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# Parsing cyclothymic disorder and other specified bipolar spectrum disorders in youth

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## Abstract

**Objective—**Most studies of pediatric bipolar disorder (BP) combine youth who have manic symptoms, but do not meet criteria for BP I/II, into one "not otherwise specified" (NOS) group. Consequently, little is known about how youth with cyclothymic disorder (CycD) differ from youth with BP NOS. The objective of this study was to determine whether youth with a research diagnosis of CycD (RDCyc) differ from youth with operationalized BP NOS.

**Method—**Participants from the Course and Outcome of Bipolar Youth study were evaluated to determine whether they met RDCyc criteria. Characteristics of RDCyc youth and BP NOS youth were compared at baseline, and over eight-years follow-up.

**Results—**Of 154 youth (average age 11.96 (3.3), 42% female), 29 met RDCyc criteria. RDCyc youth were younger ($p$=.04) at baseline. Over follow-up, RDCyc youth were more likely to have a disruptive behavior disorder ($p$=.01), and were more likely to experience irritability ($p$=.03), mood

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reactivity ($p$=.02), and rejection sensitivity ($p$=.03). BP NOS youth were more likely to develop hypomania ($p$=.02), or depression ($p$=.02), and tended to have mood episodes earlier in the eight-year follow-up period.

**Limitations—**RDCyc diagnoses were made retrospectively and followed stringent criteria, which may highlight differences that, under typical clinical conditions and more vague criteria, would not be evident.

**Conclusion—**There were few differences between RDCyc and BP NOS youth. However, the ways in which the groups diverged could have implications; chronic subsyndromal mood symptoms may portend a severe, but ultimately non-bipolar, course. Longer follow-up is necessary to determine the trajectory and outcomes of CycD symptoms.

## Keywords

bipolar disorder; cyclothymic disorder; youth; longitudinal; diagnosis

Cyclothymic disorder (CycD) is a chronic and impairing subtype of bipolar disorder (BP), but it has been under-studied in children and adolescents (Van Meter & Youngstrom, 2012), resulting in a poor understanding of its clinical presentation and correlates. Related, it is rarely diagnosed clinically, though some epidemiological studies, of both youth and adults, suggest it may be the most prevalent form of BP (Angst et al., 2003; Lewinsohn, Klein, & Seeley, 1995; Merikangas et al., 2007).

In pediatric studies of BP, CycD is commonly combined with other presentations of BP that do not meet criteria for BP I or II, under the label “bipolar disorder not otherwise specified” (BP NOS). Research indicates that CycD can be reliably distinguished from other childhood disorders and, on some measures, from BP I and II (Van Meter, Youngstrom, Demeter, & Findling, 2012; Van Meter, Youngstrom, Youngstrom, Feeny, & Findling, 2011). However, characteristics that differ between CycD and BP NOS have not been described. The diagnostic criteria for CycD are defined in the DSM-5 (American Psychiatric Association, 2013), but they focus primarily on exclusions (e.g., never having met criteria for an episode of [hypo]mania or depression, not being symptom-free for more than two months), and require detailed reporting to determine duration. In contrast, BP NOS has loose criteria; namely manic symptoms that cause impairment, but do not meet criteria for any of the other BP subtypes. Understandably, when making a diagnosis, the majority of clinicians and research investigators choose BP NOS over CycD; the criteria are easier to apply and, because little work has been done to understand differences in etiology, prognosis, or treatment response, the added value of the complicated CycD diagnosis is not clear. This is not the case for other subtypes of BP; BP I indicates mania, a severe mood state that typically requires treatment with a mood stabilizing agent (Birmaher & Brent, 2007), whereas BP II is characterized by depression and hypomania, and may require a different treatment approach (Diler et al., 2017).

Across BP subtypes, long-term trajectories can vary widely; in the Course and Outcome of Bipolar Youth study (COBY; Axelson et al., 2006; Birmaher et al., 2006) those who met the COBY operationalized criteria for BP NOS (for criteria see Method section) at baseline

tended to follow one of three trajectories in the first five years of the study; 14% had achieved full or partial remission, 41% still met criteria for BP NOS, and 45% experienced a manic or depressive episode (Axelson et al., 2011). Other studies have similarly found that, over time, some youth with subsyndromal manic symptoms will experience remission, some will continue with the same presentation, and others will develop a manic or depressive episode (Cicero, Epler, & Sher, 2009; Martinez & Fristad, 2013). These results demonstrate the heterogeneous nature of the youth within the BP NOS category, but we do not know whether one reason for this heterogeneity is the inclusion of CycD cases in the BP NOS category.

Importantly, absence of evidence is not evidence of absence - although previous cross-sectional studies have indicated similarities between BP NOS and CycD in terms of phenomenology and impairment (Van Meter et al., 2012; Van Meter et al., 2011), little is known about whether trajectory or treatment response differ. There is some evidence that the difference could be meaningful; it may be that youth with BP NOS as a whole are more impaired than youth with CycD, given that they may experience episodes of major depression (Birmaher, Axelson, Strober, et al., 2009; Cosgrove, Roybal, & Chang, 2013; Van Meter, Henry, & West, 2013). On the other hand, youth with CycD experience chronic symptoms lasting at least a year. This chronicity may ultimately lead to impairment on par with the more intense symptoms experienced by youth with other subtypes of BP (Van Meter et al., 2017). It is also possible that this more chronic presentation portends a different life course, such as borderline personality disorder (BPD), which shares many features with CycD (Reich, Zanarini, & Fitzmaurice, 2011).

The goals of the present study are to: (1) examine the baseline prevalence, and new onset cases, of youth who meet research diagnostic criteria for cyclothymic disorder (RDCyc) in the COBY sample; (2) examine differences in baseline characteristics and outcomes between those in the RDCyc group and those who have operationalized BP NOS (at baseline), but never meet RDCyc criteria; and (3) determine whether diagnostic category at baseline (RDCyc or BP NOS) predicts the likelihood that a youth will experience an episode of depression, hypomania, or mania over the follow-up period.

We hypothesize that across the follow-up period, RDCyc youth will be less likely to experience a mood episode than the BP NOS youth (Van Meter et al., 2017). Related, we anticipate that youth who meet the RDCyc criteria will have less intense and/or fewer manic and depressive symptoms than youth with BP NOS, but that the RDCyc youth will be equally impaired due to the chronicity of their symptoms. Additionally, we expect that RDCyc youth will differ from BP NOS youth on the following baseline characteristics: family history of psychopathology (RDCyc will have higher prevalence of non-mood psychiatric illness, but no difference in family history of mania or depression; Van Meter et al., 2012; Van Meter et al., 2011) and medication (although in a previous study, there were no statistical differences, more than twice as many youth in the BP NOS group took a mood stabilizer, and 17% more took an antipsychotic than in the RDCyc group (Van Meter et al., 2017), consequently we expect the RDCyc youth to be less likely to be prescribed lithium or a mood stabilizer). We anticipate that the RDCyc and BP NOS youth will have similar age of BP onset (Van Meter et al., 2012; Van Meter et al., 2011), rates of comorbid disorders,

consistent with previous research on both adults and children (Van Meter et al., 2012; Van Meter, Youngstrom, & Findling, 2012), and rates of suicidal ideation and behavior (Van Meter et al., 2017).

## Method

### Participants

The methods for COBY have been described in detail previously (Axelson et al., 2006; Birmaher et al., 2006). Youths aged 7 to 17 years 11 months with DSM-IV diagnosis of BPI, BP II, or operationally defined BP NOS were recruited at three sites. For the present study, only those participants who were classified as BP NOS at baseline ($n$=154) were included. The operationalized criteria for BP NOS (at least two concurrent manic symptoms, three if the primary mood state was irritable, that represented a change in functioning; symptoms that lasted a minimum of four hours within a 24-hour period; at least four days - lifetime, not necessarily consecutive - during which the above criteria were met) would not preclude a diagnosis of CycD, because the criteria do not require a hypomanic episode. In contrast, those youth who were diagnosed with BP I or II would have experienced one or more mood episodes (mania, hypomania, and/or depression), which is an exclusion for CycD.

The operational definition of cyclothymic disorder was defined as: a score of 2, 3, or 4 on the Longitudinal Interval Follow-Up Evaluation (LIFE)(Keller, Lavori, Friedman, & et al., 1987) Psychiatric Status Rating (PSR) Depression scale, or a score of 3 or 4 on the PSR Hypomania scale for at least 26 of 52 consecutive weeks (at any point in the follow-up). This parallels the DSM criterion that “the hypomanic and depressive periods have been present for at least half the time,” (pg. 139) during the year-long symptomatic-period. Additionally, during the initial year-long symptomatic period, they could not have a period of eight or more consecutive weeks without symptoms, consistent with the DSM criterion that “individual has not been without the symptoms for more than two months at a time”(pg. 139). *Both* depression and hypomania had to be present for at least two weeks (not necessarily concurrent) during the 26-week period. Symptomatic weeks could not be preceded by an episode of hypomania, mania, or depression (based on summary report from the diagnostic interview about episodes prior to study enrollment, or based on a PSR score of 5 or 6 on Manic, Hypomanic, or Depression PSR scales during the follow-up period) because this would result in a diagnosis of BP I or II.

Participants and their parent(s) were scheduled to be interviewed every six months over the course of the follow-up. Retention through an eight-year follow-up was 75%. On average, participants were interviewed 10.46 times (SD=4.3), over an average follow-up period of 92 months (SD=19).

### Procedure

The Institutional Review Board of each study site reviewed and approved the study protocol. Informed consent/assent was obtained from all participants and their parent(s) at baseline. For the current study, summary scores of both participant and parent responses were used for all analyses.

### Measures.

Participants and their parents were interviewed at baseline using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997), the Kiddie Mania Rating Scale (MRS; Axelson et al., 2003) and the depression section of the KSADS-P (DRS), to assess for both current and lifetime psychiatric illnesses; kappas were >.80 (Birmaher, Axelson, Goldstein, et al., 2009). At each follow-up, the MRS and DRS were used to rate the current severity of manic and depressive symptoms.

Treatment history at baseline was collected using the Psychotropic Treatment Record of the LIFE (Keller et al., 1987), which indicated lifetime exposure to lithium, anti-psychotic medications, selective serotonin reuptake inhibitor (SSRI) antidepressants, and stimulant medications. Psychosocial treatment, including hospitalization, was assessed at baseline and follow-up via the LIFE Psychosocial Treatment Schedule.

At baseline, and at each follow-up, the participant's current, best past, and worst past, functioning were evaluated using the Children's Global Assessment Scale (C-GAS; Shaffer et al., 1983).

The socioeconomic status (SES) of each family was assessed at baseline (Hollingshead, 1975). The parent was interviewed at baseline about his/her own psychiatric history using the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995), and completed the Family History Screen (Weissman et al., 2000) about the psychiatric history of all of the participant's first and second degree relatives. This study focused on psychopathology in first-degree relatives.

Participants and parents were interviewed at each follow-up using the LIFE (Keller et al., 1987), which includes the PSR scale. The PSR facilitates a systematic assessment of symptoms on a week-by-week basis for the period since the last interview. The PSR has strong reliability for both percentage of time meeting diagnostic criteria for a mood episode (intraclass correlation [ICC] = 0.85) and for percentage of time without significant symptoms (ICC= 0.82). Reliability for PSR mood disorder ratings over the course of COBY have had an average Kendall's W of 0.8. Depressive and manic symptoms were scored on a six-point scale: scores of a 5 or 6 on the depression, manic, or hypomanic symptom scales were considered a "full" episode, and would exclude a youth from the RDCyc group.

Suicidal thoughts were also scored on a six-point PSR scale to indicate the seriousness of the thoughts (e.g., a 6 would indicate thoughts, plus a plan/preparations). Symptoms of anxiety disorders were also rated on a six-point scale. Symptoms of attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), alcohol use disorders (abuse or dependence), and substance use disorders (abuse or dependence) were rated on a three-point scale: 1 no symptoms, 2 subthreshold symptoms, 3 full diagnostic criteria. A PSR score of 3 would "count" as a comorbid disorder (Yen et al., 2015). Psychotic symptoms were also assessed; if hallucinations and/or delusions were present, psychosis over the follow-up was noted.

### Statistical analyses.

Using t-tests and chi square analyses, youth who met RDCyc criteria were compared to youth who met operationalized BP NOS criteria on baseline characteristics (demographics, comorbid disorders, family history of psychiatric illness, and medication use). Chi square analysis and t-tests evaluated differences in comorbid disorders, medication use, hospitalization, functioning, and presence of specific manic and depressive symptoms over the follow-up.

Differences in the course of illness were also assessed; cox regression, controlling for age, sex, and any characteristic on which the two groups were found to differ, measured whether there were differences in the time to a manic or depressive episode. Due to the potential for attrition to bias these results, we looked at time to the onset of a mood episode only through an eight-year follow-up, at which point retention remained strong.

In a previous publication examining an operationalized definition of cyclothymic disorder in youth (Van Meter et al., 2017), we applied more stringent criteria, requiring that youth be symptomatic for 44 of 52 weeks (allowing just two months total asymptomatic) and excluding any youth who experienced a mood episode ([hypo]manic or depressive) in the first year following the baseline appointment. As a sensitivity analysis, we also tested youth meeting this strict definition to the other youth in the sample.

## Results

DSM CycD was assessed as a diagnostic category only at baseline; 10 youth had a lifetime history of cyclothymic disorder, but eight of these had had an episode of [hypo]mania or depression prior to baseline, disqualifying them from a CycD diagnosis. There were 239 youth with a lifetime diagnosis of BP NOS at baseline (five of these also had a lifetime CycD diagnosis). Of those with a lifetime CycD diagnosis, 10% had a baseline diagnosis of BP II, and 20% had a baseline diagnosis of BP I. Among those with a lifetime BP NOS diagnosis (excluding those who also had a lifetime CycD diagnosis), 6% had a baseline diagnosis of BP II, 34% had a baseline diagnosis of BP I. These rates are not statistically different, $X^2(1)=0.87$, p=.350. See Figure 1.

One hundred fifty-four youth were enrolled with a current diagnosis of operationalized BP NOS (35% of the total COBY sample), 29 of these met the RDCyc criteria, due to weekly hypomanic and depressive symptoms for at least 26 of 52 consecutive weeks and no episode of [hypo]mania or depression prior to meeting the RDCyc criteria. Two of these youth met criteria based on their reported symptoms from prior to the baseline appointment, the remaining 27 met criteria at some point over the follow-up. Of these, the majority ($n$=18) met criteria during the first year of follow-up.

### Baseline comparisons

RDCyc youth were significantly younger (mean=10.83, SD=3.2) than the BP NOS youth (mean=12.22, SD=3.2; $p$=.039) and were more likely to be Hispanic ($X^2$=3.97, $p$=.046). Youth in the RDCyc group were less likely to have a comorbid anxiety disorder at baseline ($X^2$=5.81, $p$=.016). There were no other significant differences at baseline, see Table 1.

### Follow-up comparisons

Of the 154 participants, 13 did not return for any follow-up assessments, and are not included in the comparisons. All 13 were members of the BP NOS group. As a sensitivity analysis, youth who dropped out were compared to the other youth; prevalence of females was the only difference ($p$=.034).

Across the follow-up period, the RDCyc youth reported higher average "worst" functioning, based on the C-GAS, but there were no differences in the average "best" or "current" functioning. There were no significant group differences in time spent with hypomanic or depressive symptoms over the follow-up. Related, both groups were equally likely to experience mood symptom remission (defined as eight consecutive weeks of minimal, or non-existent, non-impairing symptoms; PSR 1 or 2). See Table 1.

Over follow-up, RDCyc youth were more likely to meet criteria for a disruptive behavior disorder (DBD; $p$=.014) than the BP NOS group. There was no difference in the presence of other comorbid disorders or in the number of youth who were hospitalized.

There were several differences in terms of specific mood symptoms in the month preceding each follow-up assessment, as assessed by the MRS and DRS. One hundred percent of the youth in the RDCyc group experienced accelerated speech, compared to 84% of BP NOS youth. Similarly, labile mood (97% RDCyc, 89% BP NOS), depressed mood (97% RDCyc, 88% BP NOS), depressive irritability (100% RDCyc, 95% BP NOS), mood reactivity (100% RDCyc, 92% BP NOS), and rejection sensitivity (97% RDCyc, 88% BP NOS) were all more common among youth in the RDCyc group.

### Onset of mood episodes

Youth with BP NOS were more likely to develop hypomania ($p$=.016), and major depression ($p$=.024). Additionally, in cox regression analyses, controlling for age, sex, and comorbid DBD, RDCyc was a significant predictor of longer time to a hypomanic ($Wald$=4.84 $p$=.028; $X^2(1)$=5.91, $p$=.015), manic ($Wald$=4.58, $p$=.032; $X^2(1)$=5.23, $p$=.022), or depressive episode ($Wald$=5.39, $p$=.020; $X^2(1)$=6.01, $p$=.014). See Figure 2.

### Alternative research diagnostic criteria

Nineteen youth met the stricter research diagnostic criteria requiring that 44 of 52 weeks be symptomatic and that no mood episode ([hypo]manic or depressive) occur in the first year following the baseline appointment. When these youth were compared to the others in the sample, the results were largely consistent with the differences we found comparing the RDCyc and BP NOS youth - as described above. The only notable exceptions were that the strict cyclothymic group was more likely to have comorbid ADHD ($p$=.012, in addition to DBD $p$=.054), and was less likely to be psychotic (p=.050) or to be prescribed an antidepressant ($p$=.041). Furthermore, the youth in the strict cyclothymic group were less likely to have a manic episode across the follow-up ($p$=.005), in addition to being less likely to have a depressive ($p$<.0001) or hypomanic episode ($p$=.022), as we found with the RDCyc group.

## Discussion

The purpose of this study was to apply RDCyc criteria to youth with subclinical manic symptoms (at baseline) in the COBY study, in order to evaluate potential differences in baseline characteristics and course of illness between the RDCyc and BP NOS youth. Results indicate that the RDCyc criteria do identify a unique, but small, group of youth who - although similar on most other characteristics - are less likely than BP NOS youth to develop hypomania or depression, and for those RDCyc cases that do develop a mood episode, it is likely to come later than in the BP NOS group. Still, it is important to note that the “current” and “best” C-GAS scores across follow-up were equivalent between groups, so although those youth who experienced clinical mood episodes might experience worse functioning in the short term, both groups experienced significant impairment. This is consistent with previous studies of CycD that have shown that youth with CycD experience impairment on par with other BP youth (Van Meter et al., 2012; Van Meter, Youngstrom, Youngstrom, Feeny, & Findling, 2011; Van Meter et al., 2017).

Impairment is also affected by comorbid disorders; the results indicating that the RDCyc youth experienced higher rates of DBD than the BP NOS youth was at odds with our hypotheses. Previous reports in the child literature have indicated higher comorbidity in BP NOS youth relative to CycD (Van Meter et al., 2017), or no difference (Van Meter et al., 2012; Van Meter et al., 2011). However, these other studies did not follow youth as long (two of these studies were cross-sectional), and the present result would be consistent with the adult literature, which suggests that people with CycD have more familial psychopathology (not necessarily mania), which could lead to greater comorbidity, in addition to more chronic, but less intense, mood symptoms. It is also possible that CycD is more difficult than BP NOS to differentiate from other childhood disorders, like behavior disorders, due to the chronic nature of the symptoms. This could result in “double counting” symptoms and artificially-inflated rates of comorbid disorders (Carlson & Klein, 2014).

Another goal of the present study was to determine whether youth in the RDCyc group would be more likely than BP NOS youth to experience symptom remission; multiple studies have shown diverse trajectories for youth with subsyndromal manic symptoms (D. A. Axelson et al., 2011; Cicero et al., 2009; Findling et al., 2013; Anna R. Van Meter et al., 2017). Although the trajectories of the youth in the present sample were consistent with these studies for the most part - some youth progressed to BP I or II, others continued with subsyndromal symptoms, and some improved - the RDCyc youth were not more likely to remit. This leaves open the question of what factors determine a youth’s course of illness.

We speculated that there might be differences evident at baseline that would help clinicians in differentiating RDCyc youth from BP NOS youth early on. We did not find evidence of group differences with clear clinical utility; the only variables that were significantly different were age and lifetime history of anxiety disorder. There is some evidence that anxiety is a precursor to bipolar disorder (Sala et al., 2010), which could make this a helpful difference. However, over follow-up, one hundred percent of the youth in the sample developed an anxiety disorder, suggesting that differences in the presence of anxiety are likely to be of little utility. In addition to being younger at baseline, the RDCyc were also

younger when their symptoms started (a medium effect of $d$=.39, although the $p$-value was .058). These may be confounded; if the RDCyc group was younger at enrollment, it follows that average age of onset would also be younger. However, this suggests that RDCyc youth may experience mood symptoms at an earlier age. Although, in this sample, we did not find differences in family history of mania, other studies have shown that a family history of mania is related to earlier BP onset and a more pernicious course of illness (Birmaher et al., 2010; Johnson, Andersson-Lundman, Åberg-Wistedt, & Mathé, 2000; Post et al., 2008). This trajectory - impairing and unremitting - is consistent with the adult literature on CycD, which describes significant impairment, poor treatment response, and unremitting symptoms (Howland & Thase, 1993; Giulio Perugi, Hantouche, Vannucchi, & Pinto, 2015; Van Meter et al., 2012).

It was surprising that the number of weeks spent hypomanic or depressed was consistent across the two groups. Although the majority (79%) of youth in the BP NOS group experienced a mood episode over the course of follow-up, disqualifying them from the RDCyc diagnosis, many also experienced chronic mood symptoms consistent with a cyclothymic presentation. Previous work has shown that youth in the COBY BP NOS group spend a high number of days ill (Birmaher, Axelson, Goldstein, et al., 2009), suggesting that subsyndromal symptoms may be chronic by nature. Some have speculated that this is due to poorer treatment response, relative to BP I, among youth with subsyndromal subtypes of BP (Birmaher, Axelson, Goldstein, et al., 2009; Birmaher et al., 2006). It is also interesting to note that although the research diagnostic criteria we used were fairly lenient, requiring only 26 of 52 weeks symptomatic, the majority of the RDCyc youth had cyclothymic episodes that exceeded the stricter criterion of 44 weeks. Related, when we compared the youth meeting the strict diagnostic definition (44+ weeks, no mood episode year one) to the rest of the sample, our results were mostly consistent with what we found when comparing the RDCyc group to the rest of the sample.

We hypothesized that the RDCyc youth would be less likely to be treated with anti-manic agents, including lithium, but this was not the case. RDCyc and BP NOS youth were equally likely to have a manic episode, and spent a similar amount of time hypomanic, so perhaps the lack of difference in treatment for mania should not be surprising. However, RDCyc youth were less likely to have a hypomanic episode over the follow-up (i.e., the proportion of youth who had a [hypo]manic episode was higher in the BP NOS group), suggesting that treatment may be guided as much by impairment as by the intensity of the symptoms. Another factor may be that anti-manic agents are often prescribed to help with other symptoms, such as irritability and tantrums (Pringsheim, Panagiotopoulos, Davidson, & Ho, 2011; Scotto Rosato et al., 2012), which could increase the number of prescriptions among RDCyc youth who have high rates of comorbid DBD. It was unexpected that although both groups spent more days depressed than hypomanic, more youth were prescribed lithium or an atypical antipsychotic than an antidepressant. Though this may be evidence of the effectiveness of anti-manic agents - particularly relative to the sparse data on the effectiveness of antidepressants for bipolar depression (Goldsmith, Singh, & Chang, 2011) - it may also be indicative of concern about antidepressant-coincident mania. Although evidence that antidepressant use plays a causal role in the onset of mania is minimal (Joseph, Youngstrom, & Soares, 2009) and treatment guidelines include the use of antidepressants (in

conjunction with a mood stabilizer)(Kowatch et al., 2005), clinicians may be reluctant to use this class of medication.

The result that the RDCyc group reported more intense depressive irritability was consistent with research on both adults and children with CycD showing that irritability is a key characteristic of the illness (Akiskal, Djenderedjian, Rosenthal, & Khani, 1977; Hantouche & Perugi, 2012; Prakash & Mitra, 2008; Shen, Alloy, Abramson, & Sylvia, 2008; Van Meter et al., 2016; Van Meter et al., 2012). Related, the fact that rejection sensitivity was more common in the RDCyc group is consistent with evidence suggesting that people with CycD struggle interpersonally. Another - perhaps more controversial - interpretation of this finding could be that these youth are more likely to have a presentation consistent with BPD, rather than (or in addition to) BP. There has been speculation that BPD and BP exist on a continuum, and that the differences between the disorders are more theoretical (e.g., etiology of the illness) than clinical (Perugi, 2006; Giulio Perugi et al., 2015). Although historically, personality disorders have been diagnosed only in adults, the validity of the diagnosis in youth is gaining support (Miller, Muehlenkamp, & Jacobson, 2008; Winsper et al., 2016). In a previous paper, the presence of BPD in a subset of the COBY sample was examined (Yen et al., 2015); the results suggested that although BPD was fairly prevalent (12%), it was not more likely among any particular subtype of BP (I, II or NOS). When baseline characteristics were compared between the BPD+ and the BPD- groups, only internalizing symptoms (depression and anxiety) varied. In our study, we found inconsistent differences in internalizing symptoms between RDCyc and BP NOS, limiting the degree to which we can predict differences in in the prevalence of BPD between the RDCyc+ and RDCyc- groups. Related, in the COBY BPD paper, suicidal and self-injurious behaviors were higher in the BPD+ group, but we found no difference in these outcomes in our two groups. Further exploring the prevalence of BPD among young people is important, and even more crucial is investigating, longitudinally, whether some youth with subclinical manic symptoms meet criteria for BPD as the grow up, but never meet criteria for a [hypo]manic or depressive episode. This could help us to understand whether childhood mood lability is a risk factor for BPD, or an early expression of the illness. CycD and BPD are currently conceptualized as similar, but separate, illnesses with different expected outcomes and treatment strategies; gaining a better understanding of the etiology and early course of each is important to informing this conceptualization and future research.

## Limitations

Although the COBY sample offers a unique opportunity to study differences in CycD and BP NOS, there are some limitations. First, because the diagnosis of CycD was not included in the diagnostic categories assigned following the baseline appointment, the RDCyc diagnoses were based on symptom reports. The level of detail recorded supports this approach, but the BP NOS diagnoses and RDCyc diagnoses were not made with the same process. Related, the BP NOS criteria used in COBY are operationalized, whereas DSM-IV criteria are not. This - particularly in combination with the operationalized cyclothymic disorder criteria - may highlight differences that, under typical clinical conditions and more vague criteria, would not be evident. The conclusions we can draw are also limited by the small number of people who met the RDCyc criteria; it is possible that we did not have

adequate power to capture the effects that we were looking for, but as one of only two longitudinal studies (both secondary analyses) attempting to explore the course of cyclothymic disorder in youth, we believe these results can inform future studies designed to answer questions related to the phenomenology and course of youth with cyclothymic disorder, and how the disorder compares to other bipolar subtypes. Additionally, COBY is a naturalistic study and medication use was not controlled; however, there were no medication differences noted in follow-up treatment between the groups.

A primary aim of the study was to determine whether BP NOS youth would be more likely to develop mania or depression; although the participants were followed, on average, for more than seven years, it is possible that some will still develop mania or depression. Related, there were more participants in the BP NOS group who dropped out. Though it is possible that these youth dropped out because they were more ill (or some other clinical reason), there were no meaningful differences at baseline to suggest this. Finally, participants were recruited from three academic medical centers and were predominantly White, which may limit the generalizability of the results. Nevertheless, course and morbidity in non-clinically referred BP youth have been shown to be similar to those among referred populations (Lewinsohn et al., 1995).

## Conclusion

The RDCyc criteria identified youth who, although similar to the BP NOS youth at baseline, showed a distinct trajectory less likely to result in a hypomanic or depressive episode. Additionally, the RDCyc youth were more likely to experience irritability, mood reactivity, and rejection sensitivity over the follow-up, raising questions about whether these youth might be at risk for developing BPD. To date, no study has followed youth with CycD into adulthood; continuing to follow participants in COBY, along with other longitudinal cohorts (Van Meter et al., 2017) and new samples of youth with subsyndromal mania, will help to clarify the long-term prognosis for these youth.

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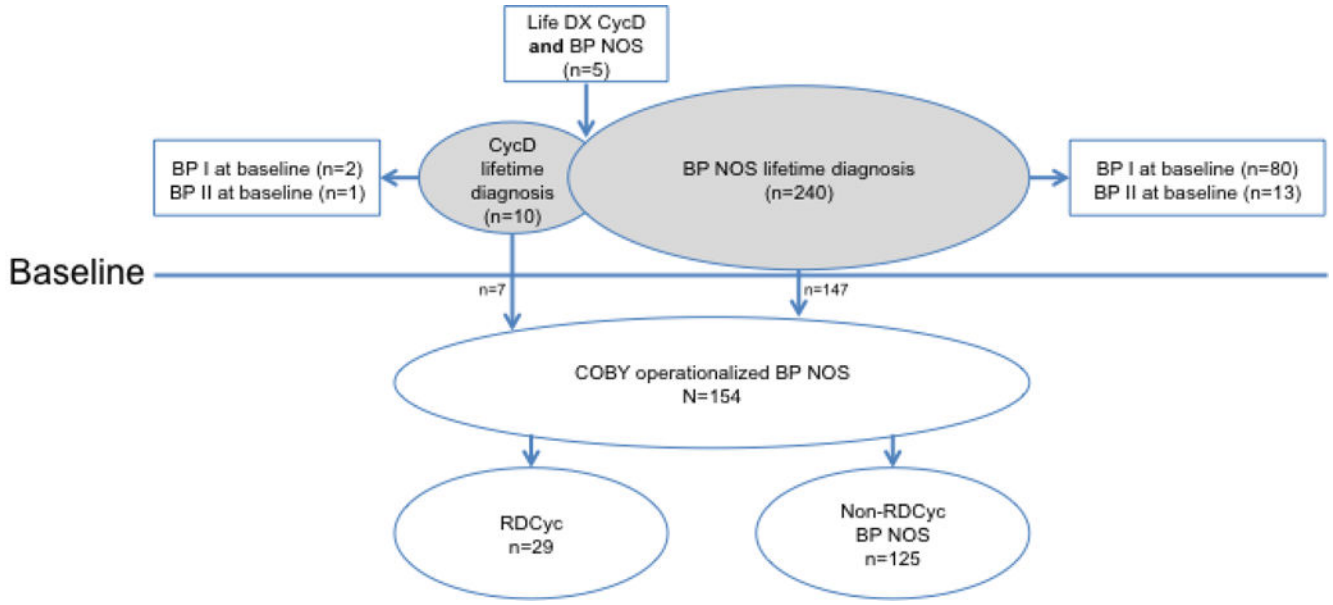


**Figure 1.**
Model of diagnostic categorization

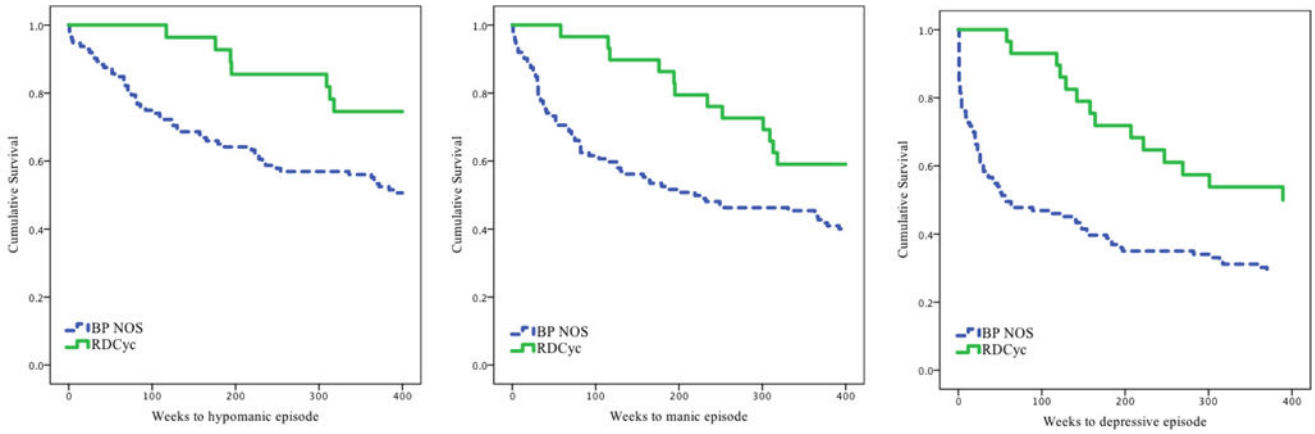


**Figure 2.**

Cox regression plots indicating the difference in the duration of symptoms, following baseline, prior to the onset of a hypomanic, manic, or depressive episode, respectively, for Bipolar Disorder Not Otherwise Specified (BP NOS) and Research Diagnosis of Cyclothymic Disorder (RDCyc). Note: Analyses control for age, sex, and disruptive behavior disorder diagnosis.

**Table 1.**

Characteristics of Research Diagnostic Cyclothymic Disorder (RDCyc) and Operationalized Bipolar Disorder Not Otherwise Specified (BP NOS)

| | **RDCyc** | **BP NOS** | |
|---|---|---|---|
| | n=29 | n=125 | |
| **Characteristics at Baseline** | Mean (SD) | | *Cohen's d* |
| SES (Hollingshead Four Factor Index) | 3.45(1.2) | 3.45(1.1) | 0 |
| Age | 10.83(3.2) | 12.22(3.2) | −0.43* |
| Age at illness onset | 7.60(3.7) | 9.02(3.6) | −0.39 |
| Duration of illness | 3.53(2.05) | 4.26(3.0) | −0.29 |
| C-GAS Score | 56.45(8.39) | 57.08(11.6) | −0.06 |
| Number of Comorbid Disorders | 3.31(1.5) | 3.71(1.7) | −0.25 |
| | Percent | | *W* |
| Percent female | 45 | 41 | 0.03 |
| Percent White | 79 | 83 | 0.04 |
| Percent Hispanic | 10 | 2 | 0.16 |
| Lifetime history of suicidal ideation | 66 | 73 | 0.06 |
| Lifetime history of suicide attempt | 10 | 23 | 0.12 |
| Lifetime history of self injury | 21 | 34 | 0.12 |
| Lifetime history of ADHD | 72 | 59 | 0.11 |
| Lifetime history of anxiety disorder | 24 | 49 | 0.19* |
| Lifetime history of ODD or CD | 48 | 50 | 0.01 |
| Lifetime history of Psychosis | 17 | 11 | 0.07 |
| Lifetime history of alcohol use disorder | 3 | 5 | 0.03 |
| Lifetime history of substance use disorder | 3 | 10 | 0.09 |
| 1st degree relative history of mania | 28 | 28 | 0.02 |
| 1st degree relative history of depression | 66 | 72 | 0.09 |
| 1st degree relative history of non-mood psychopathology | 79 | 80 | 0.01 |
| Any current medication | 97 | 83 | 0.15 |
| Lithium | 10 | 14 | 0.04 |
| Atypical antipsychotic | 41 | 34 | 0.06 |
| SSRI anti-depressant | 17 | 26 | 0.08 |
| Stimulant | 41 | 26 | 0.13 |
| | **n=29** | **n=112** | |
| **Characteristics across Follow-up** | Mean (SD) | | *Cohen's d* |
| Average "worst" C-GAS | 52.41(7.1) | 46.15(8.9) | 0.78** |
| Average "best" C-GAS | 64.70(7.0) | 64.28(9.1) | 0.05 |

| | RDCyc | BP NOS | |
|---|---|---|---|
| Average “current” C-GAS | 62.38(7.6) | 60.47(8.7) | 0.23 |
| Total weeks depressed | 191.00(97.5) | 164.94(112.8) | 0.25 |
| Total weeks hypomanic | 120.97(80.0) | 117.39(96.2) | 0.04 |
| | Percent | | *W* |
| Hypomanic episode | 24 | 49 | 0.20* |
| Manic episode | 24 | 26 | 0.02 |
| Depressive episode | 48 | 71 | 0.19* |
| Remitted at some point | 90 | 79 | 0.11 |
| Suicidal ideation | 93 | 95 | 0.03 |
| Suicide attempt | 7 | 26 | 0.02 |
| Comorbid ADHD | 83 | 67 | 0.14 |
| Comorbid anxiety | 100 | 100 | - |
| ODD or CD | 83 | 58 | 0.21* |
| Psychosis | 3 | 13 | 0.13 |
| Alcohol use disorder | 10 | 21 | 0.10 |
| Substance use disorder | 0 | 0 | - |
| Lithium | 21 | 28 | 0.06 |
| Atypical antipsychotic | 48 | 47 | 0.01 |
| SSRI anti-depressant | 24 | 34 | 0.09 |
| Stimulant | 48 | 37 | 0.10 |
| Hospitalization | 24 | 31 | 0.06 |

* $p<.05$

[a] Defined as a PSR score of 3 or 4 on the Hypomania scale

[b] Defined as a PSR score of 2, 3, or 4 on the Depression scale

SES = Socioeconomic Status; C-GAS = Children’s Global Assessment Scale; ADHD = Attention Deficit Hyperactivity Disorder; ODD = Oppositional Defiant Disorder; CD = Conduct Disorder; SSRI = Serotonin Selective Reuptake Inhibitor