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Original Article

Phenomenology of bipolar disorder not otherwise specified in youth: a comparison of clinical characteristics across the spectrum of manic symptoms

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Objectives: Controversy surrounds the diagnostic categorization of children with episodic moods that cause impairment, but do not meet DSM-IV criteria for bipolar I (BD-I) or bipolar II (BD-II) disorder. This study aimed to characterize the degree to which these children, who meet criteria for bipolar disorder not otherwise specified (BD-NOS), are similar to those with full syndromal BD, versus those with no bipolar spectrum diagnosis (no BSD).

Methods: Children aged 6–12 years were recruited from nine outpatient clinics, preferentially selected for higher scores on a 10-item screen for manic symptoms. Interviews with the children and their primary caregivers assessed a wide array of clinical variables, as well as family history.

Results: A total of 707 children [mean ± standard deviation (SD) 9.4 ± 1.9 years old] were evaluated at baseline, and were diagnosed with BD-I (n = 71), BD-II (n = 3), BD-NOS (including cyclothymia; n = 88), or no BSD (n = 545). Compared to BD-I, the BD-NOS group had less severe past functional impairment. However, current symptom severity and functional impairment did not differ between BD-NOS and BD-I, even though both groups were significantly more symptomatic and impaired than the no BSD group. Parental psychiatric history was similar for the BD-NOS and BD-I groups, and both were more likely than the no BSD group to have a parent with a history of mania. Rates of elated mood did not differ between BD-NOS and BD-I youth.

Conclusions: Children with BD-NOS and BD-I are quite similar, but different from the no BSD group, on many phenomenological measures. These findings support the hypothesis that BD-NOS is on the same spectrum as BD-I.

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While full syndromal bipolar disorder (BD) [bipolar I (BD-I) or bipolar II (BD-II) disorder] is relatively rare in children and adolescents, a much larger proportion of youth have a range of subsyndromal spontaneously episodic mood disturbances, and even more have non-specific manic-type symptoms (1–8). In both adolescents and adults, even

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mild subsyndromal manic symptoms have been shown to have important clinical implications, including a more severe clinical course and a poor response to antidepressants (9–14). An important diagnostic question is the degree to which these presentations represent a spectrum of bipolarity, versus distinct disorders with unique clinical characteristics and trajectories (15, 16).

Many studies have focused on the clinical characteristics, family history, and trajectory of youth with subsyndromal episodic mood disturbances. Overwhelmingly, this work has indicated that these youth have significant functional impairment, comparable with the degree of impairment seen in major depression or even BD-I and BD-II (6, 13, 17, 18). However, there is disagreement about whether these youth truly have a variant of BD that will indeed progress to a full syndromal presentation, and should be treated as such (19, 20). For example, while clinical samples indicate a high rate of progression from subsyndromal BD to BD-I or BD-II (on the order of 45% in five years) (12), epidemiologic samples have a much lower degree of progression (18, 21). Much of this variability likely reflects methodological differences in the assessment of subsyndromal bipolar symptomatology across clinical and epidemiologic studies (22), as well as the degree of functional impairment in these populations (23).

In an effort to identify youth with episodic mood disturbances who did not meet full criteria for BD-I or BD-II, Axelson et al. (24) operationalized criteria for bipolar disorder not otherwise specified (BD-NOS) which were then used to recruit participants for the Course and Outcome of Bipolar Youth (COBY) study. To meet the criteria for BD-NOS, participants had to have at least four lifetime days (not necessarily consecutive) with at least four hours of either (i) elated mood plus two associated manic symptoms or (ii) irritable mood plus three associated manic symptoms. Episodic mood disturbances had to be associated with a clear change in functioning, could not meet full criteria for a manic or hypomanic episode, and could not be mainly accounted for by other disorders. (This category includes youth who meet DSM-IV criteria for cyclothymia.) Using these criteria, several important findings from the COBY study have emerged. Youth with BD-NOS were shown to have a large degree of functional impairment, and a high rate of family history of BD (24). Additionally, subsyndromal and syndromal manic episodes did not significantly differ according to particular symptoms, such as elated versus irritable mood (24). Finally, longitudinal follow-up has indicated a high rate of progression from BD-NOS to BD-I or BD-II (45% in five years), with family history being the primary predictor of this progression (12, 25, 26).

These data indicate that BD-NOS and BD-I are likely to be along a spectrum of disorder; however, the question remains whether these results would also apply to a more broadly defined population of youth with non-specific (and in many cases non-episodic) manic-type symptoms. The Longitudinal Assessment of Manic Symptoms (LAMS) study provides an ideal population in which to test the degree to which the COBY findings extend to a clinically recruited population with less episodic manic-type symptoms. The LAMS study recruited eligible youth from nine outpatient clinics, disproportionately selecting youth with manic symptoms which were not necessarily episodic (27, 28). At study entry, less than one-quarter of the youth fit criteria for bipolar spectrum disorders (BSDs), defined as BD-I, BD-II, or BD-NOS (using COBY criteria, which includes cyclothymia).

Based on previous work, we predicted that youth with BD-NOS and BD-I (who, by definition, have distinct episodes of manic symptoms) would share several clinical characteristics, phenomenology, and family history, and that these groups would differ from youth with no BSD (who do not have distinct episodes of manic symptoms). Specifically, this paper tested the following hypotheses: (i) we predicted that the BD-NOS and BD-I groups would both have significant functional impairment, and that both groups would be more impaired than a group with no BSD; (ii) we predicted that BD-NOS and BD-I would show similar comorbidity, but would differ from the group with no BSD; and (iii) we predicted that, compared to the no BSD group, the BD-NOS and BD-I groups would have an elevated parental history of mania. Finally, we conducted an exploratory analysis to assess whether phenomenology of manic symptomatology (determined by individual characteristics, such as elated versus irritable mood) qualitatively differed between those with BD-I and BD-NOS.

Patients and methods

Participants

Details of the methods used in the LAMS study have been described elsewhere (28). Briefly, this study recruited participants through a two-stage approach, designed to select for elevated symptoms of mania (ESM). A total of 3329 children (ages 6 years to 12 years and 11 months) were invited to participate in initial screening; these youth were recruited from nine outpatient clinics in Pittsburgh

(PA, USA) and Cincinnati, Columbus, and Cleveland (OH, USA) that were associated with participating universities. Inclusion criteria were: (i) age within the specified range and (ii) both child and parent spoke English. Exclusion criteria were: (i) having a prior visit to a participating outpatient clinic in the past year or (ii) having a sibling already enrolled in the study.

Parents of 2622 eligible youth agreed to participate, and completed the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M) (29), a validated screen for ESM. This scale consists of ten items scored on a scale of 0–3. Based on their score, children were classified as ESM+ (score $\geq$ 12) or ESM− (<12). All of the ESM+ children (n = 1124) were invited to participate; n = 621 agreed and completed a full assessment. For every 10 ESM+ children recruited, one ESM− youth was asked to participate (the ratio was 5:1 at clinics with a low volume); these ESM− subjects (n = 86) were matched to the modal ESM+ child at the time of recruitment on demographic factors, and sampled with replacement. The threshold of 12+ was selected because it was high enough to enrich the cohort for youth with manic symptoms, but low enough to be only moderately diagnostically specific, resulting in a study sample with a heterogeneous mix of presentations.

Assessment

Baseline assessments gathered demographic data on participants, including age, sex, race, ethnicity, and health insurance. Data were also collected on indicators of socioeconomic status (parents' education and employment status) and living situation (with both parents versus not). A complete list of current and past psychotropic medications was also obtained from the parent/guardian. The Family History Screen (FHS) (30) collected information on 15 psychiatric disorders and suicidal behavior in biological parents.

Interviewers assessed DSM-IV diagnoses by completing an augmented version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Episode (KSADS-PL) (31) with youths and their parents/guardians. Additional data regarding depression and manic symptoms were collected using items derived from the Washington University Kiddie Schedule for Affective Disorders (WASH-U-KSADS) (32), augmented with items to screen for pervasive developmental disorders. The KSADS Depression Rating Scale (KDRS) and KSADS Mania Rating Scale (KMRS) provided filtered ratings of mood symptoms, meaning that symptom severity was measured exclusively in the context of a mood episode. These ratings were collected for the two-week period preceding baseline and for the most severe episode in the past.

Criteria for BD-NOS were derived from the Course Outcome of Bipolar Youth (COBY) study (26). These included: (i) a distinctive period of abnormally elated, irritable, or expansive mood plus two associated manic symptoms (three if mood is irritable); (ii) an associated clear change in functioning; (iii) episodes lasting at least four hours in a 24-hour period for $\geq$4 lifetime days (not necessarily consecutive); and (iv) the child did not meet criteria for BD-I or BD-II. Note that these criteria would include participants diagnosed with cyclothymic disorder (14, 33). DSM-IV-TR criteria were used to diagnose BD-I and BD-II, as well as other psychiatric disorders. All diagnoses were confirmed by a licensed child psychiatrist or psychologist.

The Young Mania Rating Scale (YMRS) (34, 35) and the Children's Depression Rating Scale-Revised (CDRS-R) (36) were also used to assess unfiltered mood symptoms at baseline. These scales were rated independent of mood state (in a *'what you see is what you get'* format). The Children's Global Assessment Scale (CGAS) (37) was used to provide a quantitative evaluation of the child's function (at home, at school, and with peers). Data on global functioning were obtained for the two-week period preceding data collection, as well as the past two-week period with the most severe functional impairment.

Interviewer training and reliability of assessments

Interviewers were trained during an initial three-day meeting, followed by rating assessments along with taped interviews; interviewers then administered the assessment instruments. To minimize rater drift, interviewers rated taped administrations of the KSADS throughout the data collection period. Kappa for all psychiatric diagnoses using this instrument was 0.82; the kappa for BSD was 0.93 (27).

Statistical analyses

All analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC, USA). First, unadjusted analyses were conducted. Subsequently, analyses were adjusted for demographic variables associated with BD diagnosis, using a cut-off p-value of <0.2 to ensure that no confounding variable was missed in the adjustment. For continuous variables, an analysis of variance (ANOVA) was initially used to

assess differences between the BD-NOS, BD-I, and no BSD groups. A generalized linear model (PROC GLM) was used to yield quantitative estimates of differences in means, with 95% confidence intervals, and conduct covariate-adjusted analyses. Effect sizes (Cohen's *d*) were calculated to assess quantitative differences on clinical scales between groups (38). For categorical variables, chi-square tests were used to determine unadjusted differences between the BD-NOS, BD-I, and no BSD groups. Covariate-adjusted differences were assessed using PROC GENMOD (log link, binomial distribution). PROC GENMOD also yielded quantitative estimates of differences (prevalence ratios), with 95% confidence intervals. When adjusted models did not converge (due to small numbers in a particular cell), unadjusted models were used. To determine whether observed differences between youth with and without BSD were due to the ESM− youth in the latter group, we re-ran analyses excluding those children without ESM. We also assessed the reasons that youth with BD-NOS did not meet criteria for manic episodes, and were thus not classified as BD-I.

To avoid inflating the type II error risk, results were generally not corrected for multiple corrections. However, to better assess differences in manic symptomatology between BD-NOS and BD-I, we indicate which of the uncorrected p-values would retain significance upon correction for multiple comparisons using the false discovery rate (FDR) correction.

Results

Demographics

Of the 707 study participants, 71 met criteria for BD-I, 88 met those for BD-NOS (11 of whom also satisfied DSM-IV criteria for cyclothymic disorder), and three met those for BD-II at intake; 545 did not meet criteria for a BSD. Because of the small number of youth with BDI-II, these participants were excluded from further analyses, leaving a total of 704 participants for the analyses below.

Basic demographic characteristics of the study population are shown in Table 1. Youth with BSD were slightly older than those without a bipolar diagnosis ($p = 0.01$); there was no difference in age between the youth with BD-NOS and those with BD-I. There was also no significant difference between the BD-NOS and BD-I groups in regard to the duration or onset date of BSD. Two-thirds (68%) of the overall cohort were male; however, the BD-NOS group had a lower percentage of male subjects than the no BSD group (51% versus 71%, respectively). Both race and parental employment status differed across diagnoses. Children with BD-I were more likely to be white and have at least one employed parent compared to those with BD-NOS or no BSD. One-third (32%) of all participants were living with both natural parents; this proportion did not differ across diagnostic groups.

Symptom severity and functional impairment

Both the BD-NOS and BD-I groups had more mood symptoms at baseline than the children with no BSD, as measured by the KDRS, KMRS, YMRS, and CDRS-R at intake (all $p < 0.0001$) (Table 2). Interestingly, these scores did not differ between youth with BD-NOS and those with BD-I at baseline. When comparing symptom severity during the most severe episode, youth with BD-NOS had lower KMRS scores compared to those with BD-I, while both groups had significantly elevated scores compared to youth with no BSD.

A similar pattern was seen with estimates of global function, as quantified by the CGAS. At baseline, both the BD-NOS and BD-I groups had impaired function, as compared to the children with no BSD ($p < 0.0001$). However, when asked about the most severe period, children with BD-NOS were significantly less impaired than those with BD-I, while both groups were significantly more impaired than those with no BSD.

Comorbidity

Rates of comorbidity were quite high in this clinically recruited cohort (Table 3). Attention-deficit hyperactivity disorder (ADHD) showed the highest rate of comorbidity. Two-thirds of the cohort had this diagnosis; rates did not differ across diagnostic groups. Anxiety was found in 29% of our cohort; again, rates did not differ across groups. Disruptive behavioral disorders were also very common, particularly oppositional defiant disorder (ODD), which was found in 37% of the cohort. Conduct disorder was more common in those with BD-NOS and BD-I, as opposed to no BSD. ODD was less common in the BD-I group, as compared to both BD-NOS and no BSD. Pervasive developmental disorder was fairly rare in this sample (6%), and no youth with BD-NOS were found to have this disorder.

Phenomenology and treatment history

Table 3 shows associated severe phenomenological features. Approximately 19% of the youth in this cohort had a history of suicidal ideation, while 2%

Table 1. Demographic characteristics[a]

	All subjects (n = 704)	BD-NOS (n = 88)	BD-I (n = 71)	No BSD (n = 545)	Statistic	p-value	BD-NOS versus BD-I (95% CI)	BD-NOS versus no BSD (95% CI)	BD-I versus no BSD (95% CI)	Sensitivity analysis (p-value[b])
Demographics										
Age, years, mean ± SD	9.4 ± 1.9	9.8 ± 2.1	9.8 ± 2.1	9.3 ± 1.9	$F = 4.28$	**0.014**	0.06 (−0.55, 0.66)	**0.53 (0.10, 0.96)**	**0.48 (0.00, 0.95)**	**0.028**
Sex, % male	67.8	51.1	64.8	70.8	$\chi^2 = 13.8$	**0.001**	0.79 (0.60, 1.03)	**0.72 (0.58, 0.89)**	0.91 (0.76, 1.09)	**0.011**
Race, % white	64.2	62.5	77.5	62.8	$\chi^2 = 6.04$	**0.05**	**0.81 (0.66, 0.99)**	1.00 (0.84, 1.18)	**1.23 (1.07, 1.42)**	**0.0005**
Ethnicity, % Hispanic	4.4	3.4	7.0	4.2	$\chi^2 = 1.42$	0.49	0.47 (0.11, 2.02)	0.80 (0.24, 2.73)	1.72 (0.63, 4.68)	0.76
Socioeconomic status/family characteristics,%										
≥ 1 parent has college degree	39.5 (277/702)	31.8	54.9	38.7 (210/543)	$\chi^2 = 11.2$	**0.004**	**0.58 (0.40, 0.84)**	0.82 (0.59, 1.13)	**1.42 (1.12, 1.80)**	**0.027**
≥ 1 parent employed	79.9 (561/702)	81.8	85.9	78.8 (428/543)	$\chi^2 = 2.20$	0.33	0.95 (0.83, 1.09)	1.04 (0.93, 1.16)	1.09 (0.98, 1.21)	0.14
Living with both natural parents	32.3 (223/690)	36.4	32.9 (23/70)	31.6 (168/532)	$\chi^2 = 0.80$	0.67	1.11 (0.72, 1.71)	1.15 (0.85, 1.56)	1.04 (0.73, 1.49)	0.53
BSD characteristics, mean ± SD										
Age of onset, years	6.7 ± 2.8 (n = 156)	6.8 ± 2.8 (n = 85)	6.5 ± 2.8	–	$F = 0.08$[c]	0.77	0.12 (−0.69, 0.93)	–	–	–
Duration, years	3.1 ± 2.5 (n = 156)	2.9 ± 2.4 (n = 85)	3.2 ± 2.7	–	$F = 0.08$[c]	0.77	−0.12 (−0.93, 0.70)	–	–	–

BD-I = bipolar I disorder; BD-NOS = bipolar disorder not otherwise specified; BSD = bipolar spectrum disorder; CI = confidence interval; SD = standard deviation.

[a]For categorical variables, prevalence ratios (with 95% CI) are presented. For continuous variables (age), difference in means (with 95% CI) is shown. Significant differences across bipolar diagnosis are shown in **bold**.

[b]p-value after excluding ESM− participants (elevated symptoms of mania <12) from the analysis.

[c]Adjusted for age, gender, race, and parental education.

Table 2. Clinical scales[a]

	All subjects (n = 704)	BD-NOS (n = 88)	BD-I (n = 71)	No BSD (n = 545)	Statistic (*F*)	p-value	BD-NOS versus BD-I (p-value)	BD-NOS versus no BSD (p-value)	BD-I versus no BSD (p-value)	Sensitivity analysis (p-value[b])
Symptom severity										
KDRS at baseline	6.9 ± 6.0	10.1 ± 6.2	8.8 ± 6.6	6.1 ± 5.6	16.2[c]	**<0.0001**	0.20 (0.22)	**0.59 (<0.0001)**	**0.39 (0.002)**	**<0.0001**
KMRS at baseline	9.8 ± 8.9 (n = 703)	20.5 ± 7.4	20.9 ± 10.8	6.6 ± 5.9 (n = 544)	266[c]	**<0.0001**	−0.03 (0.85)	**2.07 (<0.0001)**	**2.11 (<0.0001)**	**<0.0001**
KMRS: most severe	10.9 ± 9.4 (n = 701)	21.9 ± 5.8 (n = 87)	26.5 ± 7.3 (n = 70)	7.1 ± 6.1 (n = 544)	449[c]	**<0.0001**	**−0.73 (<0.0001)**	**2.37 (<0.0001)**	**3.10 (<0.0001)**	**<0.0001**
YMRS at baseline	16.7 ± 9.2	25.2 ± 7.5	25.9 ± 10.5	14.2 ± 7.5	131[c]	**<0.0001**	−0.08 (0.62)	**1.43 (<0.0001)**	**1.51 (<0.0001)**	**<0.0001**
CDRS-R at baseline	37.1 ± 11.6	39.8 ± 10.7	37.1 ± 11.6	33.6 ± 10.4	12.3[c]	**<0.0001**	0.26 (0.11)	**0.54 (<0.0001)**	**0.28 (0.02)**	**<0.0001**
Functional impairment										
CGAS at baseline	54.6 ± 10.3 (n = 700)	51.3 ± 8.6 (n = 87)	50.9 ± 10.5 (n = 70)	55.5 ± 10.4 (n = 543)	14.1[c]	**<0.0001**	0.09 (0.57)	**−0.44 (0.0002)**	**−0.53 (<0.0001)**	**<0.0001**
CGAS: most severe lifetime	49.1 ± 9.9 (n = 403)	46.9 ± 7.7 (n = 51)	43.2 ± 9.9 (n = 55)	50.6 ± 9.8 (n = 297)	15.5[c]	**<0.0001**	**0.42 (0.03)**	**−0.36 (0.02)**	**−0.79 (<0.0001)**	**<0.0001**

BD-I = bipolar I disorder; BD-NOS = bipolar disorder not otherwise specified; BSD = bipolar spectrum disorder; CDRS-R = Children's Depression Rating Scale–Revised; CGAS = Children's Global Assessment Scale; CI = confidence interval; KDRS = Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS) Depression Rating Scale; KMRS = K-SADS Mania Rating Scale; YMRS = Young Mania Rating Scale.

[a]Effect sizes (Cohen's *d*) are calculated across bipolar diagnosis; significant differences are shown in **bold**.

[b]p-value after excluding ESM− participants (elevated symptoms of mania <12) from the analysis.

[c]Adjusted for age, gender, race, and parental education.

Table 3. Comorbidities and clinical features[a]

	All subjects (n = 704)	BD-NOS (n = 88)	BD-I (n = 71)	No BSD (n = 545)	Statistic	p-value	BD-NOS versus BD-I (95% CI)[b]	BD-NOS versus no BSD (95% CI)[b]	BD-I versus no BSD (95% CI)[b]	Sensitivity analysis (p-value)[c]
Lifetime history of comorbid disorders										
Anxiety	29.1	27.3	29.6	29.4	Wald $\chi^2 = 0.7$[d]	0.69	1.0 (0.6, 1.7)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	0.53
ADHD	66.6	70.4	62.0	66.6	Wald $\chi^2 = 1.9$[d]	0.38	1.1 (0.9, 1.3)	1.1 (1.0, 1.3)	1.0 (0.9, 1.2)	0.43
Conduct disorder	7.7	12.5	14.1	6.1	$\chi^2 = 8.9$	**0.01**	0.9 (0.4, 2.0)	**2.1 (1.1, 3.9)**	**2.3 (1.2, 4.5)**	**0.02**
ODD	36.8	40.9	14.1	39.1	Wald $\chi^2 = 10.9$[d]	**0.004**	**2.7 (1.4, 5.1)**	1.0 (0.8, 1.3)	**0.4 (0.2, 0.7)**	**0.003**
PDD	6.4	0	7.0	7.3	$\chi^2 = 6.9$	**0.03**	–	–	–	0.046
Phenomenological features (lifetime)										
Psychotic features	7.1	10.2	22.5	4.6	Wald $\chi^2 = 27.8$[d]	**<0.0001**	**0.4 (0.2, 1.0)**	**2.2 (1.1, 4.6)**	**4.9 (2.7, 8.9)**	**<0.0001**
Lifetime depressive episode	14.6	20.4	19.7	13.0	Wald $\chi^2 = 0.9$[d]	0.63	1.0 (0.5, 1.9)	1.2 (0.8, 1.9)	1.2 (0.7, 2.0)	0.61
Suicidal ideation	18.8 (132/703)	23.0 (20/87)	36.6	15.8	Wald $\chi^2 = 19.0$[d]	**<0.0001**	**0.6 (0.4, 1.0)**	1.3 (0.9, 2.1)	**2.2 (1.5, 3.1)**	**0.0001**
Suicidal behavior/attempt	2.1 (15/703)	1.2 (1/87)	8.5	1.5	$\chi^2 = 15.1$	**0.0005**	0.1 (0.02, 1.1)	0.8 (0.1, 6.2)	**5.8 (2.1, 16.1)**	**0.012**
Ever hospitalized	9.1	5.7	42.2	5.3	$\chi^2 = 105.1$	**<0.0001**	**0.1 (0.05, 0.3)**	1.1 (0.4, 2.7)	**7.9 (5.1, 12.4)**	**<0.0001**
Medication (lifetime)										
Ever medicated	62.5	61.4	85.9	59.6	Wald $\chi^2 = 14.4$[d]	**0.0007**	**0.8 (0.7, 1.0)**	1.0 (0.9, 1.2)	**1.3 (1.1, 1.4)**	**0.0005**
Antipsychotic	26.7	29.6	67.6	20.9	Wald $\chi^2 = 96.4$[d]	**<0.0001**	**0.5 (0.4, 0.7)**	**1.5 (1.1, 2.2)**	**2.9 (2.4, 3.6)**	**<0.0001**
Mood stabilizer	12.5	14.8	49.3	7.3	χ^2 =99.3	**<0.0001**	**0.3 (0.2, 0.5)**	**2.0 (1.1, 3.6)**	**6.7 (4.6, 9.8)**	**<0.0001**
Antidepressant	19.5	20.4	29.6	18.0	Wald $\chi^2 = 0.6$[d]	0.72	0.8 (0.5, 1.4)	1.0 (0.6, 1.5)	1.1 (0.8, 1.7)	0.64
Stimulant	57.1	56.8	69.0	55.6	Wald $\chi^2 = 4.6$[d]	0.10	0.8 (0.7, 1.1)	1.0 (0.8, 1.2)	**1.2 (1.0, 1.4)**	0.02
Alpha-2 agonist	15.1	11.4	28.2	13.9	Wald $\chi^2 = 10.1$[d]	**0.006**	**0.5 (0.2, 0.9)**	0.9 (0.5, 1.6)	**1.9 (1.3, 2.9)**	**0.003**

Values are reported as percent. ADHD = attention-deficit hyperactivity disorder; BD-I = bipolar I disorder; BD-NOS = bipolar disorder not otherwise specified; BSD = bipolar spectrum disorder; CI = confidence interval; ODD = oppositional defiant disorder; PDD = pervasive developmental disorder.

[a]Prevalence ratios are calculated across bipolar diagnosis; significant differences are shown in **bold**.

[b]Prevalence ratios.

[c]p-value after excluding ESM− participants from analysis.

[d]Adjusted for age, gender, race, and parental education.

had associated behavior or attempts. Youth with BD-I (but not BD-NOS) were more likely to have a history of suicidal ideation and attempts than those with no BSD, and were more likely to have been hospitalized psychiatrically. Both the BD-NOS and BD-I groups were more likely to have psychotic features than those without BSD, although these features were less common in youth with BD-NOS than BD-I. Interestingly, only a minority of youth in this cohort had ever met criteria for a major depressive episode (15%), and this percentage did not differ significantly across groups.

Children with BD-I (but not those with BD-NOS) were more likely to have been medicated, either currently or in the past, than those without BSD (Table 3). Stimulants were the most common medication (57%), followed by antipsychotics (27%), antidepressants (20%), alpha-2 agonists (15%), and mood stabilizers (13%). Not surprisingly, antipsychotics and mood stabilizers were less commonly prescribed to those with BD-NOS versus BD-I, but both groups had higher rates of prescriptions than those without BSD ($p < 0.0001$). Youth with BD-I (but not those with BD-NOS) showed elevated rates of lifetime stimulants and alpha-2 agonists, as compared to those with no BSD. No differences in rates of lifetime antidepressant use were seen across groups.

Family history

Table 4 shows the proportion of children whose parent(s) had a psychiatric diagnosis. Rates of parental history were the highest for depression (63%) and anxiety (43%) and did not differ between the three diagnostic groups. Parental history of mania was reported in 20% of the children. Children with BD-NOS and BD-I were more likely than children without a BSD to have at least one parent with a history of a manic episode ($p = 0.0001$); this proportion did not differ significantly between those with BD-NOS and those with BD-I (33% versus 42%, respectively). Children with BD-NOS were more likely than those with no BSD to have a parental history positive for conduct disorder and for psychosis; no other between-group differences were detected.

Sensitivity analyses

It is possible that the observed differences between youth with and without BSD were driven by differential degree of ESM across bipolar diagnoses, particularly if ESM− youth were less impaired than ESM+ participants. While 86% (466/545) of

Table 4. Family history[a]

Parental history	All subjects (n = 704)	BD-NOS (n = 88)	BD-I (n = 71)	No BSD (n = 545)	Statistic	p-value	BD-NOS versus BD-I (95% CI)	BD-NOS versus no BSD (95% CI)	BD-I versus no BSD (95% CI)	Sensitivity analysis (p-value[b])
Mania	20.3 (132/652)	32.9 (27/82)	42.2 (27/64)	15.4 (78/506)	Wald $\chi^2 = 22.3$[c]	**<0.0001**	0.8 (0.5, 1.1)	**1.5 (1.1, 2.1)**	**2.0 (1.5, 2.7)**	**0.0001**
Depression	63.0 (439/697)	69.4 (59/85)	69.6 (48/69)	61.1 (332/543)	Wald $\chi^2 = 1.7$[c]	0.43	1.0 (0.8, 1.2)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	0.20
ADHD	27.1 (188/694)	29.1 (25/86)	22.9 (16/70)	27.3 (147/538)	Wald $\chi^2 = 0.9$[c]	0.65	1.3 (0.7, 2.2)	1.2 (0.8, 1.6)	0.9 (0.6, 1.4)	0.62
Conduct disorder	39.7 (276/696)	50.6 (44/87)	31.9 (22/69)	38.9 (210/540)	Wald $\chi^2 = 4.5$[c]	0.11	1.3 (0.9, 1.9)	**1.3 (1.0, 1.6)**	1.0 (0.7, 1.3)	0.09
Anxiety	52.5 (364/693)	52.3 (45/86)	54.3 (38/70)	52.3 (281/537)	Wald $\chi^2 = 0.8$[c]	0.75	0.9 (0.7, 1.2)	1.0 (0.8, 1.2)	1.1 (0.9, 1.4)	0.63
Psychosis	11.3 (79/697)	18.4 (16/87)	8.7 (6/69)	10.5 (57/541)	$\chi^2 = 5.3$	0.07	2.1 (0.9, 5.1)	**1.8 (1.1, 2.9)**	0.8 (0.4, 1.8)	0.07
Substance dependence	45.5 (319/701)	50.6 (44/87)	42.3 (30/71)	45.1 (245/543)	Wald $\chi^2 = 0.4$[c]	0.81	1.0 (0.9, 1.3)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	0.76
Suicide attempt	23.6 (166/702)	28.4	27.1 (19/70)	22.4 (122/544)	Wald $\chi^2 = 1.5$[c]	0.47	1.0 (0.6, 1.7)	1.2 (0.9, 1.7)	1.2 (0.8, 1.7)	0.41

Values are reported as percent. ADHD = attention-deficit hyperactivity disorder; BD-I = bipolar I disorder; BD-NOS = bipolar disorder not otherwise specified; BSD = bipolar spectrum disorder; CI = confidence interval.

[a]Prevalence ratios are calculated across bipolar diagnosis; significant differences are shown in **bold**.

[b]p-value after excluding ESM− participants (elevated symptoms of mania <12) from the analysis.

[c]Adjusted for age, sex, race, parental education, number of known biological parents history.

the youth with no BSD were ESM+, the ESM+ rate was higher among those with BSD. Ninety-eight percent (86/88) of those with BD-NOS and 93% (66/71) of those with BD-I were ESM+. However, analyses excluding ESM− youth revealed qualitatively similar differences between youth with and without BSD (see Tables 1–4).

Manic symptoms in BD-I versus BD-NOS

Table 5 shows the frequency with which manic symptoms were endorsed during the most severe lifetime manic episode. In general, symptoms were endorsed less frequently by youth with BD-NOS, as compared to those with BD-I. However, while these differences were statistically significant in some cases, their absolute value was fairly small. Decreased need for sleep showed the greatest difference across diagnostic categories; 41% of those with BD-NOS reported this symptom compared to 66% of youth with BD-I. Of note, while irritability was a frequently occurring symptom, it was less common in youth with BD-NOS versus BD-I (73% versus 92%, respectively). The proportion of youth with elated mood was high in both groups, and did not differ statistically across diagnoses. After adjusting for multiple comparisons (using FDR correction), irritability, decreased need for sleep, poor judgment, and distractibility retained significance at the corrected $p < 0.05$ level. Limiting the analysis to moderate or severe symptoms yielded qualitatively similar results (not shown in Table 5).

Reasons for the BD-NOS diagnosis

The most common reason that BD-NOS youth did not meet criteria for a manic episode was insufficient duration of symptoms. Eighty-six of the 88 BD-NOS participants (98%) had episodes lasting less than the seven-day requirement for mania. The degree to which BD-NOS youth met the symptom criteria for mania (elevated mood plus three associated symptoms, or irritable mood plus four associated symptoms) depended on the threshold used. Using a mild threshold for all DSM-IV symptoms, 71/88 (81%) met symptom criteria for a manic/hypomanic episode; using a moderate threshold, only 21/82 (24%) met symptom criteria. A small minority of the BD-NOS youth (6/88, 7%) met both symptom and duration criteria for hypomania, but had also had marked impairment during these episodes (which is an exclusion criterion for hypomania in DSM-IV-TR). Of these six youth, only one had a history of a major depressive episode, and would thus have met criteria for BD-II (were it not for the marked impairment during the period of abnormally elevated/irritable mood).

Table 5. Manic symptoms during most severe lifetime manic episode: BD-NOS versus BD-I[a]

Manic symptoms[b]	BD-NOS (n = 88)	BD-I (n = 71)	Statistic (Wald χ^2)[c]	p-value	BD-NOS versus BD-I (95% CI)
Irritability	72.7	91.6	8.80	**0.0031**[d]	**0.93 (0.88, 0.98)**
Elation	78.4	83.1	0.50	0.47	0.97 (0.90, 1.05)
Decreased need for sleep	40.9	66.2	12.10	**0.0005**[d]	**0.82 (0.73, 0.92)**
Energetic	84.1	87.3	0.10	0.75	0.99 (0.93, 1.05)
Increased goal-directed activity	43.2	57.8	2.80	0.09	0.91 (0.82, 1.02)
Grandiosity	37.5	53.5	3.80	0.051	0.88 (0.79, 1.00)
Pressured speech	72.7	85.9	1.79	0.18	0.96 (0.90, 1.02)
Racing thoughts	63.6	77.5	5.98	**0.01**	**0.91 (0.84, 0.98)**
Flight of ideas	45.5	60.6	4.68	**0.03**	**0.88 (0.79, 0.99)**
Psychomotor agitation	78.4	69.0	1.49	0.22	1.05 (0.97, 1.13)
Poor judgment	51.1	71.8	8.62	**0.0033**[d]	**0.88 (0.81, 0.96)**
Distractibility	63.6	81.7	8.79	**0.003**[d]	**0.90 (0.84, 0.97)**
Motor hyperactivity	77.3	73.2	1.17	0.28	1.04 (0.97, 1.11)
Inappropriate laughing	56.8	70.4	3.48	0.06	0.92 (0.85, 1.00)
Uninhibited, gregarious behavior	28.4	35.2	0.90	0.34	0.92 (0.79, 1.08)
Increased productivity	29.6	36.6	1.29	0.26	0.91 (0.78, 1.07)
Increased creativity	21.6	35.7 (25/70)	2.56	0.11	0.87 (0.73, 1.03)
Hypersexuality	19.5 (17/87)	19.7	0.00	0.96	0.99 (0.79, 1.24)
Mood lability	85.2	80.3	0.51	0.48	1.02 (0.97, 1.07)

Values are reported as percent. BD-I = bipolar I disorder; BD-NOS = bipolar disorder not otherwise specified; CI = confidence interval.
[a]Prevalence ratios are calculated across bipolar diagnosis; significant differences are shown in **bold**.
[b]Variables taken from K-SADS Mania Rating Scale (KMRS) (summary of parent and child report). Symptoms of any severity (mild, moderate, or severe) were included.
[c]Results adjusted for age, sex, race, parental education, and number of parents with available history.
[d]Significant after correction for multiple comparisons, using the false discovery rate and keeping alpha at 0.05, two-tailed.

Discussion

This well-characterized clinical cohort provided an ideal study population to assess the diagnostic boundaries of BD in youth. Previous clinical samples in which this issue has been assessed have consisted of individuals referred with suspicion of a bipolar or mood disorder diagnosis (e.g., COBY) (2, 11–13, 26). In contrast, this study included participants who presented at outpatient psychiatric clinics, and were recruited based on a dimensional measure of manic symptomatology. Thus, it included a large number of children who had nonspecific manic symptoms that could be attributable to a variety of psychopathologies, and could be compared to those with episodic mood symptoms on the bipolar spectrum. This design not only allowed us to compare the clinical characteristics and family history of participants with a diagnosis of BD-NOS and BD-I, but also facilitated a comparison between those with and without BSD.

These analyses of the baseline LAMS data revealed many similarities between BD-NOS and BD-I youth, which were not shared by the clinically recruited sample without BSD, most of whom also scored high on the PGBI-10M. Indicators of baseline impairment (CGAS, KMRS, KDRS, YMRS, and CDRS-R) did not differ significantly between the BD-NOS and BD-I groups, but were more severe in these youth compared to those with no BSD. Similarly, both the BD-NOS and BD-I groups had an elevated parental history of mania, which was not shared by those with no BSD. The prevalence of conduct disorder was similar in the BD-NOS and BD-I groups, but elevated relative to the group without BSD. In contrast, indicators of most severe past functioning showed a gradient according to disorder, with significant differences in both worst lifetime CGAS and KMRS scores across groups, as well as the lifetime presence of psychotic features (BD-I > BD-NOS > no BSD). Finally, certain indicators of very severe dysfunction, such as suicidal ideation, suicidal behavior, and history of hospitalization, were elevated in the BD-I group, but not the BD-NOS group (as compared to those without BSD). The latter is not surprising, given that psychiatric hospitalization is part of the DSM-IV criteria for a manic episode (33). Excluding the ESM− participants did not qualitatively change the results, indicating that differences between those with and without BSD were not driven by the youth without manic symptoms.

Comparison between the clinical presentations of BD-NOS and BD-I also indicated many similarities. BD-NOS and BD-I youth had a similar age of onset and duration of BSD. Additionally, manic symptoms did not differ extensively between BD-NOS and BD-I. Several manic symptoms were significantly more likely to be present in participants with BD-I than with BD-NOS: irritable mood, decreased need for sleep, distractibility, racing thoughts, flight of ideas, and poor judgment. However, similar to findings from the COBY study (24), effect sizes were small and did not reflect qualitatively different episodes. Interestingly, the current results do not indicate a significant difference in the proportion of BD-NOS versus BD-I with elated mood, and youth with BD-NOS were less likely to be irritable than those with BD-I. Thus, it is unlikely that the BD-NOS presentation is a variant of the chronic irritability described by previous authors (20). These results are consistent with data from Van Meter et al. that showed high levels of irritability in youth with cyclothymia and BD-NOS (as compared with ADHD and depression), but slightly lower levels relative to BD-I and BD-II (13).

The above findings are consistent with the interpretation that BD-NOS and BD-I share similar characteristics, and are along a spectrum of bipolarity, while youth without distinct episodes of manic symptoms do not seem to share many of these characteristics. However, as would be expected, youth with BD-I were more likely than those with BD-NOS to have more severe past presentations, with worse functional impairment during the most serious lifetime episode, as well as an increased rate of hospitalizations and suicidality. These results are remarkably consistent with the COBY data, which also showed no significant difference between BD-NOS and BD-I on many factors (such as family history and comorbidity), though there were differences on indicators of severe illness (hospitalization, psychosis, and suicide attempts) (24). The findings are also consistent with those of other groups that have found an elevated family history of mania in youth with both syndromal and subsyndromal BD, but not major depressive disorder (11, 18).

This study indicates a high degree of comorbidity in this cohort, similar to previous work, particularly in pediatric samples. ADHD and ODD were the most common disorders in this cohort, with 2/3 of youth meeting diagnostic criteria for ADHD and 1/3 meeting those for ODD. These are comparable to previous clinical samples (2, 24, 39), but are higher than co-morbidities seen in epidemiologic samples (18, 40). Rates of ADHD and anxiety did not differ across bipolar diagnostic categories, consistent with prior results (11, 40). However, the disruptive behavioral disorders showed an interesting pattern of results. Both

BD-NOS and BD-I groups had a higher frequency of conduct disorder, as compared to the group with no BSD. This is consistent with previous research, which has shown elevated conduct disorder and criminal activity in youth and adults on the bipolar spectrum (6, 41). In contrast, ODD was found to be less common in the BD-I group, as compared to both those with BD-NOS and those without BSD. This result was unexpected, has not been found in COBY or other similar studies, and is difficult to interpret. One possible explanation is that, with the lengthier and more discrete episodes that define BD-I (as opposed to BD-NOS), it is easier to distinguish whether symptoms of oppositionality and defiance are associated with mood episodes versus the more chronic pattern that occurs with a diagnosis of ODD.

The vast majority of BD-NOS youth in this cohort failed to meet duration criteria for mania or hypomania, similar to findings from the COBY study (24). However, a sizeable minority of BD-NOS youth also failed to meet symptom criteria for a manic episode, which is in contrast to the COBY study sample (where 99.6% of the BD-NOS youth met symptom criteria). These differences are likely attributable to differences in recruiting strategies, since COBY youth were referred based on the suspicion of having bipolar disorder. Thus, it is not surprising that almost all of the BD-NOS youth in COBY met symptom criteria.

A number of limitations should be taken into account when interpreting these data. First, this was a clinically derived sample, and thus was not necessarily characteristic of youth in the community. Additionally, these youth were recruited from clinics associated with major medical centers in western Pennsylvania and Ohio, so they might not be representative of other regions of the country. Secondly, analyses focused on the baseline data from the LAMS study, and, as with any cross-sectional analysis, there are limitations when interpreting the causality of observed associations. Longitudinal data are currently being collected, and will likely yield valuable insights regarding clinical trajectory and biomarkers distinguishing youth with subsyndromal presentations of BD. It also is important to note that we included cyclothymic disorder with BD-NOS. The combined operational definition is consistent with much prior research (11, 24) and facilitates comparison across studies as well as providing larger n for statistical analyses. However, it is possible that cyclothymic disorder may have some different clinical features from other presentations included in the NOS category (13, 14). Finally, although the LAMS study has a large sample size, the number of youth with BD-NOS or BD-I is a smaller proportion of the population, and thus we might not have the power to detect small differences, particularly between BD-NOS and BD-I. We did not have a sufficient number of cases with BD-II to permit statistical analyses.

The existing literature and the current results indicate that BD-NOS and BD-I are on a spectrum of bipolarity youth with these disorders share clinical characteristics, phenomenology, and family history of mania, that are not shared by youth with less episodic mood symptoms. The differences seen between those with and without BSD are especially striking, given that the majority of this cohort (including those with no BSD) were selected to have ESM. Thus, this analysis provides evidence for qualitative differences between those with episodic and those with non-episodic manic symptoms, even when the episodes are too short to meet duration criteria for mania or hypomania.

While this was a cross-sectional analysis, it provides important insight into the appropriate diagnostic boundaries of bipolar disorder in youth, which will likely have implications for prognosis and treatment. These results support the hypothesis that current duration criteria in the DSM-IV-TR are perhaps too stringent, given the evidence that youth with even short manic episodes might have an underlying bipolar diathesis. If supported by future longitudinal analyses, this has important implications for diagnostic criteria in future versions of the DSM. These findings also highlight the clinical importance of assessing subsyndromal manic symptoms in pediatric populations, even if they don't meet full syndromal criteria for BD-I or BD-II, and the need to develop appropriate treatments for these youth. Future work will determine the clinical trajectory of these participants, as well as seek to identify neuroimaging and neurocognitive biomarkers of progression.

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