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Original Article

Comparison of manic and depressive symptoms between children and adolescents with bipolar spectrum disorders

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Objective: To compare the most severe lifetime (current or past) mood symptoms, duration of illness, and rates of lifetime comorbid disorders among youth with bipolar spectrum disorders [BP (bipolar-I, bipolar-II and bipolar–not otherwise specified)].

Methods: A total of 173 children (< 12 years) with BP, 101 adolescents with childhood-onset BP, and 90 adolescents with adolescent-onset BP were evaluated with standardized instruments.

Results: Depression was the most common initial and frequent episode for both adolescent groups, followed by mania/hypomania. Adolescents with childhood-onset BP had the longest illness, followed by children and then adolescents with adolescent-onset BP. Adjusting for sex, socioeconomic status, and duration of illness, while manic, both adolescent groups showed more 'typical' and severe manic symptoms. Mood lability was more frequent in childhood-onset and adolescents with early-onset BP. While depressed, both adolescent groups showed more severe depressive symptoms, higher rates of melancholic and atypical symptoms, and suicide attempts than children. Depressed children had more severe irritability than depressed adolescents. Early BP onset was associated with attention-deficit hyperactivity disorder, whereas later BP onset was associated with panic, conduct, and substance use disorders. Above-noted results were similar when each BP subtype was analyzed separately.

Conclusions: Older age was associated with more severe and typical mood symptomatology. However, there were differences and similarities in type, intensity, and frequency of BP symptoms and comorbid disorders related to age of onset and duration of BP and level of psychosocial development. These factors and the normal difficulties youth have expressing and modulating their emotions may explain existing complexities in diagnosing and treating BP in youth, particular in young children, and suggest the need for developmentally sensitive treatments.

Boris Birmaher[a], David Axelson[a], Michael Strober[b], Mary Kay Gill[a], Mei Yang[a], Neal Ryan[a], Benjamin Goldstein[a], Jeffrey Hunt[c], Christianne Esposito-Smythers[c], Satish Iyengar[d], Tina Goldstein[a], Laurel Chiapetta[a], Martin Keller[c] and Henrietta Leonard[c]

[a]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA, [b]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, [c]Department of Psychiatry and Butler and Bradley Hospitals, The Warren Alpert Medical School at Brown University, Providence, RI, [d]Department of Statistics, University of Pittsburgh, Pittsburgh, PA, USA

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Corresponding author: Boris Birmaher, MD, Department of Psychiatry, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA, 15213, USA. Fax: 412-246-5230;
e-mail: birmaherb@upmc.edu

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Although it is accepted that children and adolescents may develop bipolar spectrum disorders [BP (bipolar-I, bipolar-II and bipolar–not otherwise specified)], there is considerable variability in the frequency of presentation of the manic symptoms across the extant studies, particularly for elation and irritability (1–7). These diverse clinical presentations between children and adolescents may be attributable, at least in part, to the psychosocial and maturational changes that occur after puberty (8, 9). Furthermore, the age at which the child or adolescent first experiences symptoms of illness may also have important implications for clinical presentation, with early deficits promoting later impairment as the child arrives at each progressive stage of development with inadequate resources available to meet the challenges unique to the ensuing period (10). Additionally, children and adolescents whose illness started during childhood may be more likely to be exposed to stressful life events and diverse types of treatment which may modify the phenomenology and course of their illness.

To date, few studies have compared the symptoms of mania and comorbid disorders between children and adolescents with BP, and no study has compared the BP depressive symptomatology across age groups. Faraone and colleagues (11) compared manic symptoms among a group of children with bipolar-I disorder (BP-I) (n = 68) to adolescents with early-onset (n = 25) and late-onset (n = 17) mania. Euphoria was more common in the adolescents with early-onset mania and irritability was least common in the adolescents with late-onset mania. Rates of increased energy were similar in children and in adolescents with early-onset mania, but both groups had increased energy scores that were twice as high as the adolescents with late-onset mania. Except for higher rates of attention-deficit hyperactivity disorder (ADHD) in children with BP, Geller and colleagues (12) did not find any differences in the rates of manic symptoms in a sample of children (n = 53) and young adolescents (n = 40) with BP-I. Except for higher rates of substance abuse in adolescents, Findling and colleagues (3) did not find any differences in manic symptomatology or psychosis between children (n = 56) and adolescents (n = 34) with BP-I. Finally, Masi and colleagues (13) reported more comorbid ADHD and oppositional-defiant disorder and a less episodic course in children (n = 80) compared to adolescents (n = 56) with BP. There were no differences between groups in rates of irritability, elation, or severity of illness.

The above-noted studies seem to indicate that, with few exceptions, symptoms of mania are equally manifested in children and adolescents. However, generalizability of these findings is limited because these studies have one or more of the following limitations: small samples, most subjects had BP-I, lack of direct interviews with children, absence of analysis of depressive symptomatology, and lack of stratification of the adolescent group by age at illness onset. In addition, none of these studies adjusted for potentially important confounding factors such as demographic factors (e.g., sex, socioeconomic status), duration of illness, and presence of comorbid disorders.

The goal of this study was to replicate and extend the above-noted studies in a large sample of children and adolescents with BP spectrum disorders recruited into the Course and Outcome of Bipolar Youth (COBY) multicenter study. In prior publications we reported the clinical picture for the entire age group, focusing on the clinical differences between BP-I, bipolar-II disorder (BP-II), and bipolar–not otherwise specified (BP-NOS) (5) and psychosis (14). Also, a prior COBY report showed that after adjusting for significant demographic and clinical factors, BP children and adolescents with childhood-onset BP had higher rates of psychopathology in their first- and second-degree biological relatives as compared to adolescents with adolescent-onset BP (≥12 years) (15). The present study compares the most severe lifetime (current or past) manic and depressive symptoms, other clinical variables, and rates of comorbid disorders among BP youth.

Subjects

A complete description of the methodology used in COBY was reported in detail elsewhere (5, 16). Briefly, after institutional review board approval and after obtaining appropriate consent or assent, children and adolescents fulfilling DSM-IV criteria for BP-I or BP-II, or COBY's criteria for BP-NOS (5) were enrolled at Brown University, Providence, RI; University of California Los Angeles, Los Angeles, CA; and the University of Pittsburgh Medical Center, Pittsburgh, PA, USA. About 70% of the sample were recruited from outpatient clinics and the rest through advertisement and inpatient units. Subjects with current or lifetime DSM-IV diagnoses of schizophrenia, mental retardation, severe autistic spectrum disorders, or mood disorders due to substance abuse, a medical condition, or secondary to use of medications were excluded.

In order to evaluate the differential clinical picture between children and adolescents with

BP, the sample was divided into three subgroups according to onset of significant mood symptomatology and the age at the time of the initial assessment as follows: (i) children with BP (< 12 years; n = 173); (ii) adolescents with childhood-onset BP (age ≥ 12 and BP onset < 12; n = 101); and (iii) adolescents with adolescent-onset BP (age ≥ 12 and BP onset ≥12; n = 90). Age of BP onset was defined as the age of onset of DSM-IV manic, hypomanic, and/or depressive episodes (5). Illness duration was defined as the subject's current age minus the age of BP onset. In about 6% (22/364) of cases, parents reported that their child's mood symptoms (mania, hypomania, and/or depression) appeared ≤4 years old. However, given the controversies diagnosing BP in very young children, the minimum age of onset for BP spectrum illness was arbitrarily set at age four (5).

Since the DSM definition of BP-NOS is not operationalized, BP-NOS was defined as a minimum of elated mood plus two associated DSM symptoms, or irritable mood plus three associated DSM symptoms and a change in functioning. In addition, the above-noted symptoms were required to last a minimum of four hours within a 24-hour period and to have occurred at least four cumulative lifetime days. Prior papers using the COBY sample showed that children with BP-NOS have similar but less severe clinical picture, comorbid disorders, family history, and longitudinal outcome than the BP-I subjects. Moreover, about 25% of the youth diagnosed as BP-NOS converted into BP-I or BP-II (5, 16).

Subject assessment

Children, adolescents, and parents (about their children) were directly interviewed for the presence of current and lifetime non-mood psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version (K-SADS-PL) (17, 18). As the K-SADS-PL only ascertains the presence or absence of symptoms, the K-SADS Mania Rating Scale [(K-MRS) (19); available at http://www.wpic.pitt.edu/research, under 'Assessments'] and the depression section of the K-SADS-P (K-DEP) (20) were used to assess the severity of each mood symptom in detail (see Tables 2 and 3 for the symptoms included in these scales). Mood symptoms that were in common with other psychiatric disorders (e.g., distractibility) were not rated as present unless they intensified with the onset of abnormal mood. Lifetime comorbid diagnoses were not assigned if they occurred exclusively during a mood episode.

A current mood episode was defined as the worst week of the month prior to intake. Past mood episodes were identified using a mood timeline with the child and parents and asking them which of these episodes (mania and/or depression) was the most severe. Duration of the episode, level of impairment, and/or hospitalization were some of the factors considered when determining which past mood episode was the worst. Manic and depressive symptoms with the higher scores of either the current or past mood episode as rated in the K-MRS and depression section of the K-SADS-P were selected for the analyses in this paper. We chose to evaluate the most severe lifetime manic and depressive symptoms in order to capture the illness when manifested at its full expression and not when only mild to moderate symptoms were present. Moreover, this strategy increased the likelihood that parents and children would be better able to remember specific mood symptomatology.

The Petersen Pubertal Developmental Scale (PDS) (21) was used to evaluate pubertal stage and the Hollingshead scale (22) was used to evaluate socioeconomic status (SES).

All assessments were completed by research staff trained to reliably administer the above-noted interviews and presented to child psychiatrists/psychologists, who confirmed the diagnoses. The overall K-SADS kappas for psychiatric disorders were ≥0.8.The intraclass correlation coefficients for the K-MRS and the K-DEP total scores were ≥0.95.

Statistical analyses

Differences in demographics and clinical symptomatology among the three BP groups were analyzed using standard parametric (e.g., ANOVA) and nonparametric univariate tests (e.g., Kruskal-Wallis) when appropriate. Generalized linear modeling was used to evaluate the effects of group and any significant between-group differences in demographics, duration of illness, and other clinical variables.

Age and pubertal status were highly correlated in the three age-of-onset BP groups ($r \geq 0.73$, $p < 0.001$); therefore, analyses included age only.

Analyses examining continuous and categorical data from the K-MRS and K-SADS depression items yielded similar results. Also, results were similar when each BP subtype was analyzed separately. Thus, for simplicity, only the results using continuous data and the combined BP data are included in this paper.

To inform new hypotheses and guide future studies, the data are presented with and without Bonferroni corrections (indicated in Table 2 with a superscript 'd,' Table 3 with a superscript 'c' and in Table 4 with a superscript 'b'). Furthermore, to have an idea of the statistical strength of the comparisons, size effects (*d*) were calculated as described by Cohen (23) and included in all tables.

All values are reported as means ± standard deviations. All p-values are based on two-tailed tests with $\alpha = 0.05$.

Results

Demographics and general clinical characteristics (Table 1)

As expected, the three groups significantly differed in age and pubertal status. Children with BP included significantly more boys than the other two groups and the SES of both childhood-onset groups was significantly lower than that of the adolescents with adolescent-onset BP. Adolescents with childhood-onset BP had the longest duration of illness, followed by children and then adolescents with adolescent-onset BP. The onset of significant mood symptomatology preceded the onset of episodes by an average of 1.0 ± 1.7 years. Children experienced their first mood episode at an earlier age, followed by adolescents with childhood-onset and adolescents with adolescent-onset BP. Adolescents with childhood-onset BP had significantly more 'at least one depressive episode' than the adolescents with adolescent-onset BP, followed by the children. However, differences between the two adolescent groups disappeared when adjusting for duration of illness. Both adolescent groups were more likely to have a major depressive episode as their first BP episode and both childhood-onset groups more commonly presented with initial symptoms meeting COBY's criteria for BP-NOS than adolescents with adolescent-onset BP.

Given the above results, all following analyses were adjusted for sex, SES, duration of illness, and rates of comorbid disorders (see results below).

Table 1. Demographic and general clinical characteristics

	BP children (<12 years) (n = 173)	Adolescents with childhood-onset BP (n = 101)	Adolescents with adolescent-onset BP (n = 90)	Statistics	p-values	Pair-wise comparisons p-values (Effect size *d*) Group 1 versus Group 2[a]	Group 1 versus Group 3[a]	Group 2 versus Group 3[a]
Age (years)	9.4 ± 1.5	14.5 ± 1.7	16.0 ± 1.3	KWχ^2 = 281.9	<0.001	<0.001 (3.2)	<0.001 (4.6)	<.001 (1.0)
Sex (% male)	63.0	44.6	33.3	χ^2 = 22.9	<0.001	0.003 (0.4)	<0.001 (0.6)	0.2 (0.1)
Race (% Caucasian)	82.7	77.2	76.7	χ^2 = 1.8	0.4			
Pubertal status				χ^2 = 171.4	<0.001	<0.001 (2.4)	<0.001 (3.2)	0.05 (0.4)
I	62.6	4.9	0.0					
II-III	33.9	23.5	16.0					
IV-V	3.5	71.6	84.0					
Socioeconomic status	3.2 ± 1.2	3.3 ± 1.1	3.8 ± 1.1	$F_{2, 361}$ = 8.3	<0.001	0.5 (0.1)	<0.001 (0.5)	0.02 (0.5)
Duration of BP (years)	3.2 ± 1.9	5.1 ± 3.2	1.5 ± 1.2	KWχ^2 = 90.5	<0.001	<0.001 (0.8)	<0.001 (1.0)	<0.001 (1.5)
Age of onset of mood symptoms (years)	5.3 ± 2.0	7.8 ± 2.8	14.1 ± 1.6	KWχ^2 = 229.8	<0.001	<0.001 (1.1)	<0.001 (4.7)	<0.001 (2.7)
Age of first manic episode[b]	7.0 ± 2.2	11.3 ± 3.6	15.0 ± 1.6	KWχ^2 = 93.1	<0.001	<0.001 (1.5)	<0.001 (4.0)	<0.001 (1.3)
Age of first depressive episode[b]	6.5 ± 1.8	10.4 ± 3.0	14.5 ± 1.4	KWχ^2 = 116.4	<0.001	<0.001 (1.6)	<0.001 (4.9)	<0.001 (1.7)
At least one major depressive episode (%)	35.3	64.4	50.0	χ^2 = 40.8	<0.001	<0.001 (0.6)	0.021 (0.3)	0.05 (0.3)
At least one mixed episode (%)	24.9	35.6	28.9	χ^2 = 3.6	0.2			
Type of first episode (%)				χ^2 = 29.0	0.001	0.04 (0.4)	<0.001 (0.7)	0.01 (0.5)
Manic/hypomanic	22.5	23.8	32.6	χ^2 = 3.3	0.2			
Mixed/hypomixed	13.3	8.9	16.9	χ^2 = 2.7	0.3			
Major depression	20.2	34.7	37.1	χ^2 = 10.9	0.004	0.01 (0.3)	0.003 (0.4)	0.8 (0.1)
BP-NOS	43.9	32.7	13.5	χ^2 = 24.5	<0.001	0.07 (0.2)	<0.001 (0.7)	0.002 (0.5)

Values are mean ± SD except where indicated otherwise.
BP = bipolar spectrum disorders; NOS = not otherwise specified; KW = Kruskal-Wallis.
[a]Group 1 = BP children; Group 2 = adolescents with childhood-onset BP; Group 3 = adolescents with adolescent-onset BP.
[b]Onset of an episode fulfilling the DSM-IV criteria.

Manic symptoms (Table 2)

Adjusting for confounding factors, both adolescent groups showed significantly higher K-MRS–13-item total manic scores and more severe grandiosity, racing thoughts, poor judgment, and increased productivity as compared to children. Adolescents with adolescent-onset BP had more severe elation, goal-directed activity, racing thoughts, and high energy than both children and adolescents with childhood-onset BP and more decreased need for sleep, accelerated speech, delusions, and sharpened thinking compared to children. Finally, both childhood-onset groups had significantly more severe mood lability as compared to adolescents with adolescent-onset BP.

Depressive symptoms (Table 3)

Adjusting for confounding variables, both adolescent groups had significantly higher K-DEP–12-item total scores (see Table 3 for the items) and more severe hopelessness, anhedonia, fatigue, concentration difficulty, psychomotor retardation,

Table 2. Most severe lifetime manic symptoms

K-MRS items (score range)	BP children (<12 years) (n = 173)	Adolescents with childhood-onset BP (n = 101)	Adolescents with adolescent-onset BP (n = 90)	Wald χ^2	Adjusted p-values[c]	Pair-wise comparisons p-values (Effect size *d*) Group 1 versus Group 2[e]	Group 1 versus Group 3[e]	Group 2 versus Group 3[e]
MRS-13[a] item scale (0–64)	31.9 ± 8.0	36.1 ± 7.9	35.0 ± 8.5	19.6	<0.001[d]	0.003 (0.3)	<0.001 (0.4)	0.28 (0.1)
Elation (1–6)	3.9 ± 1.2	4.3 ± 1.0	4.4 ± 1.0	18.1	<0.001[d]	0.13 (0.1)	<0.001 (0.4)	0.01 (0.3)
Irritability/anger (1–6)	4.1 ± 1.5	4.3 ± 1.4	3.7 ± 1.4	3.0	0.23			
Grandiosity (1–6)	3.0 ± 1.4	3.5 ± 1.5	3.6 ± 1.3	18.6	<0.001[d]	0.02 (0.2)	<0.001 (0.4)	0.11 (0.2)
Decreased need for sleep (1–6)	3.7 ± 1.9	4.1 ± 1.8	4.5 ± 1.7	13.0	0.001[d]	0.1 (0.1)	<0.001 (0.3)	0.05 (0.3)
Accelerated speech (1–6)	3.9 ± 1.2	4.3 ± 1.2	4.2 ± 1.1	11.4	0.003	0.06 (0.2)	0.001 (0.3)	0.21 (0.2)
Rapid thinking[b]								
Racing thoughts (1–6)	3.0 ± 1.6	3.7 ± 1.7	4.0 ± 1.3	20.0	<0.001[d]	0.02 (0.2)	<0.001 (0.4)	0.05 (0.3)
Flight of ideas (1–6)	3.5 ± 1.4	3.7 ± 1.4	3.4 ± 1.4	1.7	0.42			
Distractibility (1–5)	3.5 ± 1.1	3.5 ± 1.2	3.5 ± 1.1	2.7	0.26			
Increased activity[b]								
Goal-directed activity (1–6)	2.6 ± 1.5	3.0 ± 1.5	3.8 ± 1.6	32.2	<0.001[d]	0.06 (0.2)	<0.001 (0.5)	0.001 (0.5)
Motor hyperactivity (1–6)	4.3 ± 1.2	4.3 ± 1.1	4.3 ± 1.1	1.7	0.43			
Poor judgment (1–6)	3.6 ± 1.6	4.2 ± 1.4	4.0 ± 1.6	7.6	0.02	0.02 (0.2)	0.04 (0.2)	0.96 (0.0)
High energy (1–6)	4.3 ± 1.4	4.6 ± 1.2	4.8 ± 1.0	18.1	<0.001[d]	0.07 (0.2)	<0.001 (0.4)	0.03 (0.3)
Hallucinations (1–6)	1.8 ± 1.2	2.1 ± 1.6	1.6 ± 1.3	4.4	0.11			
Delusions (1–6)	1.3 ± 0.7	1.5 ± 1.0	1.6 ± 1.2	4.9	0.09	0.18 (0.1)	0.04 (0.2)	0.5 (01)
Mood lability (1–6)	4.1 ± 1.1	4.4 ± 0.9	3.7 ± 1.3	8.6	0.01	0.25 (0.1)	0.02 (0.2)	0.004 (0.4)
Inappropriate laughing (1–4)	2.8 ± 1.0	3.0 ± 1.0	2.7 ± 1.1	0.9	0.65			
Uninhibited people seeking (1–4)	2.4 ± 1.2	2.4 ± 1.2	2.7 ± 1.2	1.6	0.46			
Increased productivity (1–4)	1.9 ± 1.1	2.5 ± 1.1	2.7 ± 1.2	28.4	<0.001[d]	<0.001 (0.3)	<0.001 (0.5)	0.2 (0.2)
Sharpened creative thinking (1–4)	2.1 ± 1.0	2.5 ± 1.2	2.4 ± 1.2	8.6	0.01	0.1 (0.1)	0.004 (0.3)	0.2 (0.2)
Hypersexuality (1–4)	2.2 ± 1.2	2.3 ± 1.3	2.3 ± 1.2	1.4	0.50			
Sentence incoherence (1–6)	1.6 ± 1.1	1.9 ± 1.2	1.5 ± 1.0	3.1	0.21			
Derailment (1–6)	1.5 ± 1.0	1.6 ± 1.1	1.5 ± 1.0	0.2	0.90			

All vales are indicated as mean ± SD.
K-MRS = Schedule for Affective Disorders and Schizophrenia for School Age Children Mania Rating Scale; BP = bipolar spectrum disorders.
[a]For the MRS-13 items see http://www.wpic.pitt.edu/research under 'Assessments'.
[b]Rapid thinking consisted of the highest score of 'Racing thoughts' or 'Flight of ideas'; and Increased activity consisted of the highest score of the increased 'Goal activity' or 'Motor hyperactivity'.
[c]After adjusting for sex, socioeconomic status, duration of illness, and significantly different comorbid disorders.
[d]Remained significant after Bonferroni correction.
[e]Group 1 = BP children; Group 2 = adolescents with childhood-onset BP; Group 3 = adolescents with adolescent-onset BP.

Table 3. Most severe lifetime depressive symptoms

K-SADS-P depression items (score range)	BP children (<12 years) (n = 173)	Adolescents with childhood-onset BP (n = 101)	Adolescents with adolescent-onset BP (n = 90)	Wald χ^2	Adjusted p-values[b]	Pair-wise comparisons p-values (Effect size *d*) Group 1 versus Group 2[d]	Group 1 versus Group 3[d]	Group 2 versus Group 3[d]
K-Depression-12 item[a] scale (0–61)	18.8 ± 8.1	28.1 ± 10.9	24.3 ± 13.0	30.2	<0.001[c]	<0.001 (0.4)	0.001 (0.3)	0.3 (0.1)
Depressed mood[a] (1–7)	3.9 ± 1.5	4.9 ± 1.5	4.5 ± 1.7	13.2	0.001[c]	<0.001 (0.3)	0.07 (0.2)	0.24 (0.2)
Irritability and anger (1–7)	4.5 ± 1.3	4.7 ± 1.3	4.0 ± 1.6	5.4	0.07	0.6 (0.1)	0.02 (0.2)	0.1 (0.2)
Reactivity of depressed mood (1–6)	4.4 ± 1.7	4.9 ± 1.4	4.2 ± 1.7	2.0	0.37			
Diurnal mood variation (1–4)	2.1 ± 1.3	2.4 ± 1.4	2.2 ± 1.3	0.8	0.67			
Excessive guilt[a] (1–6)	2.4 ± 1.4	2.9 ± 1.5	2.5 ± 1.6	5.2	0.07	0.03 (0.2)	0.9 (0.0)	0.07 (02)
Negative self-image (1–6)	3.4 ± 1.5	4.2 ± 1.6	3.5 ± 1.6	11.8	0.003	0.002 (0.2)	0.5 (0.1)	0.003 (0.4)
Hopelessness (1–6)	2.3 ± 1.3	3.7 ± 1.4	3.1 ± 1.6	54.2	<0.001[c]	<0.001 (0.6)	<0.001 (0.5)	0.3 (0.2)
Aches and pains (1–6)	2.7 ± 1.7	3.0 ± 1.8	3.0 ± 1.9	0.4	0.84			
Anhedonia[a] (1–6)	3.1 ± 1.5	4.2 ± 1.6	3.6 ± 1.7	17.3	<0.001[c]	<0.001 (0.3)	0.01 (0.3)	0.5 (01)
Fatigue[a] (1–6)	2.7 ± 1.6	4.1 ± 1.5	3.8 ± 1.6	40.3	<0.001[c]	<0.001 (0.4)	<0.001 (0.5)	0.99 (0.0)
Difficulty concentrating[a] (1–6)	3.2 ± 1.6	4.1 ± 1.7	3.7 ± 1.6	10.2	0.006	0.01 (0.2)	0.01 (0.2)	0.9 (0.0)
Psychomotor agitation[a] (1–6)	2.7 ± 1.7	2.8 ± 1.7	2.5 ± 1.6	0.2	0.92			
Psychomotor retardation[a] (1–6)	2.3 ± 1.3	2.8 ± 1.6	2.7 ± 1.5	9.8	0.007	0.01 (0.2)	0.03 (0.2)	(0.8 (0.0)
Social withdrawal (1–6)	3.2 ± 1.5	4.1 ± 1.5	3.5 ± 1.8	10.0	0.007	0.002 (0.3)	0.1 (0.1)	0.3 (0.1)
Insomnia[a] (1–6)	3.1 ± 1.6	3.6 ± 1.5	3.1 ± 1.7	3.7	0.16			
Initial insomnia (1–4)	2.6 ± 1.3	3.0 ± 1.2	2.7 ± 1.3	1.6	0.45			
Middle insomnia (1–4)	1.9 ± 1.1	2.1 ± 1.2	1.9 ± 1.2	0.4	0.82			
Terminal insomnia (1–4)	1.8 ± 1.2	1.9 ± 1.2	1.5 ± 1.0	5.0	0.08	0.8 (0.0)	0.04 (0.2)	0.04 (0.3)
Circadian reversal (1–4)	1.1 ± 0.6	1.7 ± 1.1	1.6 ± 1.1	20.4	<0.001[c]	0.001 (0.3)	<.001 (0.4)	0.6 (0.1)
Non-restorative sleep (1–4)	2.0 ± 1.1	2.8 ± 1.2	2.4 ± 1.3	19.2	<0.001[c]	<0.001 (0.4)	0.01 (0.3)	0.3 (0.1)
Daytime sleepiness (1–4)	1.7 ± 1.0	2.9 ± 1.2	2.3 ± 1.3	40.1	<0.001[c]	<0.001 (0.5)	0.001 (0.3)	0.07 (0.3)
Hypersomnia[a] (1–6)	1.9 ± 1.5	3.4 ± 1.9	3.2 ± 1.9	42.5	<0.001[c]	<0.001 (0.5)	<0.001 (0.5)	0.9 (0.0)
Decreased appetite[a] (1–6)	1.9 ± 1.4	2.8 ± 1.9	2.4 ± 1.7	8.0	0.02	0.01 (0.2)	0.1 (0.2)	0.5 (0.1)
Weight loss[a] (1–6)	1.2 ± 0.7	1.8 ± 1.3	1.8 ± 1.4	15.2	0.001[c]	0.01 (0.2)	<0.001 (0.3)	0.3 (0.1)
Increased appetite (1–6)	1.9 ± 1.6	2.2 ± 1.8	1.9 ± 1.7	1.2	0.54			
Craving for sweets (1–4)	1.9 ± 1.1	2.1 ± 1.2	1.8 ± 1.0	3.4	0.18			
Weight gain (1–6)	1.6 ± 1.3	2.1 ± 1.7	1.9 ± 1.7	2.3	0.32			
Leaden paralysis (1–6)	1.6 ± 1.1	2.1 ± 1.6	2.2 ± 1.6	11.1	0.004	0.04 (0.2)	0.002 (0.3)	0.3 (0.2)
Rejection sensitivity (1–6)	3.5 ± 1.3	3.6 ± 1.3	2.8 ± 1.5	5.7	0.06	0.81 (0.02)	0.02 (0.2)	0.07 (0.3)
Suicidal ideation[a] (1–6)	2.7 ± 1.3	3.5 ± 1.6	3.1 ± 1.8	7.3	0.03	0.01 (0.23)	0.3 (0.1)	0.2 (0.2)
Suicidal attempts-seriousness (1–6)	0.8 ± 1.2	1.7 ± 1.9	1.4 ± 1.6	13.1	0.001[c]	0.001 (0.3)	0.05 (0.2)	0.3 (0.1)
Suicidal attempts-medical lethality (1–6)	0.5 ± 0.8	1.2 ± 1.4	1.1 ± 1.4	11.4	0.003	0.003 (0.3)	0.02 (0.2)	0.8 (0.0)
Recurrent thoughts of death (1–6)	2.4 ± 1.3	3.4 ± 1.7	2.9 ± 1.7	12.4	0.002	<0.001 (0.3)	0.5 (0.1)	0.04 (0.3)
Nonsuicidal self-damaging acts (1–6)	2.2 ± 1.5	2.6 ± 1.7	2.1 ± 1.5	2.3	0.32			

Values are indicated as mean ± SD.
BP = bipolar spectrum disorders.
[a]Items from the 12-item Schedule for Affective Disorders and Schizophrenia for School Age Children, Present Version (K-SADS-P): Depressed mood; Excessive or inappropriate guilt; Anhedonia, Lack of interest, Apathy, Low motivation, or Boredom; Fatigue, Lack of energy, Tiredness; Difficulty concentrating, Inattention, Slowed thinking; Psychomotor agitation; Psychomotor retardation; Insomnia; Hypersomnia; Anorexia; Increased appetite; Suicidal ideation.
[b]After adjusting for sex, socioeconomic status, duration of illness, and significantly different comorbid disorders.
[c]Remained significant after Bonferroni correction.
[d]Group1 = BP children; Group 2 = adolescents with childhood-onset BP; Group 3 = adolescents with adolescent-onset BP.

circadian reversal, nonrestorative sleep, daytime sleep, hypersomnia, weight loss, leaden paralysis, and medical lethality of suicidal attempts as compared to children. In addition, adolescents with adolescent-onset BP showed more severe depressed mood, excessive guilt, social withdrawal, decreased appetite, rejection sensitivity, suicidal ideation, and seriousness of suicidal attempts as

compared with children, and more terminal insomnia than both childhood-onset groups. Adolescents with childhood-onset BP also exhibited significantly more negative self-image and recurrent thoughts of death than the adolescents with adolescent-onset BP and children. Finally, children had more severe irritability/anger than the adolescents with adolescent-onset BP.

Lifetime comorbid disorders (Table 4)

Adjusting for any confounding factors, both adolescent groups had higher prevalence of lifetime conduct and substance use disorders than children. Also, adolescents with adolescent-onset BP had more substance abuse than adolescents with childhood-onset BP and more panic disorder than children. Both childhood-onset groups had more lifetime ADHD than did the adolescents with adolescent-onset BP.

Discussion

In this large sample of youth with BP, both adolescent groups had their first episodes meeting criteria for major depression, and were more likely to have a lifetime history of a major depressive episode. In contrast, younger children were more likely to have had subsyndromal manic/hypomanic symptoms as their first episode. After adjusting for sex, SES, and duration of illness, more 'typical' and severe symptomatology was observed in both adolescent groups while manic, especially those with adolescent-onset BP. In contrast, mood lability was more frequent in children and adolescents with childhood-onset BP than adolescents with adolescent-onset BP. While depressed, both adolescent groups showed more severe depressive symptoms and higher rates of melancholic, atypical depressive symptoms and suicide attempts than children with BP. Irritability was the only symptom that was moderately higher in depressed children when compared with adolescents with adolescent-onset BP. As expected, earlier onset of BP was most commonly associated with lifetime comorbid ADHD. In contrast, older age was associated with higher rates of lifetime panic, conduct, and substance use disorders.

Before discussing the above-noted results, it is important to note the limitations of this study. First, recollection bias may have influenced the reported rate of symptoms. However, to minimize this problem, this study focused on the worst lifetime (present or past) manic and depressive symptoms. Second, the frequency and quality of the symptoms may change from one episode to the

Table 4. Lifetime prevalence of comorbid disorders (%)

Disorders	BP children (<12 years) (n = 173)	Adolescents with childhood-onset BP (n = 101)	Adolescents with adolescent-onset BP (n = 90)	Wald χ^2	Adjusted p-values[a]	Pair-wise comparisons p-values (Effect Size *d*)		
						Group 1 versus Group 2[c]	Group 1 versus Group 3[c]	Group 2 versus Group 3[c]
Any anxiety disorder	39.3	46.5	31.1	0.2	0.9			
Panic disorder	0.6	7.9	7.8	8.2	0.02	0.2 (0.3)	0.03 (0.3)	0.2 (0.2)
Separation anxiety	28.3	27.7	13.3	3.2	0.20			
Social phobia	5.2	4.0	6.7	2.5	0.29			
General anxiety disorder	12.7	12.9	13.3	0.2	0.89			
Obsessive compulsive disorder	4.6	11.9	3.3	2.3	0.32			
Posttraumatic stress disorder	4.0	11.9	5.6	3.3	0.20			
Attention-deficit hyperactivity disorder	71.7	69.3	31.1	18.9	<0.001[b]	0.9 (0.0)	<0.001 (0.6)	0.001 (0.4)
Oppositional defiant disorder	43.4	35.6	31.1	2.8	0.20			
Conduct disorder	6.4	19.8	15.6	13.7	0.001[b]	0.002 (0.4)	0.02 (0.4)	0.5 (0.1)
Substance/alcohol abuse/dependence	0.0	10.9	23.3	30.3	<0.001[b]	0.03 (0.3)	<0.001 (0.2)	0.01 (0.4)

Values are indicated as percent.
BP = bipolar spectrum disorders.
[a]After adjusting for sex, socioeconomic status, and duration of illness.
[b]Remained significant after Bonferroni correction.
[c]Group 1 = BP children; Group 2 = adolescents with childhood-onset BP; Group 3 = adolescents with adolescent-onset BP.

next and may vary with the reporter (child versus parent) (24). Future papers using prospective longitudinal data will address these two issues. Third, the base rates of some symptoms (e.g., lifetime delusions) were low. Fourth, the data analyzed for this report included only the worst lifetime (current or past) symptoms. These symptoms did not necessarily represent the mood symptomatology experienced by the child during her or his first mood episodes. Fifth, as depicted in Tables 2 and 3, some symptoms, although significantly different, showed low effect sizes. Nevertheless, even if these symptoms are not taken into account or after adjusting for multiple comparisons, the main story of this paper holds: older age was associated with more typical and severe manic and depressive symptoms. Sixth, lifetime comorbid disorders were not necessarily present during the same time period as the worst mood symptoms. Nevertheless, after adjusting for duration of illness, the types and rates of comorbid disorders follow the expected developmental trajectory (e.g., more ADHD in childhood-onset BP and more substance use disorder in adolescents). Finally, since most subjects included in this study were recruited from outpatient clinics and were Caucasian, the results of this study may not apply to other populations.

It appears that mood lability, as defined in this study by the K-MRS ['rapid mood variation with several mood states within a brief period of time which appears internally driven without regard to the circumstances' (19)], and to a lesser degree irritability/anger are more characteristic of childhood-onset rather than adolescent-onset mania even when adjusting for potential confounding factors such as comorbid disorders. Mood swings or lability are often described by parents of children with BP and have been reported in other cross-sectional and longitudinal prospective pediatric BP studies (2–5, 13, 16). However, it is important to note that these mood changes are not equivalent to the DSM 'rapid cycling' classification and that not every child with severe mood lability, especially if the symptoms are not episodic, has BP (4, 6, 7, 9, 25).

In contrast with prior reports (1, 11, 12), this study found that DSM manic symptoms were more severe in adolescents, particularly in those with adolescent-onset BP, than in children with BP. The reasons for this discrepancy are unclear, but it may be accounted for by methodological differences such as sample size, subject age, instruments used to ascertain symptoms, diagnostic criteria, and thresholds used to classify a symptom as positive and counting symptoms that overlap between disorders as positive for two or more disorders without taking into account the overall clinical picture of the child. It is also possible that early-onset BP has a different trajectory than adolescent-onset BP, which appears to be more similar to adult BP. Ongoing prospective follow-up of this early-onset group potentially could answer this question.

Speculatively, the greater prominence of cognitive elements of mania such as grandiosity may simply reflect the more advanced cognitive operations that are normatively associated with adolescent development. Also, differentiating abnormal grandiosity from normal fantasy is less difficult in adolescents that in younger children (7). The presence of these symptoms and the increased ability of an adolescent to express his or her affective state as compared to a younger child may explain, at least in part, why it is easier and more acceptable to diagnose BP in adolescents than in children. However, it remains for future, more refined neuropsychological research on prospectively observed samples to determine if very early onset of illness compromises the acquisition of more complex cognitive structures, which in turn impact on the phenomenology of BP.

Both the duration of illness and the transition into adolescence affected the rates and severity of depressive symptoms, with both adolescent groups having their first episode as major depression, higher rates of lifetime major depressive episodes, and more melancholic and atypical depressive symptomatology and suicidality when compared to children. In contrast, children showed less severe depressive symptomatology and more irritability. Thus, similar to the unipolar depression literature, the expression of major depression seems to be related to developmental pubertal changes and early age of onset (26–30). There is only one other study that carried out a post hoc analysis of the symptoms of bipolar depression in a sample of youth with bipolar depression and ADHD compared to youth with unipolar depression and ADHD (31). This study reported higher familial loading for mood disorders and more severe symptomatology, suicidal behaviors, anxiety, and conduct disorders in the depressed BP/ADHD youth.

The rates of lifetime comorbid disorders reported in this study are consistent with developmental correlates of psychopathological disorder, with childhood-onset BP having higher rates of ADHD and adolescents showing higher rates of substance abuse and conduct disorders than children. Also, comparable to other pediatric and adult studies of BP, anxiety disorders were common across groups, with panic disorder being found most frequently in adolescents (32–34).

Interestingly, the rate of comorbid disorders in this study tended to be lower than those reported in some studies (4). This may be due to fact that in COBY, a comorbid diagnosis was not assigned if overlapping symptoms presented only during a mood disorder episode.

This and other studies have reported that early-onset BP has a somewhat different phenotype, higher familial loading for mood disorders, and a different picture of comorbid disorders (1, 7, 9, 35–37). These findings have suggested that early age of onset may carry a different genotype for BP that differentially influences disease phenotype, course, patterns of comorbidity, and functional outcome. However, we cannot determine from this analysis whether the differences found between child and adolescent age of onset subgroups are an independent effect of age when illness begins, or are affected by susceptibility genes that confer early age of onset. However, interestingly, studies of adult BP have noted heterogeneity of linkage associated with psychotic features and anxiety (38), as well as familiality of a range of phenotypic characteristics in families with BP (39). Whatever the reason for these differences, it will be crucial for ongoing molecular, genetic, neuroimaging, and treatment studies to take into account the age of BP onset, maturational effects, and the presence of comorbid disorders and differential exposure to stress to fully explicate research findings.

In summary, older age was associated with more severe and typical mood symptomatology. However, there are differences and similarities in the type, intensity, and frequency of BP symptoms as well as comorbid disorders in youth depending, at least in part, on the age at onset and duration of BP and the level of psychosocial development. These factors, together with the normal difficulties children have expressing and modulating their emotions, may explain the existing complexities in diagnosing and treating BP in this population and suggest the need for developmentally sensitive pharmacological and psychosocial treatments.

The presence of comorbid disorders and sometimes their respective treatments may further complicate the identification and treatment of BP and be associated with worse prognosis (40, 41). Thus, it is critical that these disorders be identified and differentiated from the symptoms of BP, and if appropriate, promptly treated. For example, clinicians should be aware of the possibility that an adolescent with childhood-onset BP may also have ADHD, since some symptoms of ADHD tend to improve with age (e.g., hyperactivity). Furthermore, selective serotonin reuptake inhibitors are efficacious for the treatment of anxiety disorders in youth, but may induce mood destabilization in youth with BP.

Clinicians should be aware that BP, particularly in adolescents, often initially presents with an episode of major depression, posing an important clinical dilemma, since the treatment of these youth with antidepressants may worsen their clinical outcome. In these cases, the presence of psychosis, pharmacologically induced mania/hypomania, and high familial loading for BP may indicate increased risk of developing BP (42–44). Finally, after puberty, the frequency and severity of depression as well as potentially lethal suicidal behaviors and substance abuse become more common, indicating the need for early identification and treatment of this disorder to avoid its serious consequences.

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This paper is dedicated to Henrietta Leonard, M.D.

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