VALIDATING CYCLOTHYMIC DISORDER IN A YOUTH SAMPLE

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ABSTRACT

Anna Van Meter: Validating Cyclothymic Disorder in a Youth Sample
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Four subtypes of pediatric bipolar disorder (PBD) – bipolar I, bipolar II, cyclothymia and bipolar not otherwise specified (NOS) – are defined in DSM-IV-TR. However, these definitions are not followed consistently by research investigators or clinicians, resulting in a lack of agreement and understanding regarding the diagnosis of PBD. The present study uses the diagnostic validation method first proposed by Robins and Guze (1970), to systematically evaluate cyclothymic disorder as a distinct diagnostic subtype of bipolar disorder (BP). Using a clinical sample (N= 827), participants with cyclothymic disorder (N=52) were compared to participants with other BP disorders and to participants with non-affective disorders. Results indicate that cyclothymic disorder shares many characteristics with other bipolar subtypes, supporting its inclusion on the spectrum. Additionally, cyclothymia could be reliably differentiated from non-bipolar disorders based on irritability, sleep disturbance, age of symptom onset, comorbid diagnoses, and family history. These results highlight areas for future research.
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Validating Cyclothymia in a Youth Sample

Statement of Importance

Pediatric bipolar disorder (PBD), as a distinct diagnosis, is a relatively new concept within psychology. Only in the past 15 years or so has the field begun to actively recognize and diagnose the episodes of manic and depressive symptoms that characterize bipolar disorder in young people (B Geller & Luby, 1997). The past decade of research has yielded significant gains in better understanding the disorder (E. Youngstrom, Birmaher, & Findling, 2008). However, controversy and debate have led research groups in different directions, possibly limiting the progress in accurately defining and describing bipolar disorder and its subtypes in young people (Kessler, Avenevoli, & Merikangas, 2001).

The greatest source of diagnostic debate is in regard to the subthreshold forms of the disorder. Although there is some disagreement regarding the phenotypes for bipolar I and II, the definition of bipolar disorder not otherwise specified (BP NOS) and cyclothymic disorder are subject to greater controversy and less understanding. In fact, while there are distinct DSM criteria for each, it has been noted in the literature that many research groups do not attempt to differentiate subthreshold subtypes, relying instead on a loosely defined NOS grouping (Kessler, et al., 2001; E. Youngstrom, et al., 2008). Failing to differentiate between diagnostic subtypes limits the knowledge that can be gained. Subthreshold cases may, in fact, be in greatest need of investigation. These presentations are more common than BP I and II in young people (Lewinsohn, Klein, & Seeley, 1995) and prove to be just as impairing as the syndromal subtypes in both clinical and community studies (Axelson, et al., 2006; Birmaher, Axelson, Goldstein, et

The differentiation of subthreshold bipolar disorder into the subtypes of cyclothymia and BP NOS is important in order to elucidate the risk factors, developmental course, and potential for preventative measures that apply to each.

**Background and Significance**

Within the bipolar disorder category, symptom presentations meeting some, but not all, of the criteria for bipolar disorder I or II are common, but not well defined (Akiskal, et al., 2000). Depending on the research group and the specific phenomenology, these presentations are typically labeled as BP NOS and cyclothymia. Subsyndromal bipolar disorder has been found in 6-13% of the general adolescent population, while BP I and II are present in 0.5-3% (Chang, Steiner, Dienes, Adleman, & Ketter, 2003; Kessler, et al., 2009; Lewinsohn, et al., 1995). In spite of the higher rates of subsyndromal cases, most research groups combine all subthreshold presentations into a broad BP NOS group. This is due, in part, to the fact that the DSM inclusion/exclusion criteria for bipolar disorder subtypes are not particularly well-defined and do not fully encompass the range of symptoms commonly observed (E Youngstrom, 2009), some aspects are arbitrary (hypomania = 4+ days), and there is a belief that if the criteria were revised to better reflect patients’ symptoms, the composition of diagnostic groups would be different (Vieta & Phillips, 2007). Discontent with DSM criteria, particularly in regard to subthreshold cases, (Schotte & Cooper, 1999) has led to the advent of study-specific research diagnostic
criteria and the unintended consequence of impeding comparison of results across groups (Duax, Youngstrom, Calabrese, & Findling, 2007).

For example, in a large, longitudinal study of bipolar youth, the criteria for BP NOS have been revised to include (a) episodes of hypomania in the absence of any depressive episode, (b) episodes of mania that do not meet duration criteria, or (c) episodes of an insufficient number of manic symptoms that do meet duration criteria (Axelson, et al., 2006). The inclusion of these cases in research is important; however, placing them under the umbrella of the NOS diagnosis is problematic. Those with hypomania alone could also be categorized as cyclothymic, given sufficient duration, or given the difficulty differentiating hypomania from normal childhood behavior, might not be considered ill at all. In other studies, the NOS grouping may also include those who exhibit irritability while [hypo]manic, but whose mood is not elated or elevated (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003). These inconsistencies in diagnostic grouping are further perpetuated by the use of different diagnostic techniques. Although the use of a semi-structured interview, such as the K-SADS, is the “gold” standard for diagnosis, it is not used by all research groups. Different methodologies, particularly those that do not inquire directly about important aspects of bipolar disorder (e.g. episodicity, or “cardinal” symptoms, such as decreased need for sleep or grandiosity), are likely to yield unreliable diagnoses (Mick, Biederman, Pandina, & Faraone, 2003; E Youngstrom, Meyers, et al., 2005). So, although data exist on children with BP NOS, the heterogeneity of the sample is so great that generalizations cannot be made.

For the most part, cyclothymia is not described in research or diagnosed clinically (E Youngstrom, Youngstrom, & Starr, 2005). It was not included in the “Diagnostic guidelines for bipolar disorder: A summary of the International Society for Bipolar Disorders Diagnostic
Guidelines Task Force Report” (Ghaemi, et al., 2008). Those studies that do include it, are often based on clinical diagnoses. As a result, little is known about cyclothymia in young people. Furthermore, given the fact that evidence indicates that cyclothymia may be one of the more prevalent subtypes of bipolar disorder in adults (Akiskal, Lancrenon, & Hantouche, 2006; Hantouche, 2009), the absence of this group in youth research suggests that the other diagnostic subtypes – particularly BP II and NOS – are likely contaminated with youth meeting criteria for cyclothymia. If cases of cyclothymic disorder exist, but are not being diagnosed, then they are either being (1) misdiagnosed as another mood disorder, (2) misdiagnosed as a non-affective disorder, or (3) not coming to clinical attention. The diagnosis of cyclothymia can be made reliably in research (Depue, 1981; Mazure & Gershon, 1979), but for some reason, it has been largely ignored in pediatric studies, resulting in a potentially inaccurate picture of pediatric bipolar disorder overall.

Why do we care about categories? There is a movement now within psychology – and developmental psychopathology specifically – to move to a dimensional, rather than categorical system of classification (Kraemer, 2007). If a dimensional scale were adopted for pediatric bipolar disorder, it would eliminate the need to discuss the fine demarcations of different subtypes, and the pros and cons of combining some or all bipolar disorders under the same category would not matter. However, research suggests that different presentations of bipolar disorder are heterogeneous in their etiology and course (E Youngstrom, 2010) and, without describing these differences, the ability to forecast prognosis with any precision, or to create targeted treatments might be limited. Furthermore, diagnostic systems based on theory, rather than clinical presentation may be more technically valid, but tend to be inflexible and under-utilized (Brieger & Marneros, 1997).
The scope of this paper does not allow for a full discussion of the benefits and limitations of a categorical versus dimensional approach to diagnosis. Although the symptoms/presentation of bipolar disorder may, in fact, be dimensional, the system within which mental health services are currently administered requires categorical definitions (Ruscio & Ruscio, 2002; Widiger & Clark, 2000). Therefore, the prudent thing to do is to make the system work as well as possible, by utilizing a comprehensive set of subtypes that allow for the most appropriate diagnosis and treatment. A more well-defined set of diagnostic categories seems to be indicated for pediatric bipolar disorder in particular (Kessler, et al., 2001). There is a wide range of symptomatology that gets labeled with the bipolar banner. Because we do not yet know the developmental course of different symptom presentations or the best way to treat them, it is important to study them with as much detail as possible. Within research, using broad categories has been shown to weaken diagnostic precision, inhibit the development of diagnostic tools, undermine prognostic accuracy, confuse efforts to understand the biological and genetic underpinnings of a disorder and lead to ineffective treatments (Baldessarini, 2000). Distinct diagnoses are necessary to make progress toward fully understanding a disorder.

In addition to the intellectual merit of finely-demarcated diagnoses, there are compelling clinical considerations in favor of accurately diagnosing subthreshold cases (Brieger & Marneros, 1997). Previous mood disorder research has shown that failure to recognize subthreshold cases may leave up to one-third of treatable cases under-served (Angst, Merikangas, & Preisig, 1997). This is a real concern considering that early onset bipolar disorder may represent a more pernicious type than adult onset, and treatment could stave off some consequences associated with the disorder (Berk, et al., 2007; Perlis, et al., 2004). Those patients who present with clear mania and/or depression are easier to make treatment decisions about,
insofar as it is clear that they need treatment. Fuzzier cases, on the other hand, introduce more room for interpretation and uncertainty about whether to treat and how to treat (Kowatch, Fristad, et al., 2005). Clear classifications should facilitate the accurate diagnosis and treatment of subthreshold cases and may offer an opportunity for preventive intervention and improved prognosis over time (Schotte & Cooper, 1999; Vázquez & Tondo, 2007).

**Why do we care about cyclothymic disorder?** There are two DSM diagnoses that currently qualify as subthreshold bipolar disorder, cyclothymia and BP NOS. Cyclothymia is the forgotten class of bipolar disorder, at risk for extinction, as it has gotten largely absorbed into the NOS category, and / or confounded with cyclothymic temperament, within both clinical and research settings (Brieger & Marneros, 1997; E Youngstrom, 2009). However, there is ample evidence that cyclothymia deserves to be maintained as a distinct diagnostic category.

Cyclothymia was first described by Ewald Hecker, in 1898, in much the same way that the disorder is now characterized in the DSM – brief depressions followed by brief manias (Koukopoulos, 2003). Later, Kraepelin further described cyclothymia on the spectrum of bipolar disorders as a mild form or predisposition to the more severe subtypes (Akiskal, 2001; Trede, et al., 2005). Remarkably, a large portion of these early descriptions remains relevant today and, although history cannot be equated with truth, the persistence of cyclothymic features as a known clinical presentation justifies the further exploration of its validity as a diagnosis in children (Brieger & Marneros, 1997).

One of the challenges of maintaining cyclothymic disorder as a clinical diagnosis is the fact that, due to the less-intense depressed and manic episodes, many people with cyclothymia do not seek / receive treatment. When people with cyclothymic disorder do seek treatment, it is most often during a depressive episode, as hypomania can be a relatively pleasant state for the
person experiencing it (Akiskal, Djenderedjian, Rosenthal, & Khani, 1977). If the chief complaint is depression, people with cyclothymia may be misdiagnosed with dysthymic disorder or unipolar depression unless they are carefully questioned about past symptoms of hypomania. Similarly, if the patient and parent are not asked about episodic mood, the externalizing behaviors associated with hypomania may be the primary focus, leading to diagnoses of oppositional defiant disorder or conduct disorder (Fields & Fristad, 2009; E Youngstrom, 2009). This problem is particularly salient in youth populations, as hypomania can be hard to distinguish from normal childhood activity (E. Youngstrom, et al., 2008) and, in general, the reliability of mania diagnoses is low (Kessler, Rubinow, Holmes, Abelson, & Zhao, 1997). In addition, though scales exist to measure mania, none have been standardized on a large community sample (E Youngstrom, 2010). This is a particular limitation when considering subthreshold presentations of mania, as tools standardized only on clinical samples may not be sensitive enough to pick up on hypomania. As a result, hypomania may go undiagnosed, even when an assessment of manic symptoms is made.

In spite of the low rates of diagnosis and poor representation in research, cyclothymia may be the most common form of bipolar disorder (Hantouche, 2009; Lewinsohn, Klein, & Seeley, 2000). This is especially true in youth (Duax, et al., 2007), as cyclothymia may be a prodrome to BP I and II (Lewinsohn, et al., 2000). Due to the subthreshold symptomatology and tendency toward diagnostic escalation (Shankman, et al., 2009), those meeting criteria for cyclothymia in their youth may provide the best example of the course of bipolar disorder; including factors that act in protective or risk-generating capacities (Akiskal, et al., 1985). Additionally, the protracted course of cyclothymia may be an important outcome determinant. Previous research has shown that a more chronic symptom presentation often indicates a
treatment-refractory form of the disorder (Birmaher, Axelson, Goldstein, et al., 2009; Birmaher, et al., 2006) associated with greater comorbidity (McElroy, Strakowski, West, Keck, & McConville, 1997; Schraufnagel, Brumback, Harper, & Weinberg, 2001). The evidence suggests that, although the specific depressive and hypomanic symptoms may be less severe in cyclothymia than in other forms of bipolar disorder, the duration of these symptoms is an important clinical consideration. Similarly, a proposal for the classification of depression in DSM-V advocates the use of a two-axis system – severity and chronicity – it may be that bipolar disorders could also be classified using this system (Klein, 2008). Regardless, it is important to account for the chronic nature of cyclothymia in research, and to investigate the other factors associated with this presentation. Without the kind of definitive diagnostic data provided by genetic or biological tests, the study of pediatric bipolar disorder can only benefit from research that includes cyclothymia. Similarly, within clinical settings, having options that describe symptomatology more precisely should aid clinicians in making more accurate diagnostic and treatment decisions (Schotte & Cooper, 1999). With the hope of providing added diagnostic utility to both academic and clinical settings, the goal of this study is to validate the diagnosis of cyclothymia in young people.

**Validation approach.** There is no one accepted practice by which psychiatric diagnoses are validated. In fact, many childhood disorders have not been validated, beyond phenomenology, which is a major limitation, especially for research (Cantwell, 1996). This issue came to the forefront a decade ago, in Cantwell’s 1996 paper *Classification of Child and Adolescent Psychopathology*, but the challenges posed then remain today:

1. Is a categorical or dimensional approach more appropriate?
2. Can the disorder be conceptualized as quantitatively or qualitatively different from normal?

3. Can categories described in DSM be considered to be discrete entities?

4. How is comorbidity handled?

5. How are subthreshold conditions considered?

The issue of validation may be of particular interest now, as DSM V and WHO/ICD-11 committees are meeting to determine the future classification system. In the absence of a laboratory test, diagnostic validation is complicated. The questions posed above are not easily answered, particularly within young populations where developmental considerations cloud the picture. Still, it is important to approach validation systematically and to use methods that allow for consistency in both academic and clinical settings (Cantwell, 1996).

There are a number of competing validation approaches; for the purposes of this paper, two primary models were considered. First, the psychological approach, which is often described as the “nomological net,” and, second, the system first proposed by Robins and Guze (1970) and used widely (with modifications) in psychiatry.

The nomological net approach is based on the idea that many concepts in psychology, including diagnoses, do not have clear boundaries that can be directly measured (Ruscio & Ruscio, 2004). It may be impossible to measure exactly where a given factor begins and ends. So, rather than relying on an arbitrary measurement system, a nomological net for the construct of interest can be created from related factors that are measurable (Cronbach & Meehl, 1955). For example, we cannot directly measure a person’s personality: there is no blood test or brain scan that will reveal what an individual is like. However, we can measure behaviors that are influenced by personality and, in doing so, create a picture of an individual’s personality that can
be compared to others’. This approach is relatively flexible; scales can be constructed to include a wide range of possible presentations and do a nice job of describing a latent factor.

The nomological net approach holds some advantages for the consideration of bipolar spectrum disorders. Evidence increasingly suggests that these disorders are the result of numerous risk factors and that the disease characteristics (age of onset, length and frequency of episodes, severity, etc.) vary widely between individuals (Birmaher, Axelson, Goldstein, et al., 2009). The use of a nomological net would allow for the description of these and other constructs related to the disease on an individual basis. Historically, there has been some tension between a “one size fits all” model of diagnosis and a polythetic approach, allowing for greater individuality in diagnostic decisions (Tucker, 1998). Greater detail regarding symptomatology and diagnostic description holds advantages for research; the more clearly we can define constructs of interest, the better we may be able to understand the underlying factors. However, though there is a certain intellectual appeal in this approach, clinically, a multi-dimensional approach may not be the most logical (Ruscio & Ruscio, 2004; Widiger & Clark, 2000).

The Robins and Guze approach has been used widely in diagnostic validation studies, and its publication marked a shift in the basis of the DSM from a primarily clinical judgment-based system to one based on an evidence-based model (Andreasen, 1995; Feighner, et al., 1972). In its original form, it provides a framework of five categories (described as “phases”) of evidence collection that contribute to the validation of a diagnostic classification – Clinical Description, Laboratory Studies, Delimitation from Other Disorders, Follow-Up Studies, and Family Studies. The categories lend focus to the consideration of new psychiatric diagnoses and may help clinical researchers to identify areas in the literature that need further development in order to better understand or describe a diagnosis. It is a practical structure that promotes a rigorous
system for the categorization of disorders without being prohibitively rigid (Widiger & Trull, 1991). For most psychiatric disorders, the field is just beginning to understand the biological and genetic underpinnings. The Robins and Guze approach makes room for discoveries from the lab without discounting the importance of clinical judgment.

For the purpose of validating cyclothymic disorder in youth, and reconciling clinical utility with academic merit, the Robins and Guze approach may be a more appropriate starting point. Although cyclothymia is an intermediate diagnosis on the bipolar spectrum, for which an argument in favor of a dimensional approach could be made, within a clinical setting, a truly dimensional framework is impractical. Although each case of bipolar disorder may be slightly (or even drastically) different, the way in which they are treated is not; in practice, psychiatry and psychology rely on classification to delineate the healthy from the sick and make treatment decisions accordingly (Widiger & Trull, 1991). As such, the use of a system that is integrated with the DSM is indicated. In previous studies, cyclothymia in adults has been successfully validated using modified versions of the Robins and Guze phases, (1) family history, (2) follow-up studies, (3) delimitation from other disorders, (4) psychopharmacologic-induced hypomania, (5) lithium response (Akiskal, et al., 1977; Klein, et al., 1986). Additionally, the Robins and Guze phases have been used to validate pediatric bipolar disorder, demonstrating the fit of this framework to this class of disorders (Biederman, et al., 2003; Findling, et al., 2001; B Geller & Tillman, 2005). In the interest of consistency and generalizability, using the same framework for validation has advantages (Birmaher, et al., 2006).

A more theory-driven approach, like the nomological net, should not be rejected, it is important to pursue an understanding of this disorder beyond symptomatology. The Robins and Guze method is a nice compromise between a theoretical and clinical approach; it combines
clinical observation with more theory-driven research. Importantly, the Robins and Guze method can provide a clear picture of what is missing from the research, in a way that a less-defined framework cannot.

For the purpose of validating cyclothymia in youth, the existing data will be organized into three of Robins and Guze’s five categories, Clinical Description, Delimitation from Other Disorders, and Family Study, demonstrating the evidence in support of it as a diagnostic category and highlight the areas in which further research is warranted.

**Clinical description.** A review of the pediatric bipolar disorder literature and previous studies of cyclothymia in adults led to the identification of seven constructs to explore as potential discriminating clinical features of pediatric cyclothymia. Of the five categories of validation, clinical description may be the most important diagnostically, as clinicians are likely to focus on presenting symptoms, over some of the other categories – laboratory studies, family studies, and follow-up studies – that serve more of a research purpose.

**Depression and hypomania.** Cyclothymia is defined by a clinical course alternating between periods of depressive and hypomanic symptoms for at least one year in youths or two years in adults, during which time the individual is not symptom-free for more than two months (American Psychiatric Association, 2001). Any symptom presentation meeting full criteria for mania and/or depression would result in a diagnosis of bipolar I or II. As mentioned previously, one of the debates about pediatric bipolar disorder has been the criteria applied to episodes of mania and hypomania, specifically, whether or not the same criteria should be used for children and adults (Fields & Fristad, 2009; E. Youngstrom, et al., 2008). Although research has shown that pediatric bipolar disorder, including cyclothymia, can be diagnosed using adult criteria, many research groups choose to use less stringent criteria for both duration and intensity of
manic symptoms (Faedda, Baldessarini, Glovinsky, & Austin, 2004; B Geller & Luby, 1997; E. Youngstrom, et al., 2008). As a result, it may be that cyclothymia is often misdiagnosed as another subtype of bipolar disorder, when subthreshold symptoms are treated as meeting full criteria.

For this study, the Longitudinal Evaluation of All Available Data (LEAD) standard of diagnosis was used to designate the youth with cyclothymic disorder, in addition to all other diagnostic categories (Spitzer, 1983). The LEAD standard was developed in the absence of a laboratory test for the accurate diagnosis of mental illness, it takes into account longitudinal information in order to assess the disorder over time, it is executed by experts who have demonstrated proficiency in the diagnosis of the disorder in question and agree by consensus on the appropriate diagnosis, and it relies not only on information provided by the subject, but also collects information from family members, previous healthcare providers and others as appropriate. The inclusion of information beyond that provided in the K-SADS interview may improve the validity of the diagnosis, as research shows that the use of standardized diagnostic interviews alone can result in misdiagnosis (Rettew, Lynch, Achenbach, Dumenci, & Ivanova, 2009) In this study, the LEAD diagnoses take into account the information collected through the K-SADS interview, study questionnaires, family history and clinical judgment. Youth with cyclothymia will be expected to suffer impairing symptoms, of both depression and mania, that fail to meet full criteria for either number of symptoms or duration.

**Irritability.** Cyclothymic temperament is one possible explanation for the elevated levels of irritability seen among people with cyclothymia. Regardless of its origin, the irritability seen among people with cyclothymia during both hypomanic and depressive periods is a marker of the disorder. Unfortunately, irritability is also a symptom of many other childhood disorders,
resulting in the frequent misdiagnosis of conduct disorder and oppositional defiant disorder (Biederman, et al., 2000; E. Youngstrom, et al., 2008). This is further complicated by the very high rates of comorbidity found in pediatric bipolar disorder (Faedda, et al., 2004; Wozniak, Biederman, Kiely, et al., 1995). In the case of cyclothymia, the irritability should coincide with episodes of hypomanic and depressive symptoms, not occur all the time, as it might in ADHD or other comorbid disorders. Concentrating on the episodic nature of the disorder is the best way to ensure that a symptom is due to the bipolar disorder (E. Youngstrom, et al., 2008). The irritability experienced during depressive and hypomaniac episodes may be qualitatively different. People with cyclothymic disorder tend to be impulsive and unpredictable during hypomaniac or mixed states with irritable mood directed at others, whereas during depressive periods, they may be touchy and sensitive, but also tend to have self-directed irritability consistent with guilt, rumination, and low self-esteem (Akiskal, et al., 1977; Akiskal, et al., 1985).

Irritability is a complicated symptom to assess in pediatric bipolar disorder. It is included among the DSM criteria for mania, and considered by many to be a hallmark symptom of pediatric mania, but it may also be present during depressive phases (Birmaher, Axelson, Strober, et al., 2009; Kowatch, Youngstrom, Danielyan, & Findling, 2005). Experts in pediatric bipolar disorder confirmed that over 90% of youth with bipolar diagnoses show moderate or severe irritability during periods of elevated mood. This type of irritability is often associated with aggression and outward hostility (Jensen, et al., 2007). Irritability experienced during depression may be qualitatively different from the variety found during periods of elevated mood. Therefore, in order to address the hypothesis that people with cyclothymia will exhibit trait-like irritability, occurring in both hypomaniac and depressive episodes, two constructs of irritability will be assessed.
Comorbidity. The presence of other psychiatric disorders is common in youth with bipolar disorder, often making diagnosis difficult and complicating treatment (Lewinsohn, et al., 1995; Spencer, et al., 2001; Wozniak, Biederman, Kiely, et al., 1995). Two of the most common comorbid diagnoses are ADHD and anxiety disorders (Kowatch, Youngstrom, et al., 2005). Due to significant symptom similarities, bipolar spectrum disorders are also often misdiagnosed as one of these disorders (Akiskal, et al., 1985; Faraone, Biederman, Wozniak, & Mundy, 1997; Reich, Neuman, Volk, Joyner, & Todd, 2005; Singh, DelBello, Kowatch, & Strakowski, 2006).

Given the symptoms of cyclothymia, particularly restlessness, irritability and impulsivity, is often misdiagnosed as ADHD, and it may be several years before a proper diagnosis is made (Faedda, et al., 2004). Some experts hypothesize that a prolonged period to diagnosis may result in greater burden of illness, including more comorbid diagnoses (McElroy, et al., 1997; Schraufnagel, et al., 2001). Given the average length of duration until diagnosis, a higher number of comorbid diagnoses may be present among people with cyclothymia. Additionally, people with cyclothymia tend to have a variety of psychiatric disorder present in their family history, which may lead to more comorbidity (Akiskal, Hantouche, & Allilaire, 2003; Findling, et al., 2005).

Two types of comorbid diagnoses are of particular conceptual interest: ADHD and anxiety disorders. The impulsive and restless nature of people with cyclothymic disorder, along with the chronicity of symptoms, make ADHD and cyclothymia hard to differentiate (Schraufnagel, et al., 2001) and the two often co-occur (Holtmann, et al., 2009). Due to their temperamental nature, and proclivity to overreact in situations perceived as stressful, people with cyclothymia may also be more inclined toward anxiety disorders (notably panic and separation anxiety) (Akiskal, et al., 1985; Perugi, 2002; Wagner, 2006).
**Age of Onset.** The age of symptom onset in bipolar disorder has important implications for prognosis (Craney & Geller, 2003). Generally, the earlier symptoms begin, the more severe the disease will ultimately become (Perlis, et al., 2004). Considering that (1) cyclothymia appears to have a temperament foundation, (2) that cyclothymia can be the prodrome to other forms of bipolar disorder (Akiskal, et al., 1985), and (3) that studies show subsyndromal bipolar may have a younger mean age of symptom onset than BP I and II (Lewinsohn, et al., 2000), it is likely that cyclothymia has an earlier age of onset than other forms of bipolar disorder (Dickstein, et al., 2005). The other aspect of onset that may be important is whether a person’s first episode is elevated or depressed. Evidence indicates that in early onset bipolar disorder, the first episode is usually depressed. This is important because people with a depressed index episode may remain symptomatic much longer than those who present with [hypo]mania (Strober, et al., 1995). Because cyclothymia has such a protracted course, the initial episode is more likely to be depressed.

**Sleep disturbance.** A reliable way to identify youth with bipolar disorder is by identifying changes in sleep patterns / sleep disturbance coinciding with mood episodes (B Geller, et al., 2002; Harvey, Mullin, & Hinshaw, 2006). Although people with cyclothymic disorder do not experience full-blown mania, and may not demonstrate decreased need for sleep, they often experience significant sleep disturbance, due to the restlessness and agitation associated with their disorder (Findling, et al., 2005; Kowatch, Youngstrom, et al., 2005) This disturbance may occur during both hypomanic and depressive episodes.

**Delimitation from Other Disorders.** Being able to differentiate cyclothymia from other forms of bipolar disorder is perhaps the most important – and challenging – aspect of the validation of this diagnosis. As mentioned, pediatric bipolar disorder can be difficult to
differentiate from disruptive behavior disorders, ADHD and, in some cases, from depression. To further delineate cyclothymia, a clinician must focus on very specific aspects of the child’s symptom presentation – the difference is in the details.

Pediatric bipolar may be distinguished from other childhood disorders as follows:

**ADHD.** ADHD may share many symptoms with PBD including restlessness, irritability, distractibility, and hyperactivity (Biederman, et al., 2005; Faraone, et al., 1997). However, ADHD is a chronic – not episodic disorder. Assessing for episodicty is one of the most reliable ways to distinguish PBD (E. Youngstrom, et al., 2008). Additionally, ADHD does not include several hallmark symptoms of mania, including grandiosity, hypersexuality, racing thoughts, and decreased need for sleep. Each of these symptoms may be used to help make a differential diagnosis between PBD and ADHD (B Geller & Tillman, 2005; B Geller, et al., 2002).

**Disruptive Behavior Disorders** *(Oppositional Defiant Disorder / Conduct Disorder)*. The extreme irritability accompanied by rage / tantrum behaviors in pediatric [hypo]mania may be mistaken for ODD or CD. Additionally, poor judgment and impulsivity exhibited during [hypo]manic episodes may appear similar to the deviant behavior seen in CD. Although the symptoms of these disruptive behavior disorders are similar to some seen during manic phases of PBD, the features of elevated mood and decreased need for sleep are absent in disruptive behavior disorders. Additionally, during depressed or euthymic periods of bipolar disorder, these symptoms will be largely absent. Again, the primary way by which to differentiate PBD is a change in symptomatology between episodes.

**Depression.** Assessed during manic phases, bipolar I and bipolar NOS are unlikely to be confused with depression, given the severity of the manic symptoms. However, bipolar II and
cyclothymia, which never reach full mania, may be mistaken for unipolar depression. Hypomania is unlikely to result in treatment seeking behavior, in fact, in many cases, it is a pleasant state (Akiskal, et al., 1977). Therefore, bipolar II and cyclothymia are more likely to be seen clinically during depressive episodes. Unless the clinician specifically asks about prior history of hypomania, the patient may easily be misdiagnosed. In order to ensure accurate diagnosis, it is important to ask about previous symptoms of elevated mood. Another complication is the fact that many bipolar youth have a depressive episode before ever experiencing [hypo]mania. This makes it important to inquire about family history and symptoms of atypical depression that may signal a predisposition to bipolar disorder (Birmaher, Axelsson, Goldstein, et al., 2009; E. Youngstrom, et al., 2008).

The delimitation of cyclothymia from other subtypes of bipolar disorder takes careful consideration of bipolar symptoms.

**Compared to youth with cyclothymic disorder, other BP subtypes differ on the following:**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Bipolar I</th>
<th>Bipolar II</th>
<th>Bipolar NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mania</td>
<td>More severe</td>
<td>Equivalent</td>
<td>Often more severe</td>
</tr>
<tr>
<td>Depression</td>
<td>More severe</td>
<td>More Severe</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Total episode duration</td>
<td>Shorter</td>
<td>Shorter</td>
<td>Equivalent</td>
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<tr>
<td>Irritability</td>
<td>Less chronic</td>
<td>Less severe</td>
<td>Less chronic</td>
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<tr>
<td>Age of Onset</td>
<td>Later</td>
<td>Later</td>
<td>Equivalent</td>
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<tr>
<td>Index episode</td>
<td>Less likely depressed</td>
<td>Less likely depressed</td>
<td>Less likely depressed</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>More severe</td>
<td>Equivalent</td>
<td>More severe</td>
</tr>
<tr>
<td>Family History</td>
<td>Less mental illness</td>
<td>Less mental illness</td>
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**Family Study.** There is significant evidence that bipolar disorder is heritable. Although the exact rates vary across studies, generally a child of a bipolar parent will be approximately 5x more likely to develop bipolar than a child of healthy parents (Hodgins, Faucher, Zarac, & Ellenbogen, 2002; Tsuchiya, Byrne, & Mortensen, 2003). Furthermore, children in families with
bipolar disorder tend to have elevated rates of a number of other psychiatric disorders including depression, ADHD and anxiety (DelBello & Geller, 2001).

In a study of youth with manic symptoms, the proportion of those with cyclothymic disorder with a bipolar parent (versus without) was higher than any other diagnostic group, including those participants with bipolar I and II (Findling, et al., 2005). Additionally, there is evidence that the presence of a family history of mood disorder (both unipolar depression and bipolar disorder) is the key factor in differentiating people with cyclothymia from others with subthreshold bipolar symptomatology (defined as those with clear cyclothymic symptomatology that fails to meet full criteria, particularly episodicity, or as cases with definite dysthymia and / or depression, but limited hypomanic features) (Akiskal, et al., 1977; Depue, 1981).

Family history of psychiatric disorder is a significant factor in one’s risk for bipolar disorder (Findling, et al., 2005). However, heritability of psychiatric disorder is relatively non-specific (DelBello & Geller, 2001); therefore, we will explore family history using three constructs (history of bipolar disorder, history of mood disorder, and history of nonspecific symptoms), rather than looking at history of bipolar disorder alone.

**Aims**

The primary aim of this study is to explore the validity of cyclothymic disorder as a diagnostic subtype of pediatric bipolar disorder and to make a case for its inclusion in future studies of bipolar disorder. This aim will be achieved through the testing of 11 hypotheses, formulated from the proposed diagnostic validation framework (Robins & Guze, 1970).

The first phase employs descriptive statistics to show the clinical characteristics of those cases diagnosed with cyclothymic disorder. This phase is meant to be exploratory and to help with hypothesis generation for future studies of cyclothymic disorder.
Clinical description.

The presence / absence of the following clinical features was evaluated in all youth with cyclothymic disorder:

- Irritability during both elevated and depressive mood states
- Early age of symptom onset (<10 years)
- Index episode depressed
- Multiple comorbid disorders, particularly ADHD and anxiety
- Poor sleep hygiene

Hypotheses.

Delimitation from other disorders.

Non-bipolar.

- Youth with cyclothymia will be more irritable than youth with non-bipolar spectrum disorders
- Youth with cyclothymia will have more comorbid disorders than youth with non-bipolar spectrum disorders
- Youth with cyclothymia will experience greater sleep disturbance than youth with non-bipolar spectrum disorders

Other bipolar spectrum disorders.

- Youth with cyclothymia will experience a different pattern of irritability than youth with other BP spectrum disorders (elevated irritability during both hypomanic and depressive episodes)
- Youth with cyclothymia will have more comorbid anxiety disorders than youth with other bipolar spectrum disorders
• Youth with cyclothymia will have an earlier age of symptom onset than youth with other bipolar spectrum disorders

• Youth with cyclothymia will be more likely than youth with other bipolar spectrum disorders to experience a depressive episode as their first mood episode

_Family studies._

• Youth with cyclothymia will have family history of psychiatric disorder, including, but not limited to bipolar disorder

• Youth with cyclothymia will have more total family history of psychiatric disorder than youth with other bipolar spectrum disorders

• Youth with cyclothymia will have more family history of mood disorder than youth with non-bipolar spectrum disorders

_Method_

**Participants**

Participants were recruited from an urban community mental health center (N = 647) and from an academic outpatient medical center (N = 180). A sample of patients presenting for services at the community mental health clinic were invited to participate in the study. The only eligibility requirements were that the patient was between the ages of 5 and 18 and that both the patient and their caregiver were able to speak English. The participants from the academic outpatient medical center were recruited for a variety of treatment studies for bipolar disorder, ADHD, conduct disorder and aggressive behavior. Additionally, children of parents with bipolar disorder were recruited to the academic center. The exclusionary criteria at the academic center included the same age and language requirements as the outpatient clinic; additionally, participants were excluded if they suffered from a pervasive developmental disorder, mental
retardation (as determined by educational history, cognitive test scores, or Peabody Picture Vocabulary Test - Third Edition), autism (as determined by psychiatric interview or having an Autism Screening Questionnaire score of >15).

The sample is comprised of 496 (60%) male participants and 331 (40%) female participants. The sample has an average age of 10.92 years (SD 3.44). Sixty-nine percent (N = 573) of subjects reported their race as Black, 22% (N = 185) White, 2% (N = 20) Hispanic, .2% (N = 2) Asian, and 5% (N = 45) reported race as Other. Two people refused to report race information.

**Measures**

A variety of measures will be used to assess the constructs of interest, as follows:

<table>
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<tr>
<th>Construct</th>
<th>Measure</th>
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<td>Diagnosis</td>
<td>K-SADS and LEAD</td>
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<td>Irritability</td>
<td>P-GBI – Select items</td>
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<tr>
<td>Comorbidity</td>
<td>K-SADS and LEAD</td>
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<tr>
<td>Age of Onset</td>
<td>K-SADS</td>
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<tr>
<td>Sleep disturbance</td>
<td>P-GBI – Sleep Subscale (Meyers &amp; Youngstrom, 2008)</td>
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<td>Family History</td>
<td>QFMQ</td>
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**Diagnosis.** Diagnosis is the basis on which youth with cyclothymia will be compared to the cases with other childhood disorders. Diagnoses were made following the LEAD standard (Spitzer, 1983), taking into account the information provided during the semi-structured interview using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL-Plus). All participants and their families from both the community mental health center and the academic outpatient medical center completed a semi-structured diagnostic interview, the K-SADS-PL (Kaufman, et al., 1997), modified with the mood disorders module of the WASH-U-K-SADS (B Geller, Zimmerman, & Williams, 2001). The WASH-U-K-SADS inquires about symptoms related to depression and mania that are not
well-queried in other diagnostic interviews. The K-SADS was administered to each participant and his/her parent by a highly-trained research assistant. In order to achieve interrater reliability, research assistants were required to shadow an experienced rater for at least five K-SADS interviews and demonstrate item-level kappa>.85. New raters then led five interviews while being shadowed by an experienced rater. The kappa score for these five interviews needed to be at least .85 for the RA to qualify to lead interviews on his/her own. Following the K-SADS interview, all cases were reviewed by a team of expert clinicians (always including a licensed clinical psychologist and the K-SADS interviewer). In addition to information from the semi-structured interview, the case team also reviewed psychiatric records and family history in order to reach a consensus diagnosis. In the case of a diagnostic discrepancy, the participant and parent would be reinterviewed. Kappa was 0.95 for bipolar diagnoses and 0.91 for all diagnoses when comparing consensus to the K-SADS diagnosis (E Youngstrom, Meyers, et al., 2005). In order for a participant to receive a diagnosis of cyclothymic disorder, s/he would have to meet criteria for hypomanic symptoms and depressive symptoms, along with the duration criteria of being symptomatic (to the point of clinical impairment) for at least one year. Additionally, the participant’s mood episodes could not meet criteria for mania or for a major depressive episode. In the case of a manic, major depressive or mixed episodes occurs within the course of an established cyclothymic episode (at least one year in length), the diagnosis for cyclothymia is given in addition to a diagnosis of bipolar I (for a manic or mixed episode) or bipolar II (for a major depressive episode).

Irritability. Irritability will be assessed during periods of both depressive and elevated mood using select items from the Parent-General Behavior Inventory (P-GBI) (E Youngstrom, Findling, Danielson, & Calabrese, 2001). The P-GBI is a modified version of the General
Behavior Inventory (GBI) (Depue, 1981), meant to be completed by parents about their child. The P-GBI includes questions regarding the child’s depressive, manic, hypomanic and biphasic mood symptoms. The questions comprise two scales, the depressive and the hypomanic/biphasic. Both scales have high construct validity and very high internal consistency (alphas of 0.97 for depression and 0.94 for hypomanic/biphasic) (E Youngstrom, et al., 2001). This scale was originally developed in order to be sensitive to subthreshold manifestations of mood disorder and has proven to do a good job discriminating cases from the full spectrum of bipolar disorders (Depue, 1981; E Youngstrom, et al., 2004; E Youngstrom, Meyers, et al., 2005), making it particularly valuable for the current study of cyclothymia.

Items representing depressive or hypomanic irritability were selected by three independent raters. Reliability was high; for depressive irritability, items 3, 14, 34, 39, 44, 50, and 53 (Cronbach’s α .87) and for elevated irritability, items 22, 27, 51, and 54 (Cronbach’s α .71).

**Comorbidity.** The number and type of comorbid disorders for each participant will be evaluated according to LEAD diagnoses. The LEAD diagnoses are made by consensus by a team of experts, taking into account all axis I diagnoses from the K-SADS interview, prior clinical diagnoses, family history and clinical impressions.

**Age of Onset.** As operationalized in other research studies, age of onset refers to the age at which a participant first met diagnostic criteria for a depressive, manic, hypomanic, or mixed episode (Goldstein, et al., 2005). Given the significant delay that often occurs before an accurate bipolar diagnosis is made, in this study, age of symptom onset will be assessed by determining the youngest age of symptomatology, rather than diagnosis, as reported in the K-SADS interview. The K-SADS inquires about age of onset for each of the disorders covered, including
depression and [hypo]mania. The polarity of the index episode (depressive or elevated) will be determined by evaluating the younger of the two age of symptom onset variables.

**Sleep disturbance.** Sleep disturbance will be assessed using the seven-item sleep subscale from the P-GBI. This scale has shown to have strong reliability in differentiating bipolar youth from youth with other psychiatric diagnoses based on reported sleep disturbance (Cronbach’s α 0.83) (Meyers & Youngstrom, 2008).

**Family History.** Family psychiatric health history will be reported using *The Quick Family Mood Questionnaire (QFMQ)* (Youngstrom unpublished data). The QFMQ is intended to provide a simple method by which information about study participants’ family history of mental health issues can be gathered. It consists of an array of questions about mental health history for close relatives (parents, grandparents, aunts/uncles, siblings and children), resulting in a total of 25 checkboxes that respondents can endorse. The QFMQ was validated in a pediatric bipolar study of 162 families. The family history information showed a clinically meaningful association with youth diagnoses of PBD and the number of family risk factors (a simple sum of the number of checks) discriminated cases with diagnoses of PBD from all other cases.

**Procedure**

All involved parents / caregivers signed written consent, youth participants provided written assent. The youth and parent each completed the K-SADS interview separately (administered by the same interviewer). While the parent was being interviewed, youth, 11 years and older, completed a series of questionnaires. While the child was being interviewed, the parent/caregiver completed the P-GBI, QFMQ, and other questionnaires. The scores on all questionnaires were recused from the consensus diagnosis meeting. The consensus diagnosis
meetings followed the Longitudinal Evaluation of All Available Data (LEAD) procedure (Spitzer, 1983).

Direct comparisons of questionnaire scores can be misleading when they are scaled in different metrics, or when groups have markedly different variances on instruments that otherwise look as if they share the same scale. Without a scale for which differences in individual scores can be meaningfully interpreted (as in the case with IQ scores), perceived disparities in scores may not represent true differences; one way to lend context to scales without meaningful units is to transform scores into a percent of the maximum possible score (POMP). Converting summed scores into percents provides a framework by which to interpret differences (Cohen, Cohen, Aiken, & West, 1999). For the purposes of this study, scores from the P-GBI and family risk factors will be converted into POMP scores.

A range of analyses will be conducted, as appropriate to each construct of interest. For each analysis, except where indicated, the youth with cyclothymia in the sample will be compared with every other BP subtype (BP I, BP II, and BP NOS) separately as well as with the other participants in the study without bipolar disorder. The participants without bipolar disorder will be grouped in four categories – disruptive behavior disorders (DBD), ADHD, depression, and depression plus ADHD. Because cyclothymia is most likely to be seen clinically during depressive phases and shares many characteristics with ADHD, the decision was made to parse out those participants with comorbid depression and ADHD in order to see if the co-occurrence of these two disorders results in greater similarity to cyclothymia than depression or ADHD alone.

Where appropriate, age, gender, substance use and Child’s Global Assessment Scale (C-GAS) (Shaffer, et al., 1983) score will be added to the analyses as covariates. Although previous
research has not found sex differences in the prevalence of bipolar disorder (Merikangas, et al., 2007), it may be that there are differences in youth clinical diagnosis, with boys more likely to receive a diagnosis of bipolar than girls (Moreno, et al., 2007). In the study sample, there is no difference in gender between those youth with bipolar spectrum disorders and those with non-affective disorders ($X^2(1)=2.2, p=.13$). Some effect from age may be expected, as the sample spans a wide age range (5-18) and bipolar disorder is thought to increase in prevalence with age, particularly from childhood to adolescence (Lewinsohn, et al., 2000; Perlis, et al., 2004). The average age of youth with bipolar spectrum disorders is equivalent to the average age of the youth with non-affective disorders ($F(1)=1.0, p=.31$). Substance use is often associated with other psychiatric disorders, including pediatric bipolar disorder (Brook, Cohen, & Brook, 1998; Kandel, et al., 1997; Wilens, et al., 1999). In order to control for increased risk due to concurrent substance use, a dichotomous variable was created to indicate whether the child and/or his/her caregiver endorsed any substance use (by the child). Although this is, admittedly, a liberal definition of substance use, given the age of the sample, it seemed prudent to be over-inclusive. Sixteen percent of the sample met criteria for any substance use, there was no difference between those participants on the bipolar spectrum and the rest of the sample ($X^2(1)=2.6, p=.12$) Finally, C-GAS scores were used to gauge the child’s current level of overall functioning. Participants’ C-GAS scores were used to control for degree of impairment, which may account for greater variability in symptom severity than diagnosis. There was a significant difference in mean C-GAS score between participants with bipolar spectrum disorders (49.1) and those with non-affective disorders (53.1), $F(1)=52.6, p<.0001$.

As indicated, by the results of preliminary analyses, post-hoc analyses will be conducted using Tukey’s HSD procedure, unless otherwise noted. Tukey’s HSD allows for between-group
comparisons following an ANOVA, correcting for the increased likelihood of Type I error due to multiple comparisons.

**Results**

**Irritability**

The mean POMP elevated irritability score for youth with cyclothymia was 33.01 (SD 21), diagnostic sensitivity analyses demonstrate that this is significantly higher than the mean score for the rest of the sample ($t(808)=-3.21, p <.001$). The mean POMP depressive irritability score for youth with cyclothymia was 43 (SD 19), which is also significantly higher than the mean score for the rest of the sample ($t(808) =-4.11, p>.0001$). In addition, youth with cyclothymia exhibit greater irritability during depressive, rather than elevated, episodes ($t(51)=-3.59, p<.001$).

Total POMP irritability scores (depressive and elevated) for youth with cyclothymia were compared to other youth in the sample without bipolar spectrum disorders using one-way ANOVA. Results indicate significant variability in irritability across the sample ($F(4)=18.32, p<.0001$). See Table 1. Specific comparisons were as follows: youth with cyclothymia were more irritable overall than those youth with a primary diagnosis of ADHD ($p<.0001$) and those with a disruptive behavior disorder ($p<.0001$). There was not a significant difference between youth with cyclothymia and youth with depression ($p=.18$) or depression plus ADHD ($p=.72$). Youth with cyclothymia and those with depression or depression plus ADHD were also equivalent in their ratings of the depressive component of irritability. Youth with cyclothymia did have significantly higher elevated irritability scores than the depressed youth ($p<.01$), but not the youth with depression plus ADHD.
In a linear regression model, used to control for age, gender, substance use and level of general functioning (as measured by C-GAS score), diagnosis accounted for a significant portion of the variance in irritability. Compared to those youth with cyclothymia, the other disorders (with the exception of depression plus ADHD) all resulted in a lower irritability score: DBD ($B=-25.5 \ (p<.0001)$), ADHD ($B=-15.9 \ (p<.0001)$), depression ($B=-11.1 \ (p<.005)$), depression plus ADHD ($B=-5.3 \ (p=.1)$) (intercept = 83.2, $p<.0001$). Child’s gender was also a significant predictor, with girls exhibiting greater irritability ($B=3.97 \ (p<.05)$), but age ($p=.08$) and substance use ($p=.95$) were not. Child’s level of functioning also accounted for a significant portion of variance in total irritability score ($B=-.95 \ (p<.0001)$), such that better functioning was associated with lower irritability.

Youth with cyclothymia did not differ from those participants with BP I ($p=.26$) or BP NOS ($p=.996$) in their level of depressive irritability. Those with BP II had a higher mean level of POMP depressive irritability than the youth with cyclothymia ($p<.005$). Controlling for age, gender, substance use and level of functioning did not affect this result.

Youth with cyclothymia differ only from those with BP I in their mean level of elevated irritability ($p<.05$), such that the mean POMP score for youth with cyclothymia (33.0) is lower than the mean POMP score for youth with BP I (47.8). Controlling for level of functioning reduced this to a nonsignificant difference; further adjustment for age and gender did not change the pattern of findings.

Repeated-measures ANOVA, investigating the pattern of irritability across elevated and depressive periods, was significant ($F(3)=4.63, \ p<.01$), such that change in level of irritability between elevated and depressed episodes depended on the bipolar subtype. Further consideration of the mean difference between elevated and depressive irritability across bipolar subtypes...
indicated that participants with BP II have a larger difference between levels of irritability than each of the other BP subtypes ($p<.05$). See Figure 1.

The hypothesis that youth with cyclothymia will have similar levels of irritability in both elevated and depressive episodes, was not supported; there was a significant difference between episodes, such that greater irritability is experienced during depressive periods ($t(51)=-3.59$, $p<.001$).

**Comorbidity**

Of the 52 youth with cyclothymia in the sample, 51 (98%) have a comorbid diagnosis. Nineteen (37%) have a comorbid anxiety disorder. This is not significantly different from the rest of the sample ($X^2(1)=3.37$, $p=.07$). Forty-three of the youth with cyclothymia (83%) have comorbid ADHD; this is significantly different from the rest of sample ($X^2(1)=9.13$, $p<.005$).

As a group, the bipolar subtypes do not differ in the number of total comorbid diagnoses ($F(3)=2.3$, $p=.08$).\(^1\) See Table 2. No difference was found in the presence of comorbid anxiety diagnoses ($X^2(3)=2.9$, $p=.41$). In regard to comorbid ADHD, there was a significant difference between subtypes, ($X^2(3)=10.8$, $p<.05$), such that youth with cyclothymia were the most likely to meet ADHD criteria.

Youth with cyclothymia have a higher number of comorbid diagnoses than those youth without bipolar spectrum disorders ($F(4)=23.8$, $p<.0001$). Using a linear regression model with cyclothymia and the non-bipolar spectrum disorders as predictors, and controlling for age, gender, substance use and C-GAS score, cyclothymia remains a significant predictor of increased comorbidity ($p<.0001$).

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\(^1\) Although comorbid diagnoses are a count, rather than a continuous variable, the skew was <3, so ANOVA was used to assess differences between groups. Results of a Kruskal-Wallis were equivalent, ($X^2(3)=7.00$, $p=.07$), showing no significant difference between subtypes.
Age of onset

Thirty-eight of the youth with cyclothymia (73%) had symptom onset prior to the age of 10. This is significantly different from the rest of the sample, $X^2 (1) = 14.76, p < .0001$. However, youth with cyclothymia were not more likely to have mood onset prior to age 10 than the other bipolar spectrum disorders, $X^2 (3) = 6.04, p = .11$. Cox regression, designed for analysis of time until an event, was used to examine whether or not youth with cyclothymia exhibit mood symptomatology at younger ages than children with other bipolar subtypes. Overall, the subtypes did not differ in their age of onset, $X^2 (3) = 6.7, p = .08$. However, there was a significant difference between the youth with cyclothymia and the youth with BP II ($Wald = 5.6, p < .05$). See Figure 2.

Forty-three of the youth with cyclothymia (83%) experienced depressive symptoms before experiencing hypomanic symptoms. However, there was no difference in the likelihood between bipolar subtypes that the index episode would be depressed ($p = .91$); all bipolar subtypes were more likely to report depressive, rather than hypomanic, symptoms first.

Sleep disturbance

Youth with cyclothymia had a mean POMP score of 31 (SD 21) on the seven-item P-GBI sleep subscale, significantly higher than the rest of the study sample ($t(808) = -2.77, p < .01$).

Youth with cyclothymia have a significantly higher mean score on the P-GBI sleep scale than those youth with non-bipolar spectrum disorders ($p < .01$) with the exception of those youth with depression and ADHD ($p = 1.0$). This difference holds after controlling for age, gender, substance use and C-GAS. When compared to other youth with bipolar spectrum disorders, youth with cyclothymia differ only from those with BP II ($p < .01$), after controlling for age,
gender, substance use and C-GAS score. The mean POMP score on the P-GBI sleep subscale for youth with cyclothymia (31) was lower than the mean POMP score for those with BP II (53).

**Family history**

All of the youth with cyclothymia in the sample for whom family history was reported had family history of psychiatric disorder (n=15). See Table 3. There was no difference in the level of bipolar risk between the bipolar subtypes (risk was POMP-scored out of a possible 25 disorder-family member pairings). Similarly, there was not a significant difference between bipolar subtypes in the level of general psychiatric illness risk, though the scores vary (Cyclothymia 51, BP 13, BP II 32, BP NOS 32). Unfortunately, these analyses are underpowered, family history information was only available for 15 youth with cyclothymia, three youth with BP I, six youth with BP II, and 19 youth with BP NOS.

Youth with cyclothymia have more family risk for psychiatric disorder than those with disruptive behavior disorders (p <.05), ADHD (p<.0001), depression (p<.05), but not depression plus ADHD (p =.09). Similarly, the youth with cyclothymia have more mood disorder (bipolar or depression) risk factors than those with disruptive behavior disorders (p <.05) or ADHD (p<.01). Although the results were not significant between youth with cyclothymia and the youth with depression (p=.06) or those with depression and ADHD (p=.07), given the low number of participants with full family history, and the difference in POMP family mood disorder scores (cyclothymic 46, depressed 27, depressed + ADHD 28), differences in the presence of family mood disorder in youth with cyclothymia, as compared to those with depression deserves further exploration.
Discussion

The primary aim of this study was to validate cyclothymic disorder in a youth population using the diagnostic validation system proposed by Robins and Guze (1970). This system makes use of five categories of evidence – Clinical Description, Laboratory Studies, Delimitation from Other Disorders, Follow-Up Studies, and Family Studies. In this study of 827 youth seen for outpatient services, we were able to address three of the five categories. This is the first study of cyclothymia in youth and, as such, the analyses may be considered exploratory. Still, careful consideration of the data related to Clinical Description, Delimitation from Other Disorders, and Family Studies paints a compelling picture – plainly situating cyclothymia on the bipolar spectrum and offering clues for future areas of research.

Irritability.

Youth with cyclothymia in the sample exhibited the characteristics expected for the most part. They showed high levels of irritability associated with both depressive and elevated mood. Depressive irritability was more severe, which is interesting, given the fact that people with cyclothymia are more likely to be seen for treatment during depressive episodes. It may be that the heightened irritability signals increased internal agitation, which is more unpleasant both for the individual with cyclothymia and for those close to him/her. Interpersonal difficulties could be an important motivator for individuals to seek treatment, considering associated consequences, including escalation of mood symptomatology. Additionally, with cyclothymic youth, parents might be most likely to take their child for an evaluation when s/he becomes irritable and difficult to be around.

Irritability was expected to be a distinguishing feature of people with cyclothymia. Though a diagnosis of cyclothymia was a significant predictor – more so than any of the other,
non-BP disorders – of total irritability (elevated plus depressive), after controlling for age, gender, substance use, and C-GAS, the mean irritability score (40.44) for youth with cyclothymia was not statistically different from those with depression (32.82) or depression and ADHD (36.10). This indicates that the overall irritability score may be driven by the depressive irritability score. If that were the case, differences in overall irritability scores between bipolar youth and depressed youth might not be expected; depressed youth could have greater depressive irritability to balance the elevated [hypo]manic irritability seen in bipolar youth. Further exploration suggests that this may, in fact, be the case. Looking at depressive irritability alone, youth with cyclothymic disorder have a higher mean score than the youth with DBD or ADHD, but not the depressed youth (with or without ADHD). Elevated irritability scores indicate that youth with cyclothymic disorder are significantly more irritable than all but the youth with depression and ADHD. Conceptually, this makes sense: depressed youth would be expected to show depressive irritability, and one of the main features shared by ADHD and [hypo]mania is irritability. These results are interesting in that irritability is most often associated with the elevated periods of bipolar disorder (Biederman, et al., 2000; Kowatch, Youngstrom, et al., 2005; Wozniak, Biederman, Kiely, et al., 1995), but it appears that irritability during depressive episodes is, in fact, more severe.

The pattern of irritability reported may help to differentiate youth with cyclothymia from other bipolar subtypes. However, in this study, the pattern was not as hypothesized; the only significant difference was between youth with cyclothymia and those with BP I. Youth with cyclothymia were more irritable during depressive than elevated episodes, whereas those with BP I exhibited a more consistent level of irritability across episodes. Interestingly, when level of functioning was added to the model, the difference was no longer significant. Among the
participants with bipolar disorders, level of functioning and irritability were correlated ($r=-.2, p<.01$); opening the possibility that level functioning and irritability are related, independent of mood. In fact, the correlation is stronger among those youth with non-affective disorders ($r=-.3, p<.01$). Though it is beyond the scope of this study to determine the direction of this relation, the issue deserves further exploration. Better understanding of the direction of this relation could have important clinical and research implications. Given the considerable attention irritability has been given in the pediatric bipolar literature, the fact that the level of irritability may be driven by level of impairment, is provocative. This result gives further credence to the theory that irritability is a nonspecific symptom, not a hallmark feature of pediatric mania, as some have suggested (Biederman, et al., 2000).

Depressive irritability, as might be expected, is worse in youth with BP II than youth with cyclothymia. Though other forms of bipolar may also experience major depression, this is the primary feature of BP II; the ability to differentiate BP II from the subthreshold forms of the disorder is a good indicator that irritability is a factor in bipolar depression. Within the bipolar context, irritability during depressive episodes is less often discussed than irritability during elevated periods; this may be an oversight as the results of the current study indicate that depressive irritability also offers discriminative ability.

Comorbidity.

Nineteen of the 52 youth with cyclothymia (37%) met criteria for an anxiety disorder. Though this supports the hypothesis that comorbid anxiety would be common among the youth with cyclothymia, high rates of panic disorder and separation anxiety were expected, but not found. The rate of separation anxiety among the youth with cyclothymia (6%, $n=3$) was lower than expected and quite a bit lower than previous studies have found (rates range from 13-57%).
(Wagner, 2006). Although there is not an obvious reason for the low rate of separation anxiety in this sample (among all bipolar subtypes the rate was 9%), it may be that the age of the participants played a role; research has indicated that the prevalence of separation anxiety decreases from childhood to adolescence (Masi, Mucci, & Millepiedi, 2001). The complete lack of panic disorder among the youth with bipolar disorder in this sample is also surprising. However, 23 of the youth with bipolar disorder, including nine of the youth with cyclothymia, report experiencing panic attacks. This is consistent with a previous study of 93 bipolar youth, in which no comorbid panic disorder was found, but 8% of participants had panic attacks (Tillman, et al., 2003).

In contrast to the rate of comorbid anxiety, the rate of comorbid ADHD among the youth with cyclothymia (83%) was, if anything, higher than anticipated. Previous studies have found rates closer to 60% among both youth with cyclothymia and the other bipolar subtypes (Birmaher, et al., 2006; Findling, et al., 2005), though rates as high as 97% have been reported for BP I (Biederman, et al., 2005). More interesting is the fact that the youth with cyclothymia had higher rates of ADHD than the other bipolar subtypes. This may provide some support to the theory that cyclothymia is associated with more varied family history of psychiatric disorder, beyond just mood disorder, and that those with cyclothymia are more likely to also suffer from other disorders. Additionally, such high rates of comorbid ADHD confirm one of the primary challenges in diagnosing cyclothymia – differentiation from ADHD or ADHD plus depression. This is an important issue, especially at the clinical level, introducing concern regarding appropriate treatment, whether with stimulants, mood stabilizers, or one of the other pharmaceutical treatments for PBD. Given the number of overlapping symptoms between pediatric bipolar disorder and ADHD, the most reliable way of differentiating between the two
disorders may be to establish whether the symptoms are chronic or episodic (Galanter & Leibenluft, 2008). However, this distinction can become blurred in the case of cyclothymia because its mood episodes are long and, particularly in children, may appear to be a chronic condition, if remittance has never been achieved.

When an ADHD diagnosis precedes a diagnosis of cyclothymia, it raises questions regarding the possibility of a form of ADHD that is, in fact, a bipolar prodrome. This question has been raised elsewhere (Biederman, Russell, Soriano, Wozniak, & Faraone, 1998; Chang, et al., 2003; Sachs, Baldassano, Truman, & Guille, 2000; Singh, et al., 2006), and it is clear that, though symptoms may overlap, the two disorders are distinct. However, what is less clear – and deserving of additional exploration – is the question of whether or not there are different variants of ADHD, some that are associated with greater risk of bipolar disorder, or perhaps a certain subtype of bipolar disorder, and some that are not. Currently, evidence is somewhat mixed, but it seems that people with bipolar disorder are more likely to have ADHD, whereas having ADHD is less associated with increased risk of bipolar (Galanter & Leibenluft, 2008; E Youngstrom, Arnold, & Frazier, 2010). A similar pattern is found in family studies, wherein family members of bipolar probands tend to have elevated rates of ADHD, but family members of ADHD probands are not at increased risk for bipolar disorder (Galanter & Leibenluft, 2008). While it does appear that there is a familial link between ADHD and bipolar disorder (Chang, Steiner, & Ketter, 2000; Faraone, Glatt, & Tsuang, 2003; Wozniak, Biederman, Mundy, Mennin, & Faraone, 1995), more work needs to be done to better understand this relation. There is evidence to suggest that bipolar disorder and ADHD share a number of risk factors – genetic, biologic, and environmental. It may be that, in many cases, the perceived relation between these two disorders has more to do with similarities in the underlying disease mechanism, resulting in the application
of two labels for one disorder, rather than true comorbidity (E Youngstrom, et al., 2010). Better understanding of the shared and unique risk factors and phenomenology of ADHD and bipolar disorder is important; there are significant implications for treatment and for the refinement of the current classification system.

*Age of onset.*

The mean age of mood symptom onset for youth with cyclothymic disorder was six years, five months. This is well below the hypothesized age of ten. Traditionally, an age of onset this young would have likely been taken as a sign that the child was suffering from a disorder other than bipolar – very likely ADHD, given the criteria of onset prior to age seven. However, research increasingly indicates that bipolar disorder very often does begin in childhood (Lewinsohn, et al., 2000; Perlis, et al., 2004). And, while the differences in age of onset between bipolar subtypes failed to reach significance, the age of onset for youth with cyclothymia was a full year younger than that for BP I and NOS and two and a half years younger than onset for BP II. Given the relatively small number of participants from which to make these comparisons, additional, prospective research is indicated to further explore this potential difference. An earlier age of onset associated with cyclothymia could further support the idea that cyclothymia has a more trait-like, temperamental foundation and chronic course (B. Geller, Tillman, Bolhofner, & Zimerman, 2008; McElroy, et al., 1997; Perlis, et al., 2004).

The hypothesis that youth with cyclothymia would tend to have a depressive episode before exhibiting hypomanic symptoms was supported, although they were not any more likely than the other bipolar subtypes to exhibit this pattern. Previous research has repeatedly found that depressive episodes tend to precede [hypo]manic episodes in bipolar youth (Birmaher, Axelsson, Goldstein, et al., 2009; Strober, et al., 1995). Unfortunately, these data tend to be
retrospective, as is the case with the current study; therefore, the report of symptom onset may be confounded with the increased likelihood that people with cyclothymia will seek treatment during depressive episodes (Akiskal, et al., 1977; E Youngstrom, 2009). Only a prospective study of pre-symptomatic youth can fully address this question.

**Sleep disturbance.**

As expected, youth with cyclothymia reported disrupted sleep. Though the mean score on the P-GBI sleep subscale was lower than the mean score found previously for bipolar youth (Meyers & Youngstrom, 2008), it was significantly higher than the sleep disturbance reported by those youth without bipolar disorder in this sample. There is evidence to support the theory that bipolar disorders are caused, in part, by abnormalities of an individual’s circadian rhythms that can “trigger” affective episodes (Grandin, Alloy, & Abramson, 2006). Both depressive and manic episodes are often preceded by disrupted sleep, and when disrupted sleep continues, mood symptoms tend to be worse (Totterdell & Kellett, 2008). The fact that the youth with cyclothymia in this study shared symptoms of sleep disruption with the other bipolar subtypes – but not with those unaffected by bipolar disorders – is important in that, based on the circadian rhythm theory, it suggests a shared biology among the bipolar disorders. Furthermore, it lends credence to the belief that cyclothymia is, in fact, an episodic bipolar disorder, not simply a temperament style. In a treatment study of cyclothymia, focused on improving mood with cognitive-behavioral techniques, one of the primary outcomes was an improvement in both sleep duration and regularity of sleep patterns, suggesting a bidirectional relation between internal and external mood triggers (Totterdell & Kellett, 2008). Good sleep hygiene is often incorporated in treatment for bipolar disorders (Kowatch, Fristad, et al., 2005; Otto, Reilly-Harrington, & Sachs, 2003; Schwartz & Feeny, 2007), but this result indicates that sleep disruption may be both a
symptom and a cause of mood disorder. Further investigation of the relation between circadian rhythms and bipolar mood may provide important insights regarding both the biological and environmental etiology of mood disorders.

**Family history.**

Youth with cyclothymia did not differ from other bipolar subtypes in their reported family history of psychiatric disorder (mood or other). Youth with cyclothymia did have greater family history of psychiatric disorder than the non-bipolar youth. Furthermore, they had greater family history of mood disorder than those youth with disruptive behavior disorders or ADHD, but were not distinguishable from those with depression or depression plus ADHD based on family history of mood disorder. These results offer further evidence that cyclothymia is on the mood disorder spectrum, and is associated with heritable risk. However, this particular set of analyses is underpowered; many participants did not report family history. Additionally, the measure used to collect family history data is simplistic. Although this is a benefit in terms of ease of administration, it introduces limitations regarding the level of detail and specificity of the information provided. While we believe that the yes/no questions asked offer an appropriate proxy for family history, there is certainly a trade-off using a simple questionnaire like the QFMQ rather than a more detailed, structured interview to collect the information (Maxwell, 1992; Nurnberger, Blehar, Kaufmann, & York-Cooler, 1994). Including a comprehensive evaluation of family history of mental illness is indicated for future studies of bipolar youth.

Taken as a whole, the results of the analyses for the validation of cyclothymia as a distinct subtype of bipolar disorder were inconclusive. Although the results of the hypotheses regarding differences between the youth with cyclothymia and youth with non-bipolar disorders were largely supported, the differences between the youth with cyclothymia and the other forms
of bipolar disorder – particularly BP NOS – were less consistent. However, this should not be taken as evidence that cyclothymia and BP NOS are indistinguishable or that cyclothymia is an unnecessary subtype. In fact, considering that the NOS diagnosis is meant to be assigned only to those who do not meet one of the other bipolar diagnoses, the overlap between cyclothymia and BP NOS in the present study suggests that some youth diagnosed with BP NOS belong within the cyclothymic subtype. Delineation of these subtypes is possible and important, particularly in research settings, where investigators are aiming to better understand and describe PBD.

**Conclusion.**

The present study explored both similarities and differences across the bipolar spectrum, the results indicate that cyclothymia is, in fact, on the bipolar spectrum (and would not be better cast as a temperament or personality disorder), but retains characteristics that distinguish it from the other subtypes. See Table 4. Were large differences found between subtypes on the characteristics explored, it might call into question whether or not the subtypes really belong in the same category. Distinguishing cyclothymia from BP NOS is, as hypothesized, challenging and perhaps not possible based on levels of irritability, comorbid diagnoses, or family history, alone. That is not to say that cyclothymia is distinguishable only by DSM criteria, which are admittedly flawed; many of the results seem to hint at differences that may have failed to reach significance simply because the sample was not large enough. Based on the findings in this study, further investigation of comorbid ADHD, family history and age of onset, in particular, is indicated.

**Limitations and future directions.**

The current study was proposed and executed as an exploration of the diagnosis of cyclothymic disorder in young people. Given the lack of previous research on this population,
this study contributed important information about the phenomenology, etiology and comorbid conditions associated with this disorder. Still, there are limitations worth noting. This study used a five-phase validation framework first proposed by Robins and Guze (1970), however data only exist to address three of the five categories of research. The remaining categories – Laboratory Studies and Follow-up Studies – could provide the best opportunity to learn about the origin and course of this chronic, debilitating disorder. New research investigating the biologic and genetic underpinnings of cyclothymic disorder could provide valuable insight into the disorder’s etiology, mechanics, and relation to other affective disorders. Because it is theorized that cyclothymia may result from a varied genetic foundation, resulting in more pervasive, undifferentiated impairment, the results of genetic and biologic studies are of particular interest. Greater understanding of the systems implicated in the origin and maintenance of cyclothymia could provide valuable clues into the development of effective treatments.

The present study is unable to comment on characteristics of the course of cyclothymia, including episode pattern / duration and prognosis. Given that its chronic nature is one if the primary features of the disorder, this is a significant limitation. Unfortunately, cyclothymia has not been differentiated in any of the pediatric longitudinal studies reported to-date – even though the outcome for cyclothymic youth should be of great interest. Specifically, given that cyclothymia may be the most prevalent form of bipolar in adults – and that BP NOS is (by clinical diagnosis) more prevalent in children than adults, following the course of these two subthreshold forms of bipolar disorder may help to elucidate differences. Most importantly, what is the course of chronic, early-onset bipolar spectrum disorder? Who among the subthreshold cases goes on to develop BP I or II, whose symptoms remit? Data from a large, longitudinal study suggests that subsyndromal cases of pediatric bipolar disorder are likely to convert to BP I
or II (Birmaher, Axelson, Goldstein, et al., 2009; Birmaher, et al., 2006). However, this study does not distinguish between BP NOS and cyclothymic disorder, so it is impossible to draw conclusions about why 38% of cases progressed over the four-year follow-up and the rest did not. Additionally, there is evidence to suggest that some forms of pediatric bipolar disorder may resolve in young adulthood, without future episodes (Cicero, Epler, & Sher, 2009). Without prospective tracking of the specific characteristics of subthreshold bipolar subtypes, along with risk and protective factors, the gains possible from the field of bipolar research are limited – subthreshold subtypes likely represent the greatest opportunity for preventative measures (Miklowitz & Chang, 2008).

In conclusion, the results of this study suggest that cyclothymia is firmly situated on the mood disorder spectrum. It shares characteristics with both other bipolar disorders and depression. In fact, the similarities found between people with cyclothymic disorder and those with depression plus ADHD (irritability, high comorbidity, sleep disturbance) may suggest that cyclothymia is an intermediate disorder on the spectrum between BP I and major depression. The discussion regarding whether or not depression and bipolar disorder are on the same spectrum is ongoing, but it seems that further investigation of cyclothymia may offer some answers, not only about the mood spectrum, but about its interactions with temperament, circadian rhythms and other disorders.
References


Table 1. *Mean POMP irritability scores from the P-GBI by diagnosis*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Depressive Irritability</th>
<th>Elevated Irritability</th>
<th>Total Irritability</th>
<th>Difference btwn Dep &amp; Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBD</td>
<td>31</td>
<td>12.1(16.7)*</td>
<td>9.7(15.1)*</td>
<td>11.5(15.9)*</td>
<td>2.4(10.2)</td>
</tr>
<tr>
<td>ADHD</td>
<td>346</td>
<td>23.4(22.0)*</td>
<td>23.9(22.7)*</td>
<td>24.3(21.4)*</td>
<td>0.5(16.9)</td>
</tr>
<tr>
<td>Depression</td>
<td>126</td>
<td>38.3(23.4)</td>
<td>20.5 (20.6)*</td>
<td>32.8(21.0)</td>
<td>17.8(19.6)</td>
</tr>
<tr>
<td>Depression + ADHD</td>
<td>127</td>
<td>38.4(22.4)</td>
<td>29.0(23.6)</td>
<td>36.1(21.7)</td>
<td>9.4(18.4)</td>
</tr>
<tr>
<td>Cyclothymia</td>
<td>52</td>
<td>42.8(19.1)</td>
<td>33.0(20.9)</td>
<td>40.5(17.9)</td>
<td>9.8(19.6)</td>
</tr>
<tr>
<td>BP NOS</td>
<td>52</td>
<td>41.9(21.7)</td>
<td>35.7(24.9)</td>
<td>40.9(21.2)</td>
<td>6.2(20.8)</td>
</tr>
<tr>
<td>BP II</td>
<td>18</td>
<td>60.7(16.6)*</td>
<td>37.0(20.1)</td>
<td>53.7(17.9)*</td>
<td>23.7(14.2)</td>
</tr>
<tr>
<td>BP I</td>
<td>31</td>
<td>52.6(26.0)</td>
<td>47.9(25.7)*</td>
<td>52.5(24.9)</td>
<td>4.8(19.6)</td>
</tr>
</tbody>
</table>

*Significantly different (p<.05) from cyclothymia based on Tukey’s HSD posthoc test

Table 2. *Comorbid diagnoses*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Mean number comorbid Dx</th>
<th>% with comorbid anxiety</th>
<th>% with comorbid ADHD §</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBD</td>
<td>31</td>
<td>2.7(1.0)*</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>ADHD</td>
<td>346</td>
<td>3.6(1.4)*</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Depression</td>
<td>126</td>
<td>3.6(1.8)*</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Depression + ADHD</td>
<td>127</td>
<td>4.7(1.6)</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>Cyclothymia</td>
<td>52</td>
<td>4.9(1.6)</td>
<td>37</td>
<td>83</td>
</tr>
<tr>
<td>BP NOS</td>
<td>52</td>
<td>4.2(1.6)</td>
<td>28</td>
<td>57</td>
</tr>
<tr>
<td>BP II</td>
<td>18</td>
<td>4.2(2.2)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>BP I</td>
<td>31</td>
<td>4.0(1.6)</td>
<td>35</td>
<td>61</td>
</tr>
</tbody>
</table>

*Significantly different (p<.05) from cyclothymia based on Tukey’s HSD posthoc test

§the non-affective disorders were parsed based on ADHD status, within these categories either all or none of the participants have comorbid ADHD
Table 3. Percent with family risk factors for psychiatric disorder by diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Family history of psychiatric disorder %</th>
<th>Family history of mood disorder %</th>
<th>Family history of Bipolar %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBD</td>
<td>11</td>
<td>85</td>
<td>62</td>
<td>23</td>
</tr>
<tr>
<td>ADHD</td>
<td>88</td>
<td>72</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td>Depression</td>
<td>47</td>
<td>81</td>
<td>68</td>
<td>40</td>
</tr>
<tr>
<td>Dep + ADHD</td>
<td>45</td>
<td>82</td>
<td>71</td>
<td>49</td>
</tr>
<tr>
<td>Cyclothymia</td>
<td>15</td>
<td>100</td>
<td>93</td>
<td>60</td>
</tr>
<tr>
<td>BP NOS</td>
<td>19</td>
<td>84</td>
<td>79</td>
<td>42</td>
</tr>
<tr>
<td>BP II</td>
<td>6</td>
<td>83</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>BP I</td>
<td>3</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 4. Results for original hypotheses on delimitation from other bipolar subtypes. Compared to youth with cyclothymic disorder, those with other BP subtypes differed on the following:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Bipolar I</th>
<th>Bipolar II</th>
<th>Bipolar NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mania</td>
<td>More severe</td>
<td>Equivalent</td>
<td>Often more severe</td>
</tr>
<tr>
<td>Depression</td>
<td>More severe</td>
<td>More Severe</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Total episode duration</td>
<td>Shorter</td>
<td>Shorter</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Irritability</td>
<td>Less chronic</td>
<td>Less severe</td>
<td>Less chronic</td>
</tr>
<tr>
<td></td>
<td>Elevated both high &amp; low*</td>
<td>More severe high &amp; low*</td>
<td>Equivalent both high &amp; low</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>Later</td>
<td>Later</td>
<td>Later, not sig @ p&lt;.05</td>
</tr>
<tr>
<td>Index episode</td>
<td>Less likely depressed</td>
<td>Less likely depressed</td>
<td>Less likely depressed</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>More severe</td>
<td>Equivalent</td>
<td>More severe</td>
</tr>
<tr>
<td></td>
<td>Equivalent</td>
<td>More severe*</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Family History</td>
<td>Less mental illness</td>
<td>Less mental illness</td>
<td>Less mental illness</td>
</tr>
<tr>
<td></td>
<td>Less, not sig @ p&lt;.05</td>
<td>Less, not sig @ p&lt;.05</td>
<td>Less, not sig @ p&lt;.05</td>
</tr>
</tbody>
</table>

*Significant result
Figure 1. *Difference in irritability between depressive and elevated periods*
Figure 2. Survival analysis of age of mood symptom onset by bipolar subtype

Cumulative Survival

Age of Mood Symptom Onset