80
Age (years)	72	18.39 (1.52)	
Education (years)	72	12.71 (1.50)	

Sample 2

Participants in sample 2 are 18-24 year old undergraduates from Temple University who participated in a larger study named the Longitudinal Investigation of Bipolar Spectrum Disorders (LIBS Project). Approximately 6,000 students were recruited from Temple University via SONA systems, classroom, and flier advertisements for the first stage of screening. In order to recruit a normal control group as well as a group with BSD, the General Behavior Inventory (GBI; Depue, Krauss, Spoont, & Arbisi, 1989, see Measures for more detail) was used to identify potentially eligible participants. The GBI cutoffs recommended by Depue et al. (1989) were used; participants who scored ≥ 11 on the Depression scale as well as ≥ 13 on the Hypomanic-Biphasic scale of the GBI were placed in the high GBI group, whereas participants with lower scores on both scales were placed in the low GBI group. These participants were then invited back for a second stage of screening, in which they were interviewed with an expanded Schedule for Affective Disorders and Schizophrenia – Lifetime (exp-SADS-L; Alloy et al., 2008) diagnostic interview in order to establish diagnosis. Participants in the high GBI group who met criteria for *DSM-IV* disorders of Bipolar II, Bipolar NOS, or Cyclothymia with no lifetime history of a manic or mixed episode were invited to participate in the longitudinal part of the study as the BSD group, as the original intent of this study was to examine predictors of the development of Bipolar I disorder. Those in the low GBI group who did not meet criteria for any *DSM-IV* disorders, with the exception of a specific phobia, now or in the past, and who had no family history of BD also were invited to participate as part of a healthy control group. Based on these exclusion criteria, the final sample included 67 bipolar spectrum participants. For one individual, sex and race were not reported. See Table 7 for sample statistics.

Table 7. Demographic characteristics of sample 2

Variable	*N*	*M (SD)*	%
Female	26		38.80
Racial			
Caucasian	38		56.70
African-American	17		25.40
Asian-American	1		1.50
Native Hawaiian or Pacific Islander	3		4.50
Biracial or multiracial	7		10.40
Declined to respond	1		1.50
Ethnicity			
Hispanic or latino	10		13.90
Bipolar diagnosis			
Bipolar II disorder	44		65.70
Bipolar not otherwise specified	1		1.50
Cyclothymia	22		32.80
Age (years)	67	19.80 (1.82)	

Measures

Risk status

The General Behavior Inventory (GBI, Depue et al., 1989) is a 73-item, self-report scale, in which participants rate symptoms (with intensity and duration) on a 4-point scale (1=never, 4=very often). It was used in Stage I screening to help select the bipolar spectrum and healthy control groups in sample 2. The GBI was validated by findings of similar rates of mood disorders in a large sample as in the general population, high specificity between mood disorders, and high correlations with diagnostic interview ratings. The GBI has strong internal consistency (α = 0.90-0.96), retest reliability (r = 0.71-0.74), high specificity (0.99), and adequate sensitivity (0.78) for bipolar spectrum conditions (Depue et al., 1981; 1989).

The Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS, Carver & White, 1994) and Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSRQ, Torrubia et al., 2001) were used during Phase I screening to select the HBAS and MBAS groups in sample 1. The BIS/BAS Scales are a widely used, 20-item self-report measure that assesses individual differences in BIS and BAS sensitivities. The scale is comprised of three BAS subscales and one BIS subscale and all items are rated on 4-point Likert scales ranging from 1 = *strongly disagree* to 4 = *strongly agree*. A BAS-Total score also may be calculated as the sum of all BAS items and this score was used as part of the criteria for selecting the HBAS and MBAS groups. The BIS/BAS scales have demonstrated adequate internal consistency and retest reliability (Carver & White, 1994), as well as construct validity, exhibiting expected associations with affect and performance on reaction-time and learning tasks involving incentives (Harmon-Jones & Allen, 1997; Zinbarg & Mohlman, 1998). Internal consistencies of the BAS-Total and BIS scales in the Phase I screening sample were α's = .80 and .72, respectively.

The second measure of BAS sensitivity used in sample 1 was the SPSRQ (Torrubia et al., 2001). The SPSRQ has 48 dichotomous response items on two subscales, sensitivity to punishment (SP) and sensitivity to reward (SR), which are designed to assess BIS and BAS sensitivity, respectively. Both subscales have acceptable internal consistency (Torrubia et al., 2001). In Phase I, α's for the SR and SP scales were .76 and .84, respectively. Research also supports the construct validity of the SPSRQ (e.g., Alloy, Abramson, Urosevic, Bender, & Wagner, 2009; Torrubia et al., 2001). BAS-T and SR scores correlated .40 in the Phase I sample.

Diagnostic Interviews

The exp-SADS-L is an expansion of a diagnostic tool in the field, divided into current and past psychopathology, measuring symptoms at their most severe (Endicott & Spitzer, 1978). It was used with both samples. The original measure was validated by finding high correlations of diagnostic findings with the commonly used Research Diagnostic Criteria (RDC; Spitzer et al., 1978) and its reliability was also found to be high in re-tests with different interviewers. Expansions of the original SADS-L included: (a) additional probes to allow for *DSM–IV–TR* as well as RDC diagnoses; (b) more items and improvements in the probes in the depression, hypo/mania, and cyclothymia sections; (c) additional probes to assess the precise number of days and % of waking hours on each day that participants felt depressed or euphoric/irritable in the mood sections. The exp-SADS-L has demonstrated excellent inter-rater reliability in these samples, with $\kappa \geq 0.96$ for depression and $\kappa > .90$ for BSDs (Alloy et al., 2008).

The Expanded SADS-Change (SADS-C; Alloy et al., 2008) was employed at each follow-up in both samples 1 and 2; it is an interview during which participants are asked about intervening psychiatric symptoms and episodes. The SADS-C was revised from the SADS-Change originally published by Spitzer and Endicott (1978) and also allowed for *DSM-IV* diagnoses. Inter-rater reliability for the expanded SADS-C was good ($\kappa > .80$; Alloy et al., 2008). In SADS-C interviews, raters assessed the onset, offset, duration, and severity of any mood symptoms as well as episodes meeting criteria for a full range of mental illnesses since the last interview. It was expanded in the same ways as the exp-SADS-L. In addition, features of the Longitudinal Interval Follow-up Evaluation (LIFE-II; Shapiro & Keller, 1979) were added to the exp-SADS-C to systematically track the course of symptoms and episodes during follow-up, with the exp-SADS-C inquiring about the presence of each symptom of hypo/mania and depression on a daily basis. In sample 1, SADS-C interviewers were kept blind to participants' BAS risk group as well as previous BAS sensitivity and trait scores. Likewise, in sample 2, SADS-C interviewers were blind to participants' diagnostic group.

Trait Variables

Dispositional impulsivity was assessed at Time 1 in sample 1 using the Barratt Impulsiveness Scale - Version 11 (BIS-11; Patton, Stanford, & Barratt, 1995), a widely used self-report measure that assesses three factors of impulsivity: Attentional Impulsivity, Motor Impulsivity, and Nonplanning. The three factors are significantly inter-correlated, with *r*'s of .46 to .53. Internal consistency for the full scale is high in undergraduate samples (α = .82) as well as psychiatric inpatients (α = .83) and prison inmates (α = .80). Internal consistency of the overall BIS-11 in sample 1 was α = 79. The BIS-11 predicts risk-taking behaviors in high school and college students (Stanford, Greve, Boudreaux, Mathias, & Brumbelow, 1996) and has been validated in bipolar samples (e.g., Swann et al., 2001). In sample 1, the internal consistency was moderate to high for all three subscales as well as the total score (Attentional Impulsivity α = .66, Motor Impulsivity α = .67, Nonplanning α = .61, Total score α = .79). The three factors were significantly intercorrelated ($.313 \geq r \leq .422$, p's < .014).

Trait levels of aggression were measured at Time 1 in sample 1 with the Aggression Questionnaire (AQ; Buss & Perry, 1992), a self-report measure that assesses five aggression constructs, including Hostility, Physical and Verbal Aggression, Anger, and Indirect Aggression, the last of which was added more recently (Buss & Warren, 2000). The original four factors are significantly inter-correlated, with *r*'s of .25 to .48. Internal consistency for each factor is high ($.72 \geq \alpha \leq .85$), as is the total scale ($\alpha = .89$; Buss & Perry, 1992). Retest reliability over nine weeks produced *r*'s of .72 to .80 (Buss & Perry, 1992). Each of the four subscales is significantly correlated with other measures of similar traits, as well as with peer nominations of physical and verbal aggression (Buss & Perry, 1992). In sample 1, the internal consistency was good for all five subscales as well as the total score (Physical $\alpha = .88$, Verbal $\alpha = .76$, Anger $\alpha = .83$, Hostility $\alpha = .79$, Indirect $\alpha = .71$, Total score $\alpha = .89$). All subscales except Indirect were significantly correlated with each other ($.31 \geq r \leq .64$, *p*'s < .014).

The Balloon Analogue Risk Task (BART; Lejuez et al., 2002) is a computerized behavioral measure of risk taking behavior and was administered at Time 1 in sample 1. In the task, the participant is presented with a balloon and offered the chance to earn money by pumping up the balloon. Each click to pump causes the balloon to incrementally inflate and money is added to a counter until some threshold, at which point the balloon explodes. In this way, each pump confers greater reward but also greater risk. Participants are not informed about the balloons' breakpoints, allowing for testing both participants' initial responses to the task and changes in responding as they gain experience with the task contingencies. Test-retest reliability has been shown to be adequate ($r = .77$, see White, Lejuez, & de Wit, 2008). Within adolescent studies, BART score is related to self-reported risk-taking behaviors including substance use and delinquency behaviors (Aklin, Lejuez, Zvolensky, Kahler, & Gwadz, 2005). This procedure also has been employed in studies of BD patients to assess levels of risk-taking behavior (Holmes et al., 2009). The variable used in all analyses was BART adjusted pumps average (the average number of pumps per balloon adjusted for the balloons that exploded, in which the number of pumps is necessarily curtailed).

The Short Inventory of Problems (SIP, Blanchard, Morgenstern, Morgan, Labouvie, & Bux, 2003) is a shortened version of the Drinker Inventory of Consequences (Miller, Tonigan, & Longabaugh, 1995). It is a research scale with 15 items that measures self-report of impulse control, social responsibility, and physical, interpersonal, and intrapersonal consequences from alcohol use. The SIP was administered at Time 1 in sample 1 and at all follow-up assessments, and has been used in previous studies for brief assessment of alcohol use problems (see Stuart, Moore, Ramsey, & Kahler, 2003). Internal consistency in this sample was high (α = .94).

The Adolescent Alcohol and Drug Involvement Scale (AADIS; Moberg, 2000) is an inventory of self-reported substance use over the past thirty days. Scores below 30 reflect “little to no use,” whereas scores between 30 and 40 reflect “serious drug” involvement, and scores above 40 are likely to reflect diagnosable abuse disorders (Moberg & Hahn, 1991). This scale has shown acceptable internal consistency (α = .85) and correlation with clinical assessment (r = .75). The AADIS was administered at Time 1 in sample 1 and at all follow-up assessments. Internal consistency in this sample was good (α = .74).

Procedures

In sample 1, follow-up assessments were conducted approximately every 6 months. Trait level variables (demographics, AQ, BIS-11, BART) were assessed at baseline. Mood episodes were gathered from all follow-up SADS-C assessments. Substance use diagnoses, SIP, and AADIS were gathered from baseline and follow-up assessments. For purposes of these analyses, individuals were marked as positive for substance use diagnosis if they met criteria at any time. Highest levels of substance use (AADIS) and related problems (SIP) from any assessment were also included in analyses.

In sample 2, follow-up assessments were conducted approximately every 4 months. Demographics were assessed at baseline, and mood episodes were gathered from all follow-up SADS-C assessments.

Analysis

To test the first hypothesis regarding prevalence of different episode types according to definitions in the literature, each mood episode experienced by participants in sample 1 was assessed for the following criteria: *DSM-IV-TR* depression, hypomania, mixed, or mania (APA, 2000); RDC depression, hypomania, or mania; RDC agitated depression (Spitzer et al., 1975); Cassidy and colleagues' (2000) mixed mania; McElroy and colleagues' (1992) dysphoric mania and hypomania (1992); Benazzi's mixed depression (2000); Akiskal and Benazzi's (2005) dysphoric hypomania. Simple counts of these criteria types were conducted to examine the prevalence of each type in the sample, as has been reported by previous authors (e.g., Akiskal et al., 1998).

Factor analysis also was employed in the current study to assess the underlying factor structure of mood episodes in BSD individuals, as many researchers have hypothesized that episodes are not clearly delineated as simply depressive and hypo/manic. The hypothesis outlined above was that mood episodes in a non-treatment seeking sample would be characterized by overactivity, irritable risk taking, and inhibited depression. Factor analysis is a statistical technique that defines the underlying structure among variables. Factor analysis of clinical features can be used to identify clinically meaningful subtypes of illness. Exploratory factor analysis on all individual depressive, hypo/manic, and anxiety symptoms rated as present during a mood episode by the diagnostic interviewers was carried out to identify symptom factors in sample 2, as the individuals in this sample reported more mood episodes, partially because sample 1 is still in follow-up stage, whereas sample 2's follow-up was completed. To use as much of the available data as possible, multilevel factor analysis was employed with these data, such that multiple mood episodes can be included per person (for details, see Muthén, 1994). All episodes were examined in one factor analysis, which has been done quite recently to examine mixed symptoms (Pacchiarotti et al., 2013).

Multilevel factor analysis is often employed in sociological and educational research (Muthén, 1991). One example is examining achievement factors at the individual and class level (Härnqvist, Gustafsson, Muthén, & Nelson, 1994). These data allowed for examining the factor structure of symptoms within people, as well as symptoms across people. These data were analyzed in MPlus 7 in a two-level exploratory factory analysis (Muthén & Muthén, 2012), This was a two level model, wherein a covariance analysis was conducted both between and within levels. The analysis modeled non-independence of observations due to cluster sampling. In this study, the cluster is the individual, and there are a range of observations (mood symptoms within episodes) per individual. An exploratory factor analysis is specified for both the within and between parts of the model, and rotated solutions with standard errors are obtained as well. Oblique geomin rotation is employed, and the estimator is robust weighted least squares, using a diagonal weight matrix. This estimator is the default for multilevel exploratory factor analyses with categorical data. There are several fit tests to be considered when deciding between models in EFA. The chi-square is used to test the hypothesis that the model provides an explanation of relationships in the data, and significant chi-squares suggest that this is not supported (suggesting the model explains the data). However, large sample sizes often produce nonsignficant chi-square results even when models are misspecified or cannot account for all measurement error (Bentler & Bonett, 1980; Joreskog, 1981), so other fit indices are also used. RMSEA tests fit according to the degree of freedom of the model: values less than .08 suggest acceptable fit and values less than .05 suggest good fit (Brown & Cudeck, 1990). CFI is robust to sample size, and higher values suggest better fit, ranging from 0 to 1 (Bentler, 1990). Higher values of TLI also suggest good fit, with a range of 0 to 1 (Tucker & Lewis, 1973), although sometimes values fall outside this range (Bentler, 1990).

Examining a scree plot of eigenvalues is also recommended, as eigenvalues over 1 are considered acceptable, but large drops in variance explained are a reason to stay with a more parsimonious model. Finally, researchers are encouraged to consider theory when deciding between models, as well as the ability to explain the models to other researchers (Muthén & Muthén, 2012.

A series of latent class models was carried out to identify distinct subgroups of the hypothesized predictors of mixed symptoms in sample 1 (i.e., aggression, impulsivity, risk taking, substance use). See Figure 1 for a model of these analyses. Latent class analysis allows for examining observed patterns of responses within individuals, and then grouping heterogeneous groups of individuals into classes based on similarities on dimensions of interest, performance within dimension, or both (Muthén & Muthén, 2000; Nylund, Bellmore, Nishina, & Graham, 2007). Each latent class (e.g., a risk group categorized by high levels of aggression and substance use) describes the relations among the observed items (i.e., severity of aggression and substance use).

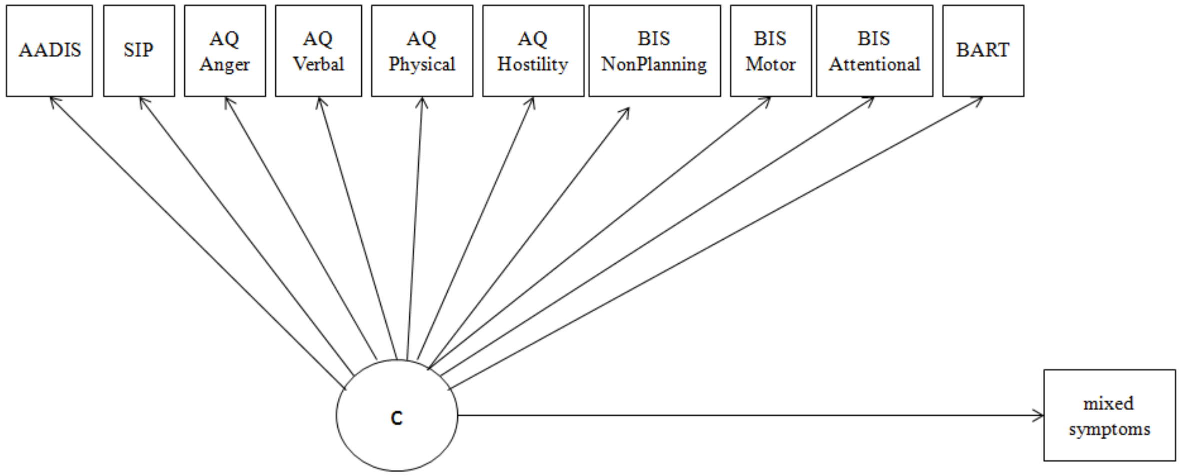

Figure 1. Model of latent class analysis

The purpose of LCA is to identify the best fitting model for the observed data based on statistical indices as well as conceptual and practical implications (Nylund et al., 2007), with the goal of finding the smallest number of classes that can sufficiently describe associations among the observed variables. First, an unconditional 1-class model is specified, which consists of the mean levels of the proposed risk factors. An increasing number of classes is then specified and compared to the previous model in an iterative process until the models no longer converge and/or no longer are conceptually meaningful. The fit of each model is examined using item probability parameters (i.e., likelihood of an individual in a given latent class endorsing an item) and class probability parameters (i.e., prevalence of each latent class in the population). Next, posterior class probabilities are examined to determine if the majority of participants in the sample are in a latent class that reflects their levels of severity of the proposed risk factors. Posterior class probabilities are based on item and class probabilities, and reflect a participant's probabilities of being in each latent class, based on their response pattern for the items. Each participant is assigned to membership in a latent class based on their highest posterior probability score (i.e., modal class assignment).

Selection from the set of models with different numbers of latent classes was conducted based on a variety of information criteria, including the Akaike Information Criterion (AIC; Akaike, 1987), Bayesian Information Criterion (BIC; Schwartz, 1978), and sample-size adjusted BIC (ABIC; Sclove, 1987). Lower values on these criteria suggest the model with the best fit and parsimony. The Bootstrap Likelihood Ratio Test (BLRT; McLachlan & Peel, 2000) and BIC indices are considered the most reliable indicators of model fit in LCA (Nylund et al., 2007). The BLRT estimates log likelihood differences, and compares the fit of a model with k classes to a model with k-1 classes to determine if model fit significantly improves with an additional class. In selecting the final model, consideration is given to how well a solution can be interpreted, whether the latent classes are distinct from the others, and whether the model fits with the theoretical background.

Following identification of classes, tests of equality of means across latent classes were conducted to determine whether classes differ in rates of mixed symptoms. In this model, mixed symptoms were operationalized as the highest number of symptoms from the opposite polarity during a mood episode; e.g., 0 signifying no opposite-polarity symptoms, 3 signifying 3 hypomanic symptoms in a depressive episode or the converse. The test of equality of means held class membership constant and provided chi-square statistics for omnibus and pairwise comparisons across latent classes. Pairwise comparisons were examined only if the omnibus tests are significant. This analysis employs bootstrapping, which allows for cases to be weighted by their class probabilities. Tests of equality of means were also be carried out for bipolar diagnosis, substance use diagnosis, and sex, to determine whether classes differ significantly on these variables as well. All analyses were conducted using MPlus 7.

Linear regressions were employed to test the hypothesis that mixed mood symptoms during episodes (depressive symptoms during hypomanic episodes or the converse) predicts suicidality and more chronic course in sample 1. Suicidality is a dichotomous variable (presence or absence of any suicidality in history), and the hypothesis was examined using logistic regression; the analysis examining chronicity employed linear regression, as chronicity was operationalized by number of mood episodes as well as total time spent in mood episodes, controlling for time in study follow-up.

CHAPTER 3

RESULTS

Preliminary analyses

Sample 1

All variables were assessed for violations of assumptions of normality. Nearly all variables were normally distributed. See Table 8 for descriptive statistics of all variables used in this sample. In this table, the mixed symptom data are taken from each individual's episode with the highest number of opposite polarity symptoms. SIP, BART, and mixed symptoms were found to be significantly positively skewed. SIP was submitted to a natural log transformation to satisfy assumptions of normality and to avoid non-convergence problems in the LCA. BART was submitted to a square root transformation. LCA models were run without sex, BAS risk, bipolar diagnosis, and substance use diagnosis variables, and these four variables were used in later analyses as auxiliary variables, to externally validate class membership derived from the LCA. Following identification of classes in the LCA, tests of equality of means across latent classes were conducted to determine whether classes differed in terms of these auxiliary variables.

Mixed symptoms, with an original range of 0 to 8, were recoded such that five or more symptoms were recoded to five symptoms, which reduced the issue of non-normality. For the purposes of linear regressions, an initial set of Pearson correlations were computed for sex and age, respectively, in relation to the mixed symptoms, the outcome of interest; as these were not significant, neither sex nor age was included as a covariate in subsequent analyses. All analyses were determined to be significant when $p < .05$.

Table 8. Descriptive statistics of sample 1

Variable	*M (SD)*	%
BAS risk		77.00
Aggression		
AQ Physical	24.83 (8.67)	
AQ Verbal	16.62 (4.35)	
AQ Anger	18.78 (6.28)	
AQ Hostility	22.87 (6.70	
AQ Total	82.29 (20.89)	
Impulsivity		
BIS Attentional	20.23 (4.01)	
BIS NonPlanning	22.48 (4.87)	
BIS Motor	26.35 (5.12)	
BIS Total	69.07 (10.78)	
Risk Taking		
BART	34.81 (11.61)	
Substance use		
AADIS total score	6.45 (5.99)	
SIP sum score	41.40 (12.28)	
Alcohol use diagnosis		34.00
Drug use diagnosis		25.00
Mood episodes		
Number of mood episodes	2.37 (3.07)	
Total time spent in episodes (in days)	54.98 (69.25)	
Mixed symptoms	1.27 (2.115)	
Any mixed symptoms		46.15
Any suicidality history		35.71
Time in study (in months)	13.11 (12.62)	

AQ = Aggression Questionnaire (Buss & Perry, 1992), BIS = Barratt Impulsiveness Scale-11 (Patton et al., 1995), BART = Balloon Analogue Risk Task (Lejuez et al., 2002), AADIS = Adolescent Alcohol and Drug Involvement Scale (Moberg, 200), SIP = Short Inventory of Problems (Blanchard et al., 2003).
Note: Mood episode data includes individuals with no mood episodes in follow-up, e.g. 0 days spent in episodes.

Sample 2

One individual in sample 2 declined to report sex and race. These values were imputed based on the sample means, and this individual was categorized as 39.4% male and of African-American race for later analyses. This sample consisted of 67 participants with bipolar spectrum disorders, followed prospectively for an average of 24.17 (*SD* = 23.43) months. These participants reported a range of 1 to 44 episodes per person (*M* = 5.25, *SD* = 6.90), for a total of 352 episodes. Interviewers using the expanded SADS-C gathered dimensional data on a total of fifty-five different mood-relevant symptoms, many of which overlap within diagnostic criteria (e.g., "increased productivity" and "increased interest in activities" are both inquired about in attempts to capture the same hypomanic symptom, which is increase in goal-directed activity). For this reason, all like symptoms were collapsed for analyses, and the highest endorsed level was used for this symptom item. For instance, a rating of "5" or "severe" on "increased productivity" would be used as the final rating for "goal-directed activity," although a rating of "2" or "subclinical" was given on "increased interest in activities." See Table 9 for intercorrelations of symptoms within mood episodes in sample 2.

Table 9. Intercorrelations between mood symptoms within episodes in sample 2

		1	2	3	4	5	6	7	8	9
1	depressed mood	-								
2	appetite decrease	.245**	-							
3	weight loss	.177**	.396**	-						
4	appetite increase	.178**	-.043	.011	-					
5	weight gain	-.040	-.148**	-.096	.477**	-				
6	early insomnia	.295**	.178**	.028	.043	-.001	-			
7	middle insomnia	.183**	.046	.014	.013	.032	.471**	-		
8	terminal insomnia	.162**	.119*	.208**	.053	-.010	.209**	.358**	-	
9	hypersomnia	.265**	.147**	.178**	.275**	.082	-.030	-.025	-.094	-
10	low energy	.358**	.007	.037	.336**	.054	.210**	.166**	.056	.315**
11	leaden paralysis	.235**	-.011	.036	.196**	-.020	.215**	.136**	.059	.121*
12	anhedonia	.327**	.136**	.171**	.265**	.086	.151**	.171**	.085	.354**
13	guilt	.239**	.089	.116*	.102	.012	.060	.076	.055	-.034
14	worthlessness	.324**	.161**	.210**	.144**	.005	.123*	.209**	.176**	.170**
15	trouble concentrating	.351**	.057	.176**	.137**	-.006	.214**	.184**	.078	.134*
16	slowed thinking	.223**	.124*	.204**	.306**	.028	.117*	.144**	.130*	.113*
17	suicidality	.079	.131*	.082	.074	-.061	.197**	.200**	-.013	.093
18	psychomotor agitation	.070	.135*	-.040	.031	.015	.173**	.148**	.032	-.086
19	psychomotor retardation	.247**	.187**	.100	.177**	.000	.242**	.221**	.159**	.227**
20	crying	.328**	.068	.216**	.117*	.032	.186**	.122*	.127*	.143**
21	wanting to cry	.114*	.031	.043	-.018	-.049	.142**	.107*	.172**	-.038
22	pessimistic, hopeless	.365**	.053	.076	.187**	-.017	.151**	.144**	.106*	.083
23	worry	.302**	.100	.085	.013	-.021	.170**	.178**	.145**	-.061

Table 9, continued

		10	11	12	13	14	15	16	17	18	19	20	21	22
11	leaden paralysis	.482**	-											
12	anhedonia	.331**	.132*	-										
13	guilt	.136*	.093	.267**	-									
14	worthlessness	.292**	.183**	.342**	.270**	-								
15	trouble concentrating	.375**	.319**	.320**	.229**	.206**	-							
16	slowed thinking	.418**	.251**	.207**	.269**	.224**	.420**	-						
17	suicidality	.198**	.196**	.266**	.324**	.440**	.238**	.216**	-					
18	psychomotor agitation	-.067	-.110*	.064	-.110*	.078	.025	-.021	.016	-				
19	psychomotor retardation	.483**	.289**	.234**	.086	.257**	.302**	.525**	.152**	.101	-			
20	crying	.246**	.217**	.309**	.165**	.143**	.356**	.219**	.166**	-.065	.224**	-		
21	wanting to cry	.021	.000	.044	.124*	.141**	.115*	.129*	.180**	.116*	.192**	.074	-	
22	pessimistic, hopeless	.312**	.166**	.354**	.350**	.516**	.399**	.390**	.401**	.052	.302**	.287**	.152**	-
23	worry	.149**	.068	.107*	.318**	.341**	.198**	.200**	.281**	.044	.113*	.115*	.220**	.445**

		1	2	3	4	5	6	7	8	9
24	low self esteem	.346**	.096	.172**	.153**	.011	.122*	.117*	.184**	.029
25	irritable	.088	.033	.007	.092	-.083	-.083	-.044	-.081	.031
26	need for reassurance	.250**	.213**	.124*	.016	-.054	.115*	.070	.029	.131*
27	self pity	.281**	.023	.060	.188**	.022	.103	.078	.153**	.030
28	somatic concern	.113*	.035	.070	.035	-.041	.123*	.219**	.038	.218**
29	less effective or productive	.347**	.117*	.070	.119*	-.064	.184**	.170**	.033	.254**
30	helpless	.290**	.049	.182**	.085	-.029	.170**	.189**	.134*	.062
31	passivity	.159**	.070	.069	.103	-.006	.190**	.128*	.045	.130*
32	negative thoughts	.036	-.028	-.060	.017	-.098	.018	.001	.094	-.092
33	euphoria elated hypomania	-.612**	-.005	-.071	-.126*	-.029	-.207**	-.175**	-.185**	-.173**
34	irritable hypomania	-.256**	-.073	-.059	.097	.004	-.156**	-.155**	-.113*	-.100
35	energy hypomania	-.561**	-.040	-.101	-.106*	-.051	-.216**	-.180**	-.181**	-.141**

Table 9, continued

		10	11	12	13	14	15	16	17	18	19	20	21	22	23
24	low self esteem	.260**	.220**	.325**	.349**	.558**	.236**	.292**	.318**	.112*	.286**	.205**	.194**	.588**	.397**
25	irritable	.158**	.104*	.078	.141**	.164**	.201**	.129*	.324**	-.005	.107*	.094	.196**	.284**	.118*
26	need for reassurance	.224**	.174**	.229**	.166**	.186**	.245**	.247**	.123*	.047	.156**	.280**	-.081	.184**	.112*
27	self pity	.268**	.177**	.190**	.220**	.386**	.227**	.299**	.286**	.104*	.302**	.209**	.277**	.463**	.320**
28	somatic concern	.104	.229**	.218**	.013	.144**	.050	.100	.084	.035	.033	-.047	-.071	-.042	-.053
29	less effective or productive	.335**	.246**	.393**	.124*	.246**	.420**	.382**	.186**	.056	.411**	.197**	.099	.374**	.220**
30	helpless	.253**	.161**	.241**	.260**	.375**	.291**	.355**	.207**	.007	.273**	.206**	.218**	.443**	.341**
31	passivity	.238**	.173**	.207**	.068	.287**	.139**	.312**	.216**	-.072	.208**	.191**	.096	.312**	.192**
32	negative thoughts	.026	.063	.109*	.249**	.218**	.104*	.170**	.241**	-.042	.092	-.004	.077	.271**	.140**
33	euphoria elated hypomania	-.216**	-.171**	-.223**	-.093	-.201**	-.313**	-.135*	-.082	.029	-.067	-.287**	-.108*	-.357**	-.270**
34	irritable hypomania	-.089	-.055	-.100	.135*	-.124*	-.063	.048	.096	-.126*	-.070	-.126*	-.009	-.088	.013
35	energy hypomania	-.241**	-.139**	-.165**	.041	-.185**	-.224**	-.108*	.062	.041	-.083	-.238**	-.047	-.283**	-.195**

		24	25	26	27	28	29	30	31	32	33	34
24	low self esteem	-										
25	irritable	.233**	-									
26	need for reassurance	.132*	.051	-								
27	self pity	.498**	.200**	.208**	-							
28	somatic concern	-.020	-.098	.192**	.095	-						
29	less effective or productive	.251**	.105*	.203**	.222**	.291**	-					
30	helpless	.358**	.138**	.267**	.446**	.156**	.357**	-				
31	passivity	.220**	.125*	.184**	.284**	.236**	.411**	.306**	-			
32	negative thoughts	.239**	.319**	.012	.215**	-.032	.070	.211**	.158**	-		
33	euphoria elated hypomania	-.292**	-.083	-.078	-.215**	.017	-.202**	-.204**	-.169**	-.044	-	
34	irritable hypomania	-.093	.231**	-.153**	-.152**	-.090	-.139**	-.182**	-.039	.200**	.239**	-
35	energy hypomania	-.202**	.038	-.187**	-.218**	-.016	-.224**	-.240**	-.141**	.078	.621**	.404**

Table 9, continued

		1	2	3	4	5	6	7	8	9
36	clarity hypomania	-.442**	-.041	-.145**	-.048	-.142**	-.231**	-.167**	-.079	-.225**
37	high energy	-.575**	.097	-.104*	-.126*	-.101	-.130*	-.193**	-.166**	-.146**
38	more active or involved	-.681**	-.141**	-.121*	-.146**	-.051	-.306**	-.148**	-.062	-.288**
39	unable to sit still, pacing	-.178**	.095	.008	-.018	-.061	.069	.008	.063	-.084
40	more talkative	-.502**	.084	-.078	-.099	-.018	-.077	-.102	-.150**	-.154**
41	racing thoughts	-.457**	.019	-.129*	-.034	-.134*	-.076	-.035	-.038	-.101
42	flight of ideas	-.044	.143**	-.088	.073	-.018	.154**	-.105*	-.020	-.049
43	increased self confidence	-.258**	.117*	-.062	-.027	-.032	.033	-.052	-.017	-.133*
44	decreased need for sleep	-.494**	.098	-.086	-.047	-.077	-.075	-.125*	-.133*	-.130*
45	trouble concentrating	-.136*	.123*	-.071	.036	-.051	.127*	-.047	-.019	-.061
46	increased concentration	-.494**	-.034	-.119*	-.122*	-.166**	-.255**	-.171**	-.104*	-.242**
47	risky behaviors	-.160**	.065	.096	-.051	-.080	-.002	-.032	-.012	.005

		10	11	12	13	14	15	16	17	18	19	20	21	22	23
36	clarity hypomania	-.250**	-.196**	-.231**	.066	-.155**	-.238**	-.078	.107*	-.118*	-.138**	-.242**	-.038	-.185**	-.075
37	high energy	-.234**	-.162**	-.175**	-.016	-.201**	-.271**	-.112*	-.033	.145**	-.057	-.291**	-.096	-.312**	-.266**
38	more active or involved	-.294**	-.250**	-.293**	-.112*	-.227**	-.301**	-.098	-.065	-.005	-.110*	-.280**	-.092	-.257**	-.151**
39	unable to sit still, pacing	.009	-.040	-.084	-.151**	-.016	-.060	.121*	-.081	.371**	.215**	-.007	.056	-.068	-.095
40	more talkative	-.162**	-.136*	-.168**	-.052	-.159**	-.231**	-.064	-.083	.196**	.024	-.237**	-.089	-.252**	-.209**
41	racing thoughts	-.072	-.067	-.093	-.046	-.052	-.178**	.010	.186**	.122*	.061	-.220**	.041	-.118*	-.130*
42	flight of ideas	.002	.034	-.042	.027	-.091	-.075	.011	.052	.069	.002	.030	.101	-.105*	.051
43	increased self confidence	-.047	.001	-.126*	-.126*	-.113*	-.114*	.027	-.088	.225**	.132*	-.066	.033	-.187**	-.100
44	decreased need for sleep	-.211**	-.153**	-.138**	.023	-.216**	-.203**	-.044	-.011	.042	-.120*	-.232**	-.127*	-.181**	-.231**
45	trouble concentrating	-.007	.002	-.079	-.111*	-.090	.032	.092	-.047	.202**	.090	-.016	-.055	-.042	-.159**
46	increased concentration	-.196**	-.165**	-.197**	.060	-.121*	-.262**	-.071	.120*	-.075	-.045	-.216**	-.007	-.186**	-.122*
47	risky behaviors	-.057	.006	-.108*	.073	-.022	-.055	-.021	.086	-.069	-.091	-.080	.108*	-.044	.120*

Table 9, continued

		24	25	26	27	28	29	30	31	32	33	34
36	clarity hypomania	-.146**	.140**	-.309**	-.194**	-.137**	-.267**	-.202**	-.126*	.185**	.376**	.461**
37	high energy	-.238**	-.039	-.020	-.254**	.039	-.240**	-.207**	-.161**	.026	.723**	.297**
38	more active or involved	-.206**	.030	-.275**	-.271**	-.191**	-.332**	-.186**	-.164**	.129*	.559**	.362**
39	unable to sit still, pacing	-.012	-.087	.183**	.055	-.072	-.037	-.064	-.080	-.134*	.198**	.009
40	more talkative	-.217**	-.067	.016	-.173**	.006	-.146**	-.175**	-.164**	-.038	.754**	.245**
41	racing thoughts	-.055	.119*	-.109*	-.124*	-.042	-.133*	-.155**	-.032	.248**	.387**	.291**
42	flight of ideas	-.052	-.134*	.063	.101	-.066	-.088	-.109*	-.106*	-.157**	.073	-.001
43	increased self confidence	-.077	-.158**	.038	-.020	-.077	-.131*	-.167**	-.044	-.201**	.464**	.161**
44	decreased need for sleep	-.168**	-.001	-.036	-.208**	.013	-.204**	-.151**	-.121*	.084	.434**	.278**
45	trouble concentrating	-.075	-.072	.235**	-.026	-.078	-.081	-.090	-.121*	-.102	.180**	-.020
46	increased concentration	-.106*	.250**	-.238**	-.161**	-.101	-.226**	-.162**	-.113*	.286**	.494**	.438**
47	risky behaviors	-.020	-.065	-.059	.054	.058	-.064	.006	.070	-.127*	.143**	.143**

		35	36	37	38	39	40	41	42	43	44	45	46
36	clarity hypomania	.559**	-										
37	high energy	.778**	.451**	-									
38	more active or involved	.639**	.601**	.596**	-								
39	unable to sit still, pacing	.202**	-.005	.373**	.203**	-							
40	more talkative	.620**	.279**	.754**	.522**	.429**	-						
41	racing thoughts	.497**	.519**	.523**	.457**	.381**	.457**	-					
42	flight of ideas	.162**	.166**	.224**	-.013	.306**	.189**	.241**	-				
43	increased self confidence	.272**	.227**	.455**	.284**	.470**	.503**	.313**	.340**	-			
44	decreased need for sleep	.541**	.386**	.649**	.444**	.233**	.420**	.366**	.096	.167**	-		
45	trouble concentrating	.034	-.082	.283**	.001	.568**	.333**	.299**	.297**	.367**	.241**	-	
46	increased concentration	.582**	.790**	.559**	.646**	.048	.406**	.489**	.112*	.245**	.450**	-.097	-
47	risky behaviors	.255**	.177**	.179**	.170**	.027	.141**	.056	.348**	.219**	.225**	-.042	.123*

*** $p < .001$, ** $p < .01$, * $p < .05$

After collapsing like items, the number of symptoms was 30, which was too high for factor analysis, as general guidelines for factor analysis conducted on one level requires ten subjects per variable (MacCallum, Widaman, Zhang, &

Hong, 1999), and our sample size required 35 or fewer items if this were to be examined on one level. To our knowledge, there is no item to sample size rule or cutoff for two-level factor analysis, yet it was decided that fewer symptoms would be better for this analysis, and would be a more conservative choice to maintain a moderate level of power. One item (somatic concern) was removed from analyses due to a very low base rate and likelihood of skewing results unnecessarily. Items assessing severity and intent of suicide attempts were also removed, leaving only severity of suicidality itself. A correlation matrix was produced examining all intercorrelations of symptoms, and symptom correlations of r = .300 or higher also were collapsed in an effort to reduce items, as well as reduce multicollinearity. For analysis, there were 16 symptom items, see Table 10 for descriptions.

Table 10. Final items used in factor analysis

Final symptom termed	: Comprised of these original items probed during interview				
Sadness	: Depressed mood	Crying	Wanting to cry		
Weight change	: Appetite change	Weight change			
Sleep disturbance	: Insomnia	Hypersomnia			
Fatigue	: Low energy	Leaden paralysis	Psychomotor retardation		
Anhedonia	: Anhedonia				
Guilt and worthlessness	: Guilt	Worthlessness	Pessimistic/hopeless	Low self esteem	Helpless
Difficulty concentrating	: Trouble concentrating	Slowed thinking	Less effective/productive	Passivity	Negative thoughts
Suicidality	: Suicidality				
Worry	: Worry				
Irritability	: Depressive irritability	Hypomanic irritability			
Self pity	: Self pity	Need for reassurance			
Euphoria/grandiosity	: Euphoria/grandiosity				
Agitation	: Psychomotor agitation	More active or involved	Increased energy	Pacing/unable to sit still	
Clarity of thought	: Mental clarity	Increased concentration			
Racing thoughts	: More talkative	Racing thoughts	Flight of ideas		
Risky behavior	: Risky behavior				

Main Analyses in Sample 1

Criteria

The first goal was to examine research definitions of mixed states in sample 1. There were 42 participants who exhibited a mood episode after Time 1, and these data were collected at prospective assessments, as described above. These 42 participants reported a total of 54 depressive and 71 hypomanic episodes, including one episode that met full depressive and hypomanic criteria simultaneously. Individuals' counts of mood episodes ranged from 1 episode to 18 episodes per person. The severity of mood episodes also ranged widely. Depressive episode counts are listed here, in descending order of severity: 10 RDC major depressive definite, 7 DSM major depressive, 16 subthreshold DSM major depressive, 6 RDC minor depressive definite, and 15 RDC minor depressive probable episodes. There were no manic episodes reported in this sample, and hypomanic episode counts are listed in descending order of severity: 22 DSM hypomanic, 7 RDC hypomanic definite, 22 RDC hypomanic probable, 19 project hypomanic, and 1 subthreshold hypomanic episode.

Given the absence of manic episodes in this sample, many of the mixed manic criteria were impossible to meet at a stringent level of consideration. However, hypomanic episodes with impairment either due to hypomania or depression were considered acceptable for these criteria sets. Even with this allowance, no episodes met Cassidy and colleagues' (2000) mixed manic criteria out of a total 124 mood episodes. Seven episodes met loosened criteria for Akiskal and colleagues (1998) dysphoric mania (9.86% of hypomanic episodes), one episode met loosened criteria for McElroy and colleagues' (1992) dysphoric mania (1.41%), and three episodes met loosened criteria for Bauer and colleagues (1994) mixed mania (4.23%). Three episodes met criteria for RDC agitated depression (Spitzer et al., 1975; 5.66% of depressive episodes). Three episodes met criteria for Benazzi's (2000) mixed depression (5.66%). The Benazzi (2000) criteria state that there can be no more than 4 hypomanic symptoms present, so we widened this criterion to have no limit, yet we did not observe any additional episodes (5.66%). No episodes met criteria for Akiskal and Benazzi's (2003) dysphoric hypomania.

The low base rates of meeting mixed criteria were surprising. We analyzed each mood episode to determine whether it was "pure," that is, characterized by only depressive or only hypomanic symptoms, as well as the amount of mixing present, or the total number of symptoms of the opposite polarity present. Of the total 124 mood episodes, 78 (62.90%) were "pure" depression or hypomania, with 37 pure depressive (69.81% of all depressive episodes) and 41 pure hypomanic (57.75% of all hypomanic episodes). Forty-six episodes (37.10%) had some level of mixed symptoms, with a range of 1 to 8 symptoms of the opposite polarity. Of these episodes with a range of 1 to 8 mixed symptoms (in some cases, multiple per person), there was an average of 2.59 symptoms of opposite polarity present (*SD* = 2.00).

Of the aforementioned mixed criteria counts, there were only 13 discrete episodes that met mixed criteria of some kind, as some but not all episodes met multiple criteria, e.g., one episode met criteria for Akiskal and colleagues' (1998), Bauer and colleagues' (1994), and for McElroy and colleagues' (1992) mixed mania, whereas another episode only met criteria for agitated depression (Spitzer et al., 1975), and another only met criteria for Akiskal and colleagues' (1998) dysphoric mania. This suggests that mixed symptoms are more common than originally expected, and yet there are few criteria in the literature that capture this phenomenon, as 33 episodes had some level of mixed symptoms that were not captured by available criteria.

Latent Class Analysis

For purposes of the latent class analysis, transformed versions of mixed symptoms variables were used. All other variables were kept in their original distributions, but a constant was subtracted from each variable for all variables to have a true zero. For this reason, all Aggression Questionnaire (AQ) and Barratt Impulsiveness (BIS) subscales, as well as the Short Inventory of Problems (SIP) total score, were transformed so that the minimum values on each scale became zero values. The following amounts were subtracted from these variables: 9 subtracted from AQ physical, 6 subtracted from AQ Verbal, 7 subtracted from AQ Anger, 10 subtracted from AQ Hostility, 10 from AQ Indirect, 12 from BIS NonPlanning impulsivity, 15 from BIS Motor impulsivity, 11 from BIS Attentional impulsivity, and 30 from SIP.

Latent class analysis is conducted in many steps, starting with fitting a one-class model to the data. Additional classes are added only if fit indices allow. Specifically, models are examined to determine whether the addition of another class is substantively and clinically meaningful and consistent with previous research and the researchers' conceptual model. In selecting the final model, the smallest class size is also considered, as classes composed of less than 5-10% of the total sample suggest overfitting of the data and that the classes may be difficult to replicate. Monte Carlo simulation studies using a variety of sample sizes suggest that the BIC and BLRT are the most robust indicators of classes. If the study were underpowered to perform these analyses or a one-class model provided the best fit to the data (suggesting that a person-centered approach is not necessary), fit statistics would converge to suggest that the one-class (unconditional) model should be selected (Iampietro, Giovannetti, Drabick, & Kessler, 2012).

LCA models were conducted with the scores of the variables of interest that are theorized to affect mixed episodes. Original values of BART were found to cause a non-positive definite matrix, so this variable was transformed with a square root transformation and submitted to another analysis. The transformed variable continued to cause convergence problems, so it was removed from all further analyses. Although SIP scores were skewed, the original values did not cause model identification problems, so the transformed values were not used in analyses.

The one-class model was fit first, followed by models with two and three classes. Examination of Table 11 indicates that the lowest BIC, AIC, and ABIC were found for the three-class model; moreover, the BLRT indicated that the three-class model provided an improvement in fit from the two-class model. The four-class model would not converge owing to a non-positive definite matrix (i.e., potentially extreme scores). The three-class model did not have inappropriately small class sizes (n = 35, 17, 18).

Table 11. Fit indices for latent class analysis models with 1-3 classes

Number of classes	Number of free parameters	Log likelihood	AIC	BIC	ABIC	BLRT
1	21	-1933.19	3908.39	3955.90	3889.75	N/A
2	33	-1900.27	3866.54	3941.21	3837.25	0
3	45	-1874.12	3838.24[a]	3940.06[a]	3798.30[a]	0

AIC = Akaike information criterion; BIC = Bayesian information criterion; ABIC = adjusted BIC; BLRT = Bootstrap Likelihood Ratio Test. A four-class model would not converge with the data and is consequently not reported.

[a]Indicates best fitting model according to that index.

Time in study varied greatly (M_{months} = 13.11, SD = 8.5) within this sample, and attrition could theoretically be related to scores on aggression, impulsivity, and substance use variables. To test whether time in study significantly affected these analyses, I re-ran all LCA models including time in study. This did not change the number of latent classes in the best fitting model, or the distribution of individuals within those classes, so time was later removed from all analyses.

Conceptual considerations were used to characterize the three-class model. Mean raw scores and standard errors for the variables across the three classes are presented in Table 12 (see Figure 2 for plot). Class 1 (low impulsivity, n = 35) was characterized by low substance use and impulsivity. Individuals in Class 1 obtained the lowest scores on substance use and problems related to substance use, as well as all impulsivity subscales. Individuals in Class 2 (substance problems, *n* = 17) obtained the lowest scores on aggression subscales, and highest values on substance use and problems related to substance use. Class 3 (aggressive, *n* = 18) was characterized by highest values on aggression subscales, and slightly lower scores on substance use problems than Class 2.

Table 12: Values of variables in 3-class model

	Latent class 1 *M (SD)*	Latent class 2 *M (SD)*	Latent class 3 *M (SD)*
AADIS	3.69 (3.94)	8.69 (9.08)	7.96 (5.94)
AQ Physical	15.60 (9.60)	9.76 (9.60)	21.23 (7.38)
AQ Verbal	10.12 (4.04)	6.35 (4.07)	14.73 (2.81)
AQ Anger	11.43 (4.92)	4.56 (4.38)	19.05 (2.56)
AQ Hostility	12.74 (9.36)	8.52 (13.02)	17.33 (4.40)
AQ Restraint	14.82 (8.51)	14.681 (5.34)	14.68 (5.29)
BIS NonPlanning	8.40 (8.95)	12.72 (4.96)	10.63 (4.45)
BIS Motor	8.42 (7.41)	13.30 (5.87)	13.23 (3.98)
BIS Attentional	6.57 (6.04)	10.31 (3.47)	11.47 (2.64)
SIP	5.00 (9.25)	17.17 (16.34)	13.17 (14.84)
Suicidality	1.10 (6.53)	0.42 (2.84)	0.09 (2.49)

AADIS = Adolescent Alcohol and Drug Involvement Scale (Moberg, 200), AQ = Aggression Questionnaire (Buss & Perry, 1992), BIS = Barratt Impulsiveness Scale-11 (Patton et al., 1995), SIP = Short Inventory of Problems (Blanchard et al., 2003), Suicidality data taken from diagnostic interviews at baseline and follow-up.

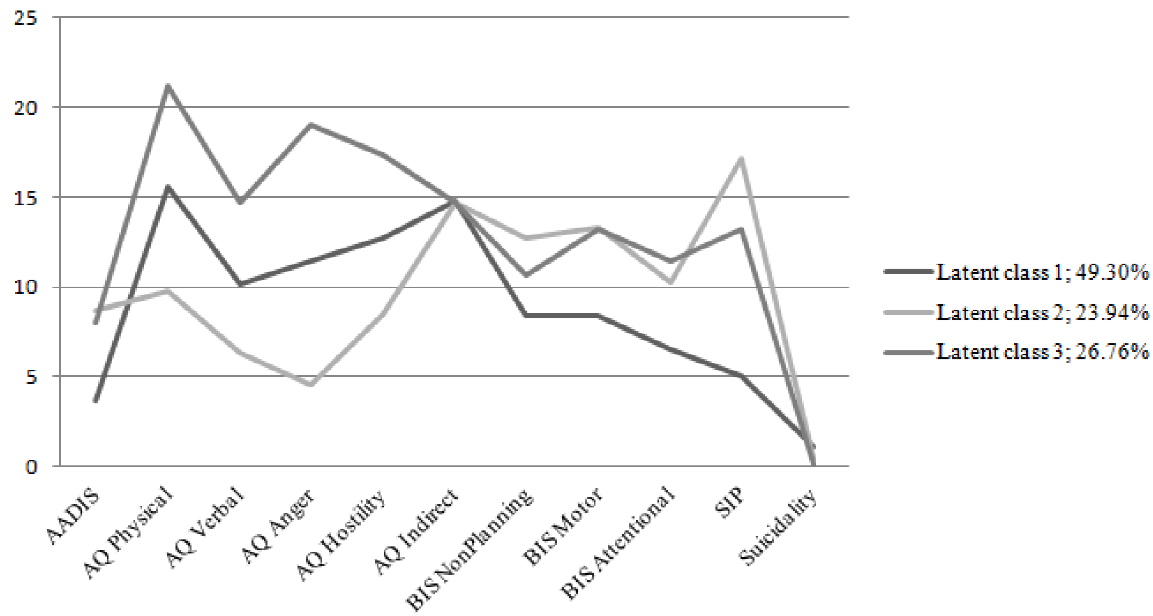

Figure 2. Plot of latent class means

Tests of equality of means were conducted to determine whether classes differed significantly by sex, bipolar diagnosis, substance use diagnosis, and BAS risk status. Substance use and sex were significantly different between classes. We found that substance use diagnosis was significantly more likely in Class 2 (77.78% of individuals) than Class 1 (25.00% of individuals; χ^2 = 1.94, p = .021) and marginally significantly more likely in Class 2 than Class 3 (38.89% of individuals; χ^2= 1.394, p = .095). This supports our class distinctions, as problems related to substance use and amount of substance use were highest in Class 2. Male sex was significantly more likely in Class 1 (34.29% of individuals) than Class 3 (11.11% of individuals; χ^2 = 1.749, p = .044).

Tests of equality of means were also conducted to determine whether classes differed significantly by the continuous variable of mixed symptoms in mood episodes (highest level per person) returned non-significant results. However, we transformed this variable to become dichotomous (53.8% had some level of mixed symptoms, 46.2% had no mixed symptoms) and ran this analysis again. With this variable, we found that Class 2 (62.50% of individuals) was significantly more likely to experience any mixed symptoms than Class 1 (29.17% of individuals; χ^2= 1.515, p = .049), and Class 3 (58.33% of individuals) was marginally significantly more likely to experience any mixed symptoms than Class 1 (χ^2= 1.472, p = .086).

Linear Regressions

As noted previously, the distribution of mixed symptoms in episode was skewed, so the recoded version of this variable (i.e., all values higher than 5 recoded as 5) was used in these analyses as well. All linear regressions were conducted using SPSS version 22.

Female sex marginally predicted mixed symptoms, $\beta = 0.22$, $p = .067$, as did suicidality history, $\beta =.28$, $p = .076$. Individuals with a substance use diagnosis were significantly more likely to report higher levels of mixed symptoms, $\beta = 0.26$, $p =.039$. Furthermore, controlling for time in study follow-up, the number of episodes during follow-up predicted mixed symptoms ($\beta = 0.57$, $p <.001$), see Table 13. Total number of days spent in mood episodes also predicted mixed symptoms, $\beta = 0.56$, $p <.001$, while controlling for time in study follow-up.

Using Hayes and Matthes' (2009) Modprobe script for SPSS to test for interactions, which also tests for simple slopes, I also found a significant interaction between number of episodes in follow-up and substance diagnosis (see Table 13). While controlling for time in study, there was a negative interaction between episodes and substance diagnosis. A test of simple slopes showed that for individuals with no substance use diagnosis, number of episodes significantly predicted mixed symptoms, B = .60, $p < .001$, yet there was no significant effect of number of episodes for individuals with a substance use diagnosis. Given issues of non-normality in the number of mood episodes, as this variable was positively skewed, I ran another regression after transforming the variable with natural log transformation. The results of model 4 and 5 (see Table 13) were the same, but for purposes of ease of understanding, the results using the original variables are reported here.

Table 13: Regressions predicting to mixed symptoms

	B	β	*t*	*p*	R^2
Model 1					
Male sex	-1.06	-0.22	-1.86	.067	
Model 2					
Suicidality history	0.93	0.28	1.83	.076	
Model 3					
Substance use diagnosis	1.08	0.26	2.11	.039	
Model 4					
Step 1					
Time in study	-0.03	-0.25	-2.07	.044	
Step 2					
Number of episodes	0.29	0.57	4.73	<.001	Δ 0.31
Model 5					
Step 1					
Time in study	-0.03	-0.19	-1.58	.121	
Step 2					
Duration of episodes	0.01	0.56	4.77	<.001	Δ 0.31
Model 6					
Step 1					
Time in study	-0.05			.096	
Number of episodes	0.60			<.001	
Substance diagnosis	2.49			.005	
Step 2					
Number of episodes X substance diagnosis	-0.47			.025	Δ 0.10

Note: Time in study measured in months. Duration of episodes measured in days.

Main Analyses in Sample 2

Other studies have found more than three factors (e.g. Pacchiarotti et al., 2013), so we allowed for up to five factors on the within and between levels. All models that yielded factors on the within level had significant Chi square tests, so all models considered had unrestricted covariance on the within level, and therefore, the analysis and factor results were focused on the between level, which allows us to use the multiple mood episodes per person, but ultimately examine the factor structure that exists between individuals (Muthén, personal communication, March 17, 2014).

Results showed four models that fit the data well: unrestricted within covariance and 1 factor between, unrestricted within covariance and 2 factors between, unrestricted within covariance and 3 factors between, and unrestricted within covariance and 4 factors between. Tests of fit for multilevel exploratory factor analysis include the chi-square test of model fit, root mean square estimation approximation (RMSEA), comparative fit index (CFI), and Tucker Lewis Index (TLI).

The first model with good fit, unrestricted within covariance and one between factor, had a nonsignificant chi square (χ^2 = 118.53, p = .156), RMSEA of 0.020 (95% confidence interval [0.000, 0.035]), CFI = 0.981, and TLI = 0.956. This one factor that accounted for all mood episodes in the sample was characterized by: negative loading of sadness, negative loading of sleep disturbance, negative loading of anhedonia, and positive loadings of euphoria, energy, clarity, racing thoughts, and risky behaviors. The second model with good fit, unrestricted within covariance and two between factors, had a nonsignificant chi square (χ^2 = 95.48, p = .300), RMSEA of 0.014, (95% confidence interval [0.000, 0.033]), CFI = 0.992, and TLI = 0.977. Two factors emerged, named 'depressive' and 'hypomanic.' The depressive factor included sad mood, sleep disturbance, fatigue, anhedonia, guilt/worthlessness, and pity, whereas the hypomanic factor included irritability, euphoria, high energy/goal directed behavior, clarity of thought, racing thoughts, and risky behavior. The third model with good fit, unrestricted within covariance and three between factors, had a nonsignificant chi square ($\chi^2 = 72.17$, $p = .571$), RMSEA of 0.000, (95% confidence interval [0.000, 0.028]), CFI = 1.000, and TLI = 1.012. Three factors emerged, named 'inhibited depressed,' 'anxious agitated,' and 'irritable euphoric.' The inhibited depressive factor included sad mood, sleep disturbance, fatigue, anhedonia, guilt/worthlessness, and pity. The anxious factor included a negative loading of trouble concentrating, and worry and agitation, and the hypomanic factor included irritability, euphoria, agitation, clarity, racing thoughts, and risky behavior. The fourth model with good fit, unrestricted within covariance and three between factors, had a nonsignificant chi square ($\chi^2 = 58.44$, $p = .605$), RMSEA of 0.000, (95% confidence interval [0.000, 0.029]), CFI = 1.000, and TLI = 1.018. Four factors emerged, named 'anhedonic,' 'inhibited,' 'catatonic,' and 'hypomanic.' 'Anhedonic' included anhedonia, guilt/worthlessness, and worry; 'inhibited' included sad mood, sleep disturbance, fatigue, pity, negative loading on clarity, and negative loading on racing thoughts. 'Catatonic' included trouble concentrating, negative loading of worry, and negative loading of high energy/goal directed behavior, and 'hypomanic' included irritability, euphoria, high energy/goal directed behavior, clarity, racing thoughts, and risky behavior.

In examining the scree plot (see Figure 3), it is clear that although the four factor model had good tests of fit and an eigenvalue above 1.00, there was not enough variance explained above the three factor model to be secure in choosing a less parsimonious model. The first four models explained the following percentage total variance: 28.62%, 47.53%, 59.92%, 70.02%, respectively. For this reason, we turned our attention to the one, two, and three factor models. The one factor model, with multiple negative loadings, was difficult to describe. Furthermore, as the episodes captured in this sample are theoretically of at least two underlying factors, we could not say that the one factor model was supported by theory. We next examined the two and three factor models. As is the default in MPlus, we assumed that if the absolute value of the estimate of the correlation divided by its standard error was larger than 1.96, the loading for a given variable would be significant. See Table 15 for these values.

Table 14. Comparing the 2- and 3-factor models resulting from EFA

	2-factor model		3-factor model		
Item	1	2	1	2	3
Sadness	**0.799***	-0.331	**0.776***	0.116	-0.314
Weight change	-0.043	0.023	-0.074	0.162	0.04
Sleep disturbance	**0.533***	-0.197	**0.526***	0.015	-0.191
Fatigue	**0.784***	0.073	**0.797***	-0.064	0.071
Anhedonia	**0.767***	-0.115	**0.752***	-0.09	-0.149
Guilt and worthlessness	**0.790***	0.023	**0.763***	-0.028	0.006
Difficulty concentrating	0.223	0.16	0.538	**-1.178***	0.001
Suicidality	0.202	0.344	0.197	-0.02	0.338
Worry	0.282	-0.105	0.204	**0.480***	-0.033
Self pity	**0.472***	0.249	**0.466***	0.313	0.344
Irritability	0.144	**0.363***	0.18	-0.198	**0.322***
Euphoria/grandiosity	0.000	**0.980***	-0.009	0.063	**0.976***
Agitation	0.093	**0.556***	0.009	**0.619***	**0.749***
Clarity of thought	0.01	**0.813***	0.005	-0.015	**0.774***
Racing thoughts	-0.253	**0.758***	-0.254	-0.033	**0.727***
Risky behavior	-0.200	**0.711***	-0.188	0.197	**0.806***

* $p < .05$

Table 15. Correlation estimates divided by standard errors from EFA

	2 factor model		3 factor model		
Item	1	2	1	2	3
Sadness	**5.89**	-1.65	**4.52**	0.28	-0.83
Weight change	-0.19	0.10	-0.31	0.77	0.17
Sleep disturbance	**3.65**	-1.29	**3.93**	0.09	-0.91
Fatigue	**4.66**	0.43	**4.94**	-0.16	0.22
Anhedonia	**4.69**	-0.69	**4.93**	0.27	-0.65
Guilt and worthlessness	**5.41**	0.14	**5.50**	-0.09	0.04
Difficulty concentrating	1.35	1.06	1.31	**-3.79**	0.30
Suicidality	0.91	1.73	0.86	-0.12	1.48
Worry	1.52	-0.61	0.88	**2.99**	-0.25
Self pity	0.85	**2.76**	1.07	-1.03	**2.18**
Irritability	**2.91**	1.49	**2.32**	1.09	1.25
Euphoria/grandiosity	-0.01	**10.93**	-0.12	0.26	**11.54**
Agitation	0.41	**2.89**	0.38	**2.87**	**3.65**
Clarity of thought	0.07	**6.00**	0.04	-0.15	**5.53**
Racing thoughts	-1.58	**5.94**	-1.59	-0.22	**4.99**
Risky behavior	-0.77	**3.20**	-0.68	0.99	**3.02**

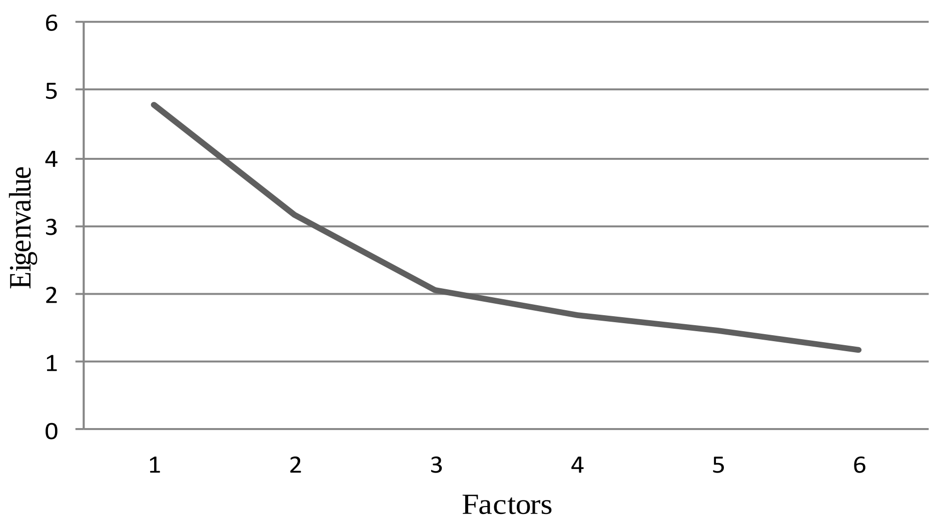

Figure 3. Scree plot generated from multilevel factor analysis

Currently, there is no way to statistically test which of two models better fits the data, as this test is available for categorical one-level data and continuous multilevel data, but our data are categorical multilevel (Muthén, personal communication, March 17, 2014).

CHAPTER 4

DISCUSSION

The current study sought to test the nature and risk for experiencing mixed episodes in bipolar spectrum samples. The principal aims were to examine the extent to which mixed symptoms pervade mood episodes, and examine theorized risk factors for mixed symptoms and more chronic course of illness. To this end, I assessed whether mood episodes met a variety of research criteria for mixed episodes, examined the underlying factor structure of bipolar mood episodes, examined latent classes of predictors and their ability to predict history of mixed symptoms, and tested whether suicidality and chronic course are associated with mixed symptoms.

The first hypotheses concerned the prevalence of different mixed state criteria as defined in the literature. There were no manic episodes reported at follow-up in this predominantly bipolar II and BNOS sample, so by definition, the hypothesis that DSM-IV-TR mixed episodes would be rare was indeed supported, although it is beyond the scope of the current study to state whether these are actually common in those with manic episodes. It was hypothesized that the prevalence of hypomania without concurrent depressive symptoms (and the converse) would capture less than 40% of those episodes. This hypothesis was not supported, as 69.81% of depressive episodes and 57.75% of hypomanic episodes, or 62.10% of all episodes in this sample did not have concurrent opposite-polarity symptoms.

Although Benazzi's definition of mixed depression (2008) was more commonly observed than Cassidy and colleagues' (2000) criteria for mixed mania, at the same level as Spitzer and colleagues' (1975) criteria for RDC agitated depression, the base rates for all of these episode types were very low. With loosened criteria for mixed manic states, such that impairment was taken from overlapping depressive impairment, still only 9.86% of hypomanic episodes met these criteria for Akiskal and colleagues' (1998) dysphoric mania, 1.41% met loosened criteria for McElroy and colleagues' (1992) dysphoric mania, and 4.23% met loosened criteria for Bauer and colleagues' (1994) mixed mania. No episodes met criteria for Akiskal and Benazzi's (2003) dysphoric hypomania.

No one set of research criteria for mixed mood state captured most of the mixed mood states reported in this sample, as only 13 discrete episodes (out of 142) met mixed criteria of any kind, including several loosened mixed mania criteria. This left 33 episodes with some level of mixed symptoms that were not captured by previously published criteria. DSM-5's mixed features specifier would adequately explain what we observed in this sample, yet sound critiques of these new criteria have their merit (see Angst, 2013), such that an overly dimensional and imprecise measurement of mixed mood state will make it difficult to examine whether treatment differs across certain types of mood states. As most studies of possible episode criteria are conducted with treatment seeking samples, it is possible that the nature of mixed states is different in non-treatment seeking samples like this one. Future studies should examine whether the nature of bipolar mood episodes change over time within individuals.

The multilevel factor analysis in sample 2 supported my hypothesis that there would be more than two factors underlying bipolar mood episodes. In particular, I hypothesized that these factors would be characterized by overactivity, irritable risk taking, and inhibited depression. The results yielded an anxious agitated factor (concentrating, worry, agitation), an irritable euphoric factor (irritability, euphoria, agitation, clarity, racing thoughts, risky behavior), and an inhibited depression factor (sad mood, sleep disturbance, fatigue, anhedonia, guilt/worthlessness, self-pity). The two-factor model also fit the data well, with more traditional hypomanic (irritability, euphoria, agitation, clarity, racing thoughts, and risky behavior) and depressive (sad mood, sleep disturbance, fatigue, anhedonia, guilt/worthlessness, self-pity) factors. It is worth noting that the depressive factors in both models have the same item loadings. Likewise, the item loadings for hypomanic in the two-factor model and irritable/euphoric in the three-factor model are the same. In the three-factor model, difficulty concentrating (negative) and worry load with agitation onto a third factor. Other researchers have found factors more specifically related to anxiety (e.g., Sato et al., 2002). Unfortunately, the only anxiety-related items probed in our version of the SADS-C were worry and agitation (psychomotor agitation, pacing/inability to sit still, along with energy). Future studies should continue to examine the underlying factors in bipolar mood episodes, while examining anxiety in a more thorough way.

Anxiety disorders and bipolar spectrum disorders are commonly comorbid, particularly panic disorder (Chen & Dilsaver, 1995); future studies should examine whether comorbid conditions affect factor structure of bipolar mood episodes. This also should be conducted with individuals with comorbid substance use diagnoses. These results support previous work suggesting that bipolar mood episodes are characterized by some level of mixed symptoms and a dysphoric or anxious component (e.g., Sato et al., 2002). These results extend previous work, which has mostly been conducted with treatment-seeking samples (e.g., Pacchiarotti et al., 2013). Individuals in our study were not generally treatment seeking, which suggests an earlier or less severe course of illness, and yet the factor structure was similar.

The purpose of the latent class analysis portion of this study was to examine whether bipolar spectrum individuals would differ on variables theoretically related to course of illness, including aggression, impulsivity, substance use, and risk taking. Unfortunately, our variable that measured risk taking would not converge in the analysis. The hypothesis held that classes would emerge, and BAS risk status, bipolar diagnosis, sex, and presence of substance use diagnosis, and mixed symptoms would differ significantly across classes. The latent class analysis did support my hypothesis that bipolar spectrum individuals would split into discrete classes on levels of aggression, impulsivity, and substance use. Future studies should replicate this with other variables of interest, including anxiety and risk taking behaviors. These results displayed a low impulsivity class, substance problems class, and an aggressive class. The hypotheses that these classes would differ by bipolar diagnosis and BAS risk status were not supported. It is unclear why BAS risk status did not differ across classes, as high BAS is related to aggression, yet BAS risk status was not more common in the aggressive class. However, 77% of this sample was high BAS risk, so perhaps this test was under-powered. Presence of a substance use disorder was significantly more likely in the "substance problems" than the "low impulsivity" class, which externally validates our classes, as those with the highest amounts of substance problems are naturally more likely to be diagnosed with substance use disorders.

Although an omnibus test yielded non-significant results between classes with regard to the continuous outcome of mixed symptoms, when this variable was transformed to be dichotomous, I found that the “substance problems” class was significantly more likely to have any mixed symptoms than the “low impulsivity” class, and any mixed symptoms also were marginally more likely in the “aggressive” than the “low impulsivity” class. As the “substance problems” class had lowest values of aggression in this sample, my hypothesis that aggression would be associated with mixed symptoms was not supported. However, this class also had high levels of impulsivity, similar to the “aggressive” class, so in part the hypothesis that high levels of impulsivity is related to mixed symptoms is supported. However, the driving factor that separates this class is substance problems, as measured by self-report of use and problems related to use, and this finding is the first of many from this sample that supports evidence that increased substance use is related to mixed symptoms. Future studies should replicate this latent class analysis with dimensional values of BAS, as our sample is by nature split into high and moderate BAS risk, leading to dichotomous values that do not converge well in LCA.

Finally, the regressions predicting to mixed symptoms supported some of my hypotheses. Female sex and suicidality history marginally predicted mixed symptoms, whereas substance use diagnosis, number of episodes, and total time spent in episodes significantly predicted mixed symptoms. The finding that number of episodes and total time spent in episodes each predicted mixed symptoms supports my overall hypothesis that mixed symptoms are related to more chronic course of illness. Again, substance use diagnosis is related to mixed symptoms, which supports our latent class analysis findings. Furthermore, number of episodes and substance use diagnosis interacted to predict mixed symptoms, such that number of episodes significantly predicted mixed symptoms only if there was no history of substance use diagnosis. This interaction could signify that substance use diagnosis itself is enough to be associated with mixed symptoms, whereas for individuals without a substance use diagnosis, increasing number of episodes increases the risk of mixed symptoms.

If chronicity of illness and substance use disorder are both considered indicators of more severe psychopathology, we can conclude that mixed symptoms are more common as psychopathology becomes more severe. We should consider then, that this milder spectrum sample (no bipolar I disordered individuals) may explain why other hypotheses, including those related to mixed state criteria, were not supported. As a whole, these results support previous research that has associated mixed states with more chronic and severe course of illness, operationalized by time spent in episodes and suicidality, as well as female sex, although some of the results from the current study were only marginally significant. The finding that substance use significantly predicted mixed symptoms supports previous work, and continues to highlight the need for this to be much more thoroughly researched in future investigations. Much research suggests that bipolar spectrum individuals with substance use diagnoses have more chronic and debilitating course of illness (see Salloum & Thase, 2000, for review), and substance use disorders have been associated with mixed states (e.g., Himmelhoch et al., 1976), yet future research must focus on whether substance use disorders predate or follow mixed symptomatology.

Further research is needed with regard to the role of aggression and impulsivity, as well as other BAS-related constructs, in the presence of mixed mood symptoms. It is clear from several different analyses that substance use problems and/or diagnosis play a large role in bipolar spectrum disorders and the presence of mixed mood symptoms. This study yielded a relatively high percentage of mixed mood symptom occurrence, yet these episodes were not captured by any research definition of mixed mood episode. Future research should continue to examine and define the types of mood episodes seen throughout the bipolar spectrum, as much research focuses on bipolar I and not other disorders on the spectrum.

The current study had several strengths. To our knowledge, the present study was the first to use the person-centered statistical approach of latent class analysis to characterize patterns of aggression, impulsivity, and substance use among individuals with bipolar spectrum disorders. These characteristics have each been associated with BSDs in previous work, yet latent class analysis had not yet been used as a method to understand how these traits are related to each other in this population. A person-centered approach is able to elucidate subgroups of the bipolar spectrum, based on their levels of associated characteristics. The subgroups that resulted from the LCA in this study (low impulsivity, substance problems, aggressive) not only indicate that individuals with BSDs differ in these ways, but also that one subgroup is more likely to experience mixed symptomatology, which furthers the field of inquiry on this matter.

Similarly, this was the first study to examine the factor structure underlying bipolar mood episodes in a BSD spectrum sample, and only the second study to examine the factor structure while combining mood episodes of both polarities (i.e., Pachiarrotti, et al., 2013). This study also employed samples in which individuals with BSDs were followed longitudinally for several years, and diagnostic interviews were conducted twice a year (in sample 1) or three times a year (in sample 2), which allows for greater confidence in demarcating mood episodes, rather than other studies that use one interview to gather lifetime data.

This study must be considered within the context of its limitations. Sample 1 was recruited on the basis of BAS risk, whereas sample 2 was recruited on the basis of having bipolar spectrum disorder, but not bipolar I disorder. For these reasons, the percentage of bipolar I disordered individuals was very low overall in this study (less than 10% in sample 1 and zero in sample 2), which indicates that these results cannot be generalized to those with bipolar I. However, it was the intent of this study to examine the lesser-studied disorders on the spectrum. Similarly, these samples were generally not treatment-seeking, and therefore these results cannot be generalized to treatment-seeking populations. Furthermore, in the LCA portion of this study, all measures used to assess class membership were self-report measures. Although these measures have been used widely throughout the literature to assess impulsivity, aggression, and substance use (BIS-11, AQ, SIP and AADIS, respectively), gathering data via self-report has its limitations. The BART initially was planned to be used in this analysis as a behavioral measure of risk-taking, but unfortunately this variable would not converge in the LCA.

The exploratory factor analysis used in this study was the first of its kind, which examined the individual-level factor structure by examining multiple episodes per person. However, the sample (sample 1) for this factor analysis was modest in size, and future studies should garner a much larger sample. Furthermore, the individuals studied were predominantly diagnosed with bipolar II disorder, and less than 10% had a diagnosis of bipolar I disorder. Future studies should gather a sample that is more evenly distributed across the bipolar spectrum, which could also allow for the possibility of examining the factor structures within each diagnostic subgroup.

Conclusions and Clinical Implications

Overall, the results from the current study provide evidence that supports findings suggesting that mixed mood states are more commonly experienced than originally believed. These results extend previous studies to include those with bipolar spectrum disorders, not solely bipolar I and II disorders. These findings also suggest that non-treatment-seeking samples may have different types of mixed mood states than those seeking treatment, as 37.10% of episodes had some amount of mixed symptoms, yet only 9.15% met criteria for previously published mixed states. Mixed symptom prevalence also was clear in the factor analysis in sample 2, which showed that rather than pure depressive and pure hypomanic factors, mood episodes were categorized into “anxious agitated,” “irritable euphoric,” and “inhibited depression.” Again, these results support previous literature suggesting that bipolar mood episodes are characterized by more than two “pure” factors, and extends this literature to include those with milder spectrum diagnoses. As such, future research should continue to examine the nature of mixed states in those with BSDs, and take care in assessing mood episodes, such that the interviewer does not unwittingly bias the individual into reporting only mood-congruent features when describing episodes. Anxiety also should be assessed carefully within and between mood episodes, as several researchers have suggested that anxiety plays a large part in the dysphoria seen in mixed episodes (e.g., Gupta et al., 2009).

These findings add support to the literature that individuals with BSDs and comorbid substance use diagnoses are at increased risk for chronic illness, and shows that these individuals are also more likely to experience mixed mood states than those without comorbid substance use diagnosis. Future research will need to determine whether comorbid substance use contributes to the occurrence of mixed symptoms or whether mixed symptoms increase the likelihood of engaging in substance use. Treatment providers should be aware of the complications that are inherent in bipolar individuals with comorbid substance diagnoses, as they are more likely to experience more episodes as well as mixed symptoms. Similarly, treatment providers should carefully probe for presence of mixed states and take this into account when prescribing medication, as well as considering psychotherapeutic treatment options.

Pharmacological Options

Very few double-blind, placebo-controlled studies have been conducted to investigate treatment of acute mixed states (see Krüger, Young, & Braunig, 2005 for review). Most pharmacological studies are designed to treat “pure” manic episodes, and patients with mixed states are only a small subset of these samples. Frequently, patients in mixed states are excluded from clinical trials (see Vieta, 2005), leading one to question whether those studies are clinically relevant, given the aforementioned evidence that mixed states are quite common. These studies also often use DSM criteria for mixed states, and it is unclear whether participants are excluded for any amount of mixed symptoms, or only if they meet full DSM criteria. Furthermore, prevention of future mixed states is even less studied.

Several studies have shown that the presence of mixed state usually predicts poor response to lithium (for review see Muzina, 2009). Anticonvulsants are preferred by many physicians and patients due to their fast-acting nature (Muzina, 2009). One study found that higher depression scores during a manic episode significantly increased the response to valproate (Freeman et al., 1992), whereas other studies have shown no difference in the response to lithium versus valproate in mixed states (Clothier, Swann, & Freeman, 1992). In a review of the literature, Calabrese, Fatemi, Kujawa, and Woyshville (1996) reported that divalproex has been shown to be effective in treating mixed states; however, the operationalization of mixed states was different in each study reviewed.

One study, employing McElroy and colleagues' (1992) criteria for dysphoric mania, showed that a sample of 14 patients treated with olanzapine and another mood stabilizer improved significantly more than the comparison groups treated with other adjunctive antipsychotics (Gonzalez-Pinto et al., 2001). However, many of the studies of olanzapine have not been methodologically strong, as there has not been randomization or blinding. Asenapine is another atypical antipsychotic that has been shown effective in treating mixed episodes, with similar results to olanzapine (McIntyre et al., 2009). In a thorough review of the efficacy of asenapine, Samalin, Tixeront, amd Llorca (2012) reported that asenapine led to significantly greater reduction of both depressive and manic symptoms by the third week of treatment. Recently, a randomized controlled study reported on the treatment of DSM mixed episodes (Azorin, Sapin, & Weiller, 2013). These patients had significantly higher manic than depressive symptoms at intake; improvement was qualified as a 50% or greater reduction in manic and depressive symptoms. Azorin and colleagues (2013) reported significantly more patients treated with asenapine had improvement, compared to placebo and olanzapine groups. However, they also reported that remission rates at follow up were significantly better in the asenapine group than the placebo group, but the asenapine group was not significantly different than the olanzapine group (Azorin et al., 2013).

Antidepressants are rarely suggested for use in treating individuals with bipolar disorder, as many research and clinical trials have shown antidepressants to lead to increases in hypo/manic symptoms (see Miklowitz & Johnson, 2006 for review). More recently, however, some investigators have been examining antidepressants as adjunctive medications when mood stabilizers are also prescribed. One study found that adjunctive antidepressants prescribed to patients with mixed depression led to significantly higher manic symptom severity at three month follow up, when compared to those prescribed mood stabilizers alone (Goldberg et al., 2007).

Neuromodulation Options

In the history of psychiatry, neuromodulation has gone in and out of favor. Earlier methods of neuromodulation included frontal lobotomy and electroconvulsive therapy (ECT), which became unpopular (see Valentí et al., 2008 for review). However, the technology behind these measures has increased enormously in the past few decades. Newer types of neuromodulation include transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS).

One preliminary study found that patients treated with valproate as well as repetitive TMS responded well over a three-week period (Pallanti, Cecchelli, Antonini, Salvadori, & Quercioli, 2011). These patients exhibited significant improvements on measures of manic and depressive symptoms, as well as overall functioning. However, as there was no sham condition in this study, much further research is needed. VNS has been shown to be effective in treating rapid cycling BD, both depressive and hypomanic symptoms (Marangell et al., 2008). Similarly, VNS has been shown effective in treating treatment-resistant bipolar depression with co-occurring manic symptoms (Rush et al., 2000). DBS has been shown to effectively treat bipolar depression (Holtzheimer et al., 2012), but had no effect on concomitant hypomanic symptoms.

Psychotherapy

Although there are several adjunctive psychotherapies that have been shown effective in the maintenance of bipolar disorder (see Johnson & Leahy, 2004 for review), there has been no specific study assessing effectiveness in treating or preventing mixed episodes, to our knowledge. However, a recent article detailing the effectiveness of Interpersonal and Social Rhythm Therapy (IPSRT) suggested that this treatment could be particularly helpful in the management of mixed states, as the participant must evaluate his/her mood state often (Swartz, Levenson, Frank, 2012).

In sum, there is a great need for more research into effective treatments for mixed states in particular. Few studies examine this clinical issue, and many studies exclude individuals exhibiting mixed states. Even more importantly, this research will not yield any conclusive treatment guidelines until there are consistent definitions of mixed states accepted and employed in research studies.

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