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Four-Year Longitudinal Course of Children and Adolescents with Bipolar Spectrum Disorder:

The Course and Outcome of Bipolar Youth (COBY) Study

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Abstract

Objective—To assess the longitudinal course of youth with bipolar spectrum disorders.

Methods—413 youth (7–17 years) with bipolar-I (n=244), bipolar-II (n=28), and bipolar Not-Otherwise- Specified (NOS) (n=141) were recruited mainly from outpatient clinics at the University of Pittsburgh, Brown, and UCLA. Symptoms were ascertained retrospectively on average every 9.4 months for 4 years using the Longitudinal Interval Follow-up Evaluation. Rates and time to recovery and recurrence and week-by-week symptomatic status were analyzed.

Results—Approximately 2.5 years after onset of their index episode, 81.5% of subjects fully recovered, but 1.5 years later 62.5% had a syndromal recurrence, particularly depression. One-third of the subjects had one syndromal recurrence and 30% ≥ 2 syndromal recurrences. The polarity of the index episode predicted the polarity of subsequent episodes. Subjects were symptomatic during 60% of follow-up time, particularly with subsyndromal symptoms of depression and mixed-polarity, with numerous changes in mood polarity. Manic symptomatology, especially syndromal, was less frequent and bipolar-II was mainly manifested by depressive symptoms. Forty-percent of subjects had syndromal and/or subsyndromal symptoms during 75% of follow-up period. During 17% of follow-up time subjects, especially those with bipolar-I, experienced psychosis. Twenty-five percent of bipolar-II subjects converted into bipolar-I and 38% of bipolar-NOS converted into bipolar -I/II. Early-onset, bipolar-NOS, long duration, low socio-economic status, and family history of mood disorders were associated with poorer outcomes.

Conclusions—Bipolar spectrum disorder in youth is an episodic disorder characterized by subsyndromal and, less frequently, syndromal episodes with mainly depressive and mixed symptoms and rapid mood changes.

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Introduction

Existing prospective naturalistic studies of children and adolescents with bipolar disorder (mainly subtype I), have shown that while rates of recovery from index episodes are high (70%–100%), of those who recover, up to 80% will experience one or more syndromal recurrences over a period of 2 to 5 years.[1–4] Moreover, prospective studies have shown that similar to findings reported for adults, [1, 3, 4] youth with bipolar disorder experience frequent mood fluctuations of varying intensities throughout 60%–80% of the follow-up time, particularly depressive and mixed symptoms.

Factors associated with worse longitudinal outcome include early age-of-onset, long duration, mixed episodes, rapid cycling, psychosis, subsyndromal symptoms, comorbid disorders, low socioeconomic status, exposure to negative life events, lack of psychotherapy treatment, poor adherence to pharmacological treatment, and family psychopathology. [1–6]

A prior "Course and Outcome of Bipolar Youth (COBY)" study in 263 youth with bipolar spectrum disorders followed for an average of 2 years, showed that most of the follow-up time youth experienced subsyndromal and syndromal mood symptomatology and frequent mood fluctuations.[4] Twenty percent of the youth with bipolar-II converted to bipolar-I, and 25% of youth with bipolar- Not Otherwise Specified (NOS) converted into bipolar-I or bipolar-II. The aim of the present paper was to extend COBY's prior findings in a larger sample of youth with bipolar spectrum disorders followed for a longer time. For this purpose, the data was evaluated with two different, but complementary analyses. First, to compare with existent literature, analyses using the standard definitions of *syndromal* recovery and recurrence and survival analytic techniques were performed. However, since pediatric bipolar disorder is not only manifested by discrete syndromal recurrences, but numerous subsyndromal episodes and mood changes, analyses of the week-by-week mood symptoms over the follow-up period were also performed. Subsequent reports will address the outcome in subjects with subsyndromal recoveries, suicidal behaviors, health services utilization, psychosocial functioning, and the effects of other factors such as exposure to negative life events, specific comorbid disorders, and treatment.

Methods

Subjects

The methods for COBY have been described in detail elsewhere.[4, 7] Briefly, youth ages 7 to 17 years 11 months with Diagnostic and Statistical Manual-IV (DSM-IV) bipolar-I, II, and operationally [4, 7] defined bipolar-NOS were included. Youth with COBY-defined bipolar-NOS were previously shown to convert to bipolar-I/II and have a comparable, but less severe clinical picture, and similar family history, rates of comorbid disorders, and longitudinal outcome as compared to bipolar-I subjects.[4, 7]

Youth with schizophrenia, mental retardation, autism, and mood disorders secondary to substances, medications or medical conditions were excluded.

Subjects were recruited from outpatient clinics (67.6%), inpatient units (14.3%), advertisement (13.3%), and referrals from other physicians (4.8%), and were enrolled independent of current mood state or treatment status.

The analyses presented in this report are based on the prospective evaluation of 413 subjects, including 244 (59.1%) with bipolar-I, 28 (6.8%) with bipolar-II and 141 (34.1%) with bipolar-NOS who had at least one follow-up assessment. At the time this article was written, subjects had been prospectively interviewed every 37.5±20.8 weeks for an average of 191.5 ± 75.7

weeks. Subjects with bipolar-II were followed significantly longer (227.4±76.6 weeks) than the other two bipolar subtypes (bipolar-I: 183.2±71.8 weeks, bipolar-NOS: 198.7±79.8 weeks) (F=5.4, p=.005).

As described in more detail in a prior publication, [7] at intake subjects with bipolar-NOS were the youngest, followed by subjects with bipolar-I and then those with bipolar-II (Table 1). More youth with bipolar-NOS were in Tanner stage-I of sexual development than those with bipolar-II and more subjects with bipolar-II were Tanner IV/V than those with bipolar-I and -II. The mean age-of-onset for mood symptoms and DSM-IV mood episodes was 8.4 and 9.3 years, respectively (for definition of age-of-onset see below). Subjects with bipolar-II had the onset of their mood symptoms and episodes significantly later than the other two bipolar subtypes. As expected, by definition, the polarity of the index episode reflected the bipolar subtype with mania or hypomania being more common in youth with bipolar-I than those with bipolar-II or NOS. However, youth with bipolar-II had significantly more depressive index episodes that the other two bipolar subtypes. Subjects with bipolar-I had more lifetime psychosis than those with bipolar-NOS (for all above comparisons p-values <.05, Cohen's *d*: 0.3–0.9). There were no other significant between group differences.

The subject retention rate at the time this manuscript was written was 86%, with 93% of subjects completing at least one follow-up interview. Except for lower rates of anxiety disorders in subjects who dropped from the study (54.5%, vs. 38.7%, p=0.02) there were no other demographic or clinical differences between the subjects who continued or withdrew from COBY.

Procedures

Each university's Institutional Review Board approved the study and consent was obtained from children and adolescents and parents. At intake, children and parents (about their children) were directly interviewed for the presence of current and lifetime psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version (K-SADS-PL), [8] the Kiddie Mania Rating Scale (K-MRS),[9] and the depression section of the KSADS-P.

Longitudinal changes in psychiatric symptomatology since the previous evaluation were assessed using the Longitudinal Interval Follow-up Evaluation and tracked on a week-by-week basis using this instrument's Psychiatric Status Rating scale.[10,11] The Psychiatric Status Ratings are numeric values that have been operationally linked to the DSM-IV criteria. DSM-IV criteria information is gathered in the interview, and then translated into ratings for *each week* of the follow-up period. The ratings indicate the severity level of an episode, as well as whether the subject has recovered or had a recurrence. For mood disorders, the PSR scores range from 1 for no-symptoms, 2 to 4 for varying levels of subthreshold symptoms and impairment, and 5 to 6 for full criteria with different degrees of severity or impairment. The consensus scores obtained after interviewing parents and their children were used for the analyses. For more information regarding the use of the Longitudinal Interval Follow-up Evaluation and an example of the week-by-week scoring of mood symptoms using the Psychiatric Status Rating scale please see (here the web link provided by the journal).

Family history of mood disorders was ascertained using the Family History Screen.[12] The Petersen Pubertal Developmental Scale (PDS)[13] and their equivalent Tanner stages were used to evaluate and categorize pubertal stages. Socioeconomic status was ascertained using the 4-factor Hollingshead scale.[14]

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 and

the Psychiatric Status Ratings. The overall KSADS kappas coefficients for psychiatric disorders were ≥ 0.8. The intraclass correlation coefficients for the KSADS-MRS and the KSADS DEP-P were ≥ 0.95. The intraclass correlation coefficients for syndromal and subsyndromal mood disorders ascertained through the Psychiatric Status Ratings and using the methods as described eslewhere[11] were 0.75. More specifically, the intraclass coefficient correlations and the Kendall's coefficients of concordance for a major depressive episode were between 0.74 and 0.79, respectively and for mania/hypomania, 0.6–0.67, respectively.

During the follow-up, the K-MRS and DEP-P, were used as an additional assessment of mood symptom severity for the week of the month prior to interview in which symptoms were the most severe. A comparison of the maximum Psychiatric Status Ratings scores for depression and mania for the 4-weeks prior to each follow-up assessment with the maximum scores on the K-MRS and DEP-P, for the same time period showed Spearman correlations of 0.82 ($p < .0001$) and 0.77 ($p < .0001$), respectively, thus lending further support for the reliability of the PSR scores.

Definitions of Clinical Course

Age of bipolar-onset was defined as the onset of a DSM-IV mood episode or an episode fulfilling the COBY's modified DSM-IV bipolar-NOS criteria. The minimum age of onset was arbitrarily set at age 4. Duration of bipolar disorder was calculated since the age of bipolar-onset. The index episode was defined as the current or most recent DSM-IV mood episode.

The percentage of follow-up weeks spent asymptomatic or symptomatic in the different mood symptom categories during the entire follow-up period were computed, based on the Psychiatric Status Rating scores for each subject. Full recovery was defined as 8 consecutive weeks with a score of ≤2 (minimal or no mood symptoms). [4, 15] Time to recovery from the index episode was measured from the onset of the index episode, which occurred prior to the intake assessment. A recurrence (new episode) required a Psychiatric Status Rating ≥ 5, with duration of 1-week for mania/hypomania and 2-weeks for depression. Similar to the existing literature,[15] "change in mood polarity" was defined as a switch between depression (rating ≥ 3) and mania/hypomania (rating ≥ 3) or vice versa with or without intervening weeks at the asymptomatic status or when a week had both mania/hypomania and depression rating scores of 3 or more. The above- noted definition of "changes in mood polarity" is not the equivalent of DSM rapid cycling. For this last category as well as for mixed episodes, COBY utilized the DSM-IV definitions.

Statistical Analyses

The syndromal recoveries and recurrences manifested in bipolar disorder were evaluated using survival analyses and Cox proportional hazards regressions.,[16] The numerous ongoing mood changes and periods of subsyndromal symptoms of bipolar disorder were evaluated using within and between group analyses of the week-by-week syndromal and subsyndromal symptoms stratifying by bipolar subtype. Differences within and between groups were analyzed using standard parametric and non-parametric univariate tests.

About 14.0% of the sample had their most recent mood episode offset and recovered before intake. Since the analyses with and without these subjects yielded similar results, all subjects were included in the analyses.

The data were censored after subjects with bipolar-II and -NOS converted into other bipolar subtypes.

For all of the above noted analyses the effects of demographic variables, age, bipolar subtype, psychosis, age of bipolar-onset, duration of bipolar disorder, presence of any comorbid disorder, and family history of mood disorders and their interactions were evaluated. The above noted variables were examined univariately and those significantly associated with the outcome of interest were analyzed using multiple linear regressions. Analyzing the data using generalized linear models yielded similar results. To assess the effects of age on the child's outcome, the sample was divided into three groups: children < 12 years, adolescents ≥ 12 years with onset of their episodes prior to 12 years, and adolescents with onset of their episodes at or after 12 years. Analyses including age or pubertal status yielded similar results. Thus, only the results including age are presented. Also, since bipolar subtype and polarity of the index bipolar episode were highly associated (φ=0.75, $p \leq 0.0001$) (also see Table 1), only the bipolar subtype was included in the analyses.

All p values are based on two-tailed tests with $\alpha = 0.05$.

Results

Survival Analyses

Recovery from the index episode (Table 2, Fig 1)—A median of 123.7 weeks after the onset of the index episode, 81.4% of subjects had full recovery. Youth with bipolar-I showed significantly higher rates of recovery compared to those with bipolar-NOS, and those with bipolar-I and -II had shorter times to recovery compared to those with bipolar-NOS. In addition to the standard 8-week duration criterion for recovery, analyses using 2, 4, and 6 weeks with minimal or no mood symptoms yielded 88%, 84%, and 81% rates of recovery, respectively.

Less likelihood of full recovery was associated with bipolar-NOS (vs. bipolar-I and II; Hazard Ratio:0.62,95%CI:0.49–0.97); children with childhood-onset (vs. adolescents with adolescent-onset, Hazard Ratio:0.50, 95%CI:0.37–0.67 and vs. adolescents with childhood onset, Hazard Ratio:0.70,95%CI:0.50–0.99); non-Caucasian race (Hazard Ratio:0.60, 95% CI:0.42–0.84), longer duration of illness (Hazard Ratio: 0.83, 95%CI:0.78–0.88), and positive family history of mania/hypomania in first- and second-degree relatives (Hazard Ratio:0.79, 95%CI:0.63–0.99). Conversely, the interaction of living with both biological parents and having higher socio-economical status was associated with greater likelihood of recovery (Hazard Ratio:1.23, 95%CI:1.01–1.51). No other significant predictors or interactions were found.

Recurrence after recovering from the index episode (Table 2, Fig 2)—Of the subjects who recovered, 62.5% (210/336) had a syndromal recurrence at a median of 71 weeks after recovering from their index episode. Higher rates of, and shorter times to, recurrence occurred among subjects with bipolar-I and bipolar-II subtypes as compared to subjects with bipolar-NOS.

Subjects who recovered had on average 1.1±1.2 syndromal recurrences during the 4-year follow-up. More specifically, 33% (110/336) had one recurrence, 20% (66/336) two recurrences, and 10% (34/336) three or more syndromal recurrences during the follow-up period. Across all bipolar subtypes, most syndromal recurrences after the index episode were major depressive episodes (59.5%), followed by hypomania (20.9%) mania (14.8%), and mixed (4.8%). Interestingly, if the index episode was a major depression, mixed, hypomania, or NOS, 64% (109/171) of the first recurrences were major depressions, followed by mania/hypomania (30%; 52/171) and then mixed episodes (6%; 10/171). For subjects whose index episode was mania, the first recurrences were mania/hypomania (59%; 23/39) followed by depression (41%; 16/39). A subanalysis including only children with bipolar-I and ages similar to a prior bipolar-I longitudinal study [3] yielded similar results.

Increased likelihood of recurrence was associated with bipolar-I and bipolar-II (vs. bipolar-NOS, Hazard Ratio:1.37,95% CI:1.01–1.88); lower socio-economical status (Hazard Ratio: 0.87, 95%CI:0.77–0.97), and $1^{st}/2^{nd}$ degree family history of mania/hypomania (Hazard Ratio: 1.38, 95%CI:1.04–1.84). No other significant predictors or interactions were found.

Week-by-Week mood analyses

Analyses for the entire sample (Table 3)—All youth spent approximately 40% of the follow-up time asymptomatic and 60% symptomatic (41.8% subsyndromal and 16.6% with syndromal symptomatology). Subjects spent significantly more time in syndromal depression or mixed/cycling than syndromal mania/hypomania. There were no differences in the time spent in each subsyndromal polarity.

Within-group analyses—Analyses *within* each bipolar subtype showed that youth with bipolar-I and bipolar-NOS spent significantly more follow-up time with subsyndromal than syndromal symptoms. There was no difference in the duration of follow-up time spent with syndromal and subsyndromal symptoms for youth with bipolar-II. While experiencing syndromal symptoms, all 3 bipolar-subtypes spent more time with depression and mixed/cycling symptomatology than mania/hypomania. While experiencing subsyndromal symptoms, youth with bipolar-I spent more time with subsyndromal mania and mixed symptoms than subsyndromal depression and youth with bipolar-NOS spent more time with subsyndromal mixed symptoms than the other two subsyndromal polarities. There were no differences in the follow-up time spent in each subsyndromal polarity for youth with bipolar-II. For all above comparisons, p-values ≤0.05, Cohen's d_s: 0.45–1.3).

Between-group analyses—Comparisons *between* each bipolar subtype showed that youth with bipolar-I spent more follow-up time asymptomatic than those with bipolar-NOS. Youth with bipolar-I and II spent similar amounts of time with syndromal symptoms, but more than those with bipolar-NOS. In contrast, youth with bipolar-NOS spent significantly more weeks with subsyndromal symptoms than the other two bipolar subtypes. Within syndromal periods, youth with bipolar-I and II spent more time with hypomania than those with bipolar-NOS, youth with bipolar-II spent more time in major depression episodes than the other two bipolar subtypes, and youth with bipolar-I spent more weeks mixed/cycling than those with bipolar-NOS. By definition, youth with bipolar-II and NOS did not spend any weeks with syndromal mania or mixed symptomatology. Within subsyndromal periods, subjects with bipolar-I spent more weeks with subsyndromal manic symptoms compared to those with bipolar-II (for all above-noted comparisons, p-values ≤0.05, Cohen's d_s: 0.24–0.63).

Multiple linear regression models—The following variables were associated with more follow-up weeks with any mood symptomatology: low socio-economical status (t=4.28, p <0.001), children with childhood-onset (vs. adolescent with adolescent-onset, t=5.07, p<0.001), adolescent with childhood-onset (vs. adolescent with adolescent-onset, t=4.05, p <0.001), any comorbid disorder (t=2.62, p=0.009). No other significant predictors or interactions were found. Except for bipolar-I and II predicting more follow-up time with syndromal symptomatology, and bipolar-NOS and being non-Caucasian predicting more time with subsyndromal symptomatology, separate linear regressions for syndromal and subsyndromal symptomatology yielded similar results.

Subjects with chronic symptoms—In addition to the analyses of the percentage of *time* that subjects spend symptomatic (syndromal plus subsyndromal symptoms) presented above, chronicity, as measured by the percentage of *subjects* who had syndromal and/or subsyndromal mood symptoms ≥ 75% of the follow-up time, was calculated. Approximately 38% of the subjects, particularly those with bipolar-I (bipolar-I > bipolar-NOS, $\chi^2 = 5.66$, p=.

02) experienced chronic mood symptoms with only 3% of subjects having full syndromal criteria for mood episodes. Most of these chronic symptoms were mixed (46%), followed by depression (33.8%) and mania/hypomania (21%).

Psychosis—Clinically relevant psychotic symptoms were defined as a Psychiatric Status Rating score for delusions and/or hallucinations = 3 (definitely present). Sixteen-percent of the subjects experienced psychotic symptoms during the follow-up. For these youth, psychotic symptoms were manifested during 17.1% of the follow-up time. Bipolar-I subjects spent significantly more time with psychotic symptoms than those with bipolar-NOS.

Change in mood polarity (Table 3)—Shifts in mood polarity occurred a mean of 36.2± 46.9 times during the entire follow-up period, or 12.1± 15.0 times per year. Specifically, a change in mood polarity once per year or less was observed in 31.2% of sample, 5 or more times per year in 51.1%, 10 times or more per year in 38.7%, and more than 20 times per year in 23.7%. Except for subjects with bipolar-NOS being more likely to have at least 10 changes in mood polarity per year compared to those with either bipolar-I or - II (p-values ≤ 0.03, Cohen's d_s: 0.23–0.45), there were no other between group differences. In a multiple linear regression, lower socio-economic status (t= 3.90, p=0.001), children with childhood-onset (vs. adolescents with adolescent-onset, t=4.02, p=0.001), adolescents with childhood-onset (vs. adolescents with adolescent-onset, t=3.73, p=0.001) and presence of any comorbid disorder (t=2.04 p=0.04) were significant predictors of greater number of changes in mood polarity per year. There were no other significant predictors and interactions.

Conversion from bipolar-II to bipolar-I and from bipolar- NOS to bipolar-I or II—Of the 169 youth with bipolar-II and NOS, 61 (36.1%) converted to a different bipolar subtype over follow-up. Of these, 25% (7/28) with bipolar-II converted into bipolar-I, 19.9% (28/141) with bipolar-NOS converted into bipolar-I, and 18.4% (26/141) with bipolar-NOS converted into bipolar-II (38.3% of bipolar-NOS subjects converted overall). Factors associated with conversion will be presented in another paper.

Discussion

Corroborating prior COBY findings,[4] this study showed that bipolar spectrum disorders in youth are episodic disorders most often characterized by subsyndromal episodes and, less frequently, by syndromal episodes, with mainly depressive and mixed symptoms and rapid mood changes.

Utilizing the standard DSM-IV and literature definitions of syndromal recovery and recurrence, survival analyses indicated that about 2.5 years after onset of their index episode approximately 80% of youth with bipolar spectrum disorder achieved full recovery. However, 1.5 years after full recovery, approximately 60% of the subjects had at least one syndromal recurrence. Compared to youth with bipolar-NOS, youth with bipolar-I and II were more likely to recover but have less durable recovery.

During the entire follow-up period, 1/3 of the subjects had at least one syndromal recurrence and 30% experienced ≥ 2 syndromal recurrences. Most of these syndromal recurrences were major depressions, followed by hypomanic, manic, and mixed episodes. In general, the polarity of the index episode predicted the polarity of subsequent episodes.

The above analyses only focused on recovery and recurrence of syndromal symptoms. Complementary week-by-week analyses provided a more in depth clinical picture of the course of bipolar disorder showing that distinct periods of full syndromal mood episodes exist in youth with bipolar spectrum disorder. However, they are embedded in more prevailing and longer

periods of subsyndromal mood symptomatology. More specifically, youth with bipolar spectrum disorders were symptomatic during 60% of the follow-up time, during which subjects spent about 2.5 times more time with subsyndromal than syndromal symptomatology. Mixed/cycling and depressive symptoms accounted for the greatest proportion of time ill. In contrast, purely manic symptomatology, especially at the full syndromic level, was less common. Rapid mood changes were ubiquitous and psychotic symptoms were relatively common, particularly in subjects with bipolar-I. Chronic symptoms, defined as 75% or more of the follow-up time with any type of symptoms, were present in 38% of the subjects. Almost all of these chronic symptoms were subsyndromal and of the depressive type.

The week-by-week analyses also shed light on the similarities and differences in the longitudinal patterns of symptom phenomenology of youth with bipolar-I, II and NOS. Bipolar-I was manifested with more time with subsyndromal than syndromal symptoms. Most of the syndromal time was characterized by mixed/cycling or depressive symptoms and most of the subsyndromal time was with subsyndromal manic or mixed symptoms. Youth with bipolar-II spent equal amounts of time in syndromal and subsyndromal states. The syndromal episodes were most commonly depression or mixed states, but there were no differences in the time spent with any type of subsyndromal symptoms. Finally, bipolar-NOS was mainly manifested by periods of subsyndromal mixed symptoms, closely followed by periods of subsyndromal manic or depressive symptoms.

Between-group comparisons provided preliminary validation for the subtyping of bipolar disorder in youth. In general, in comparison with other subtypes, each bipolar subtype continued to show some category specific symptomatology. For example, during follow-up, youth whose initial diagnosis was bipolar-I showed more syndromal, mixed/rapid cycling and manic/hypomanic symptoms than those with bipolar-NOS; youth with bipolar-II spent more time in hypomania than those with bipolar-NOS and more time in depression than those with bipolar-I and NOS; and youth with bipolar-NOS spent significantly more follow-up time with subsyndromal symptoms than did subjects with bipolar-I and II. However, there was some symptom overlap among the different bipolar subtypes, especially in those with BP-I and II. Moreover, 25% of bipolar-II subjects converted into bipolar-I and 38% of bipolar-NOS converted into bipolar-I and II.

Although there were some differences in the demographic and clinical factors associated with the outcome variables measured (e.g., recovery, time symptomatic, and changes in polarity), in general, early-onset of bipolar disorder, presence of comorbid disorders, family history of mood disorders (particularly mania/hypomania), low socio-economic status, and non-Caucasian race were associated with worse outcome. Long duration of illness was also associated with less recovery, with each year of illness decreasing the likelihood of recovery by 20%.

Before continuing the discussion of COBY's findings it is important to note the limitations of this study. First, despite the efforts to obtain precise information, the data collected through the Longitudinal Interval Following Evaluation is subject to retrospective recall bias. Although it appears that this instrument has adequate psychometric properties,[1, 4, 11] further studies using the methods described by Warsaw et al., [11] and including blind interviewers are warranted. Second, although COBY utilized the standard literature definitions of course for recovery and recurrence, [1, 3, 17] the rates and length of the mood episodes may change according to the duration criteria and symptom threshold severity chosen. Third, the results pertaining to subjects with bipolar-II should be considered tentative given the relatively small size of this group. However, across all bipolar subtypes, after depression most syndromal recurrences were hypomanias. Finally, as most subjects were Caucasian and were recruited primarily from outpatient, and to a lesser extent, from inpatient settings, the generalizability of the observations

to other populations remains uncertain. Nevertheless, non-referred adolescents with bipolar disorder have been shown to have similar course and high morbidity. [5]

Despite methodological differences, all existing studies of the course of bipolar disorder in youth, regardless of country and source of ascertainment, show that likelihood of recovery from the index episode is high. [1–4] However, as with adult populations, in spite of the high rate of recovery, the rates of recurrence, persistence of subsyndromal clinical morbidity, and rapid and frequent changes in mood polarity is also high and most syndromal and subsyndromal recurrences are depressions.[15, 18–22] However, it appears that the polarity of the index episode predicts polarity of the subsequent episodes, [20, 23–27] and suggests the possibility of using specific psychosocial and pharmacological treatments based on the polarity of the index episode.

The results of this and other emerging pediatric studies suggest strong general similarities in the longitudinal course of bipolar disorder in youth and adults with the longitudinal course mainly manifested by subsyndromal symptomatology and rapid mood changes. [1–4, 28] However, there is evidence that very early-onset appears to confer greater liability for a more chronic and fluctuating course, mixed/cycling episodes, high rates of comorbid disorders, and increased rates of mood disorders in families.[1, 3, 29–31] Converging with these accounts are reports indicating that adults whose onset of bipolar is dated to childhood have a more severe and chronic course, more episodes, changes in mood polarity, suicidality, and comorbidity, and lower quality of life. [32–34]

Comparable with other literature, childhood-onset bipolar disorder, comorbid disorders, positive family history for mood disorders, and low socio-economic status were associated with poorer outcome.[1–4, 6] Moreover, there was decreasing probability of recovery with increasing duration of illness. This further underscores the importance of early detection of illness and rapid implementation of stabilizing treatments, which may be of even greater urgency for youth with bipolar disorder and with risk factors associated with poorer outcome.

Similar to literature on major depression, [35] it appears that there are some differences in the factors associated with the various indices of clinical outcome (e.g., recovery, recurrence, time symptomatic). Moreover, as the polarity of the index episode was shown to convey different prognostic characteristics, it may be that these observations will be informative to clinical practice. As an example, since youth with depression were seen to have more depressive recurrences, they may require more aggressive and specific therapies to reduce the risk of future depressive episodes.

To our knowledge, and of importance given the modal age of onset of bipolar-II illness during adolescence, [17, 26, 36] COBY is the first naturalistic, prospective study of this affective subtype in youth. Consistent with adult data on high levels of morbidity associated with this subtype, bipolar-II had greater overall recurrence risk and more depressive morbidity compared to youth with bipolar-I, and had comparable rates of non-affective comorbidity, suicidality, non-suicidal self-injurious behaviors, functional impairment, and family history for mood and bipolar disorders as youth with bipolar-I.[6, 7, 31, 37–39] Also, bipolar-II in youth appears to be a far less stable phenotype than in adults as 25% of the bipolar-II youth in this cohort converted to bipolar-I, a rate higher than that reported in adult studies.[40] Since this disorder is mainly characterized by episodes of syndromal and subsyndromal depression across the lifespan, it is well appreciated that periods of hypomania can be misconstrued as normal fluctuations in mood or erratic behavior, and perhaps more so in adolescents,[26, 41] such that the risk of misclassification as recurrent unipolar depression or other non-affective disorders is high.

Bipolar-NOS was characterized by rates of comorbidity, suicidality, functional impairment (except hospitalizations), and family history for mood disorders equivalent to those in subjects

with bipolar-I and II.[6, 7, 31, 37–39] These findings together with the high rates of conversion to bipolar-I or II, provide preliminary validation of its nosological affinity with bipolar disorder. It is to be stressed, however, that our classification relied on the presence of an affective phenotype that differed from bipolar-I or II due to failure to meet DSM-IV duration requirements for these subtypes. Thus, our findings are in concert with adult literature [17, 41, 42] emphasizing the clinical relevance of this phenomenon, yet one that is often overlooked given the predominance of syndromal depression and subsyndromal manic/mixed symptoms of short duration in its expression. Results from COBY suggest that bipolar-NOS is an *episodic* illness, albeit often comprising subsyndromic episodes that should be considered different from youth with behavior disorders and "severe mood dysregulation".[43]

In summary, although distinct episodes of full syndromic mood symptomatology as well as durable periods of euthymia can be identified in youth with bipolar disorder, the course of bipolar spectrum disorders among children and adolescents is predominantly characterized by subsyndromal and, much less frequently, syndromal episodes. Rapid mood changes are evident during these episodes, which are mainly of depressive and mixed polarity. At follow-up each bipolar subtype showed some distinct clinical characteristics and course, but there was overlap in their symptoms and substantial conversion from bipolar II and NOS into other bipolar subtypes. The course of bipolar disorder, the relative infrequency of syndromic DSM manic episodes, the effects of development in symptom manifestation and the high prevalence of comorbid disorders may account, at least in part, for the difficulties in recognizing and managing this illness in youth. The recurrence, chronicity, and psychosocial morbidity associated with this illness in critical developmental stages calls for its prompt recognition and the development of more efficacious treatments, particularly since each year of illness appears to decrease the likelihood of recovery.

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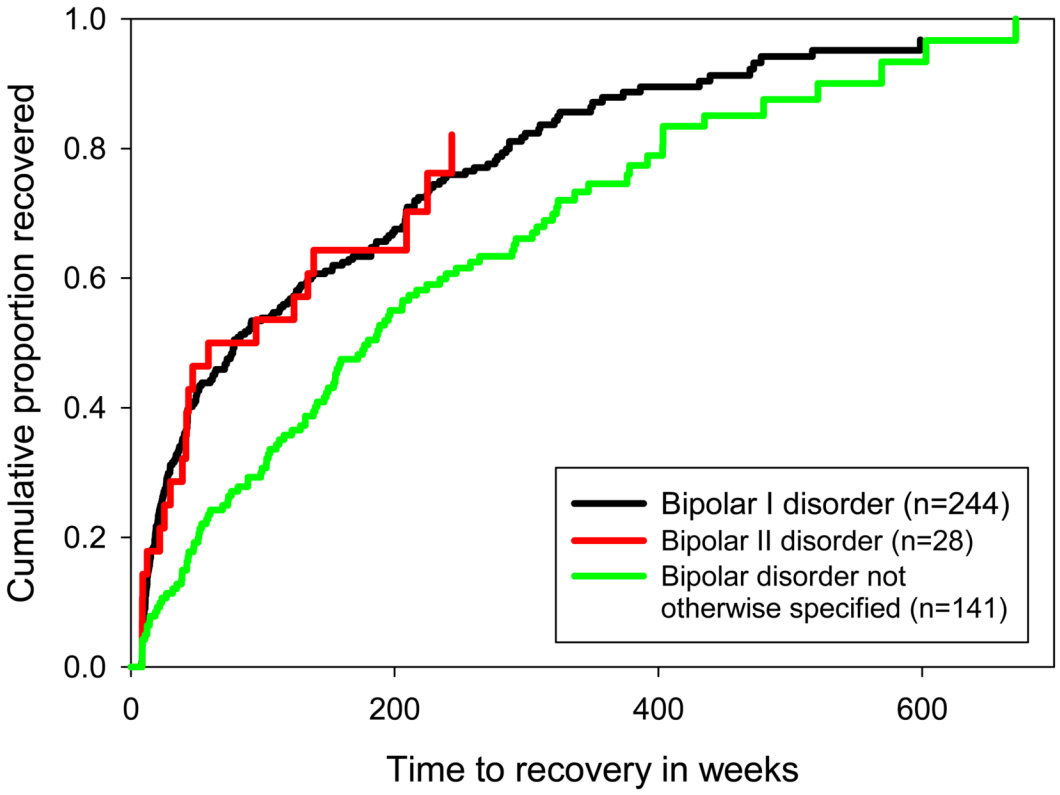

Figure 1.

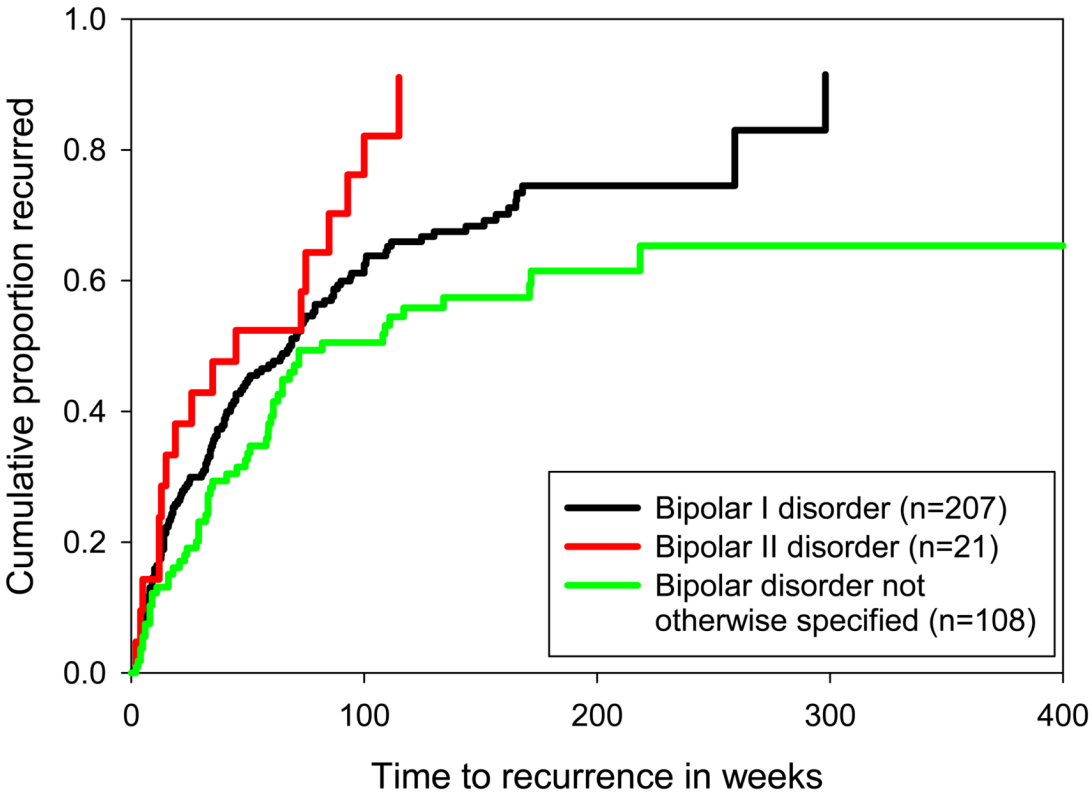

Figure 2.

Table 1

Demographic and Clinical Characteristics Among Subjects by Bipolar Subtype

	All Sample (n=413)		Bipolar-I (n=244)		Bipolar-II (n=28)		Bipolar-NOS (n=141)		Analyses		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	df	Statistic	p
Age	12.6	3.3	12.8[a]	3.2	14.8[b]	2.7	11.9[c]	3.2	2,140	F=11.0	<0.001
SES	3.4	1.2	3.4	1.3	3.8	0.9	3.4	1.1	2	Kruskal-Wallis:3.1	0.2
	N	%	N	%	N	%	N	%			
Sex (Male) %	221	53.5	123	50.4	12	42.9	86	61.0	2	χ^2=5.4	0.07
Race (Caucasian)%	339	82.1	200	82.0	24	85.7	115	81.6	2	χ^2=0.3	0.9
Living with Both natural parents %	174	42.1	94	38.5	17	60.7	63	44.7	2	χ^2=5.6	0.06
Pubertal Status I	87	27.0	47	25.5 [a]	2	7.4 [b]	38	34.2[a]			
Pubertal Status II–III	89	27.6	50	27.2	8	29.6	31	27.9	4	χ^2=9.6	0.05
Pubertal Status IV–V	146	45.3	87	47.3 [a, b]	17	63.0 [a]	42	37.8 [b]			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Age of onset of mood symptoms (years)	8.4	4.0	8.4[a]	4.3	10.5[b]	3.9	7.9[a]	3.4	2	Kruskal-Wallis:19.5	0.009
Duration of mood symptoms(years)	4.4	3.0	4.5	3.1	4.3	2.6	4.2	2.9	2,410	F=0.4	0.7

	All Sample (n=413)		Bipolar-I (n=244)		Bipolar-II (n=28)		Bipolar-NOS (n=141)		Analyses		
Age onset of a DSM mood episode*	9.3	3.9	9.3[a]	4.1[a]	11.8[b]	3.2	8.7[a]	3.5	2	Kruskal-Wallis:4.5	0.001
Duration of bipolar disorder (years)**	3.3	2.5	3.5	2.7	3.0	1.3	3.2	2.3	2	Kruskal-Wallis:0.5	0.8
	N	%	N	%	N	%	N	%			
Polarity of Index Episode											
Depressed	58	14.0	34	13.9 [a]	11	39.3 [b]	13	9.2 [a]			
Hypomanic	34	8.2	17	7.0 [a]	10	35.7 [b]	7	5.0 [a]			
Manic	77	18.6	77	31.6 [a]	0	0.0 [b]	0	0.0 [b]	8	χ^2=229.29	0.001
Mixed	70	17.0	68	27.9 [a]	0	0.0 [b]	2	1.4 [b]			
NOS	174	42.1	48	19.7 [a]	7	25.0 [a]	119	84.4 [b]			
Psychosis (%)	92	22.3	69	28.3 [a]	4	14.3[a, b]	19	13.5 [b]	2	χ^2=12.4	0.002
Any Comorbidity (%)	351	85.0	206	84.4	22	78.6	123	87.2	na	Fisher's Exact	0.4
					Family History %						
1st degree with Mania/ Hypomania	143	36.8	87	38.0	12	44.4	44	33.1	2	χ^2=1.6	0.4
1st degree with Depression	295	75.6	168	73.0	23	85.2	104	78.2	2	χ^2=2.6	0.3
2nd degree with Mania/ Hypomania	143	37.6	80	36.0	14	50.0	49	37.7	2	χ^2=2.1	0.4
2nd degree with Depression	276	72.3	157	70.4	25	89.3	94	71.8	2	χ^2=4.4	0.1

*Age 4 is set as the minimum value.

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** since age of onset of any DSM mood episode;

Different superscripts indicate significant pair-wise differences at $p \leq 0.05$

Table 2

Summary of Recovery and Recurrence by Bipolar Subtype

	All Sample		Bipolar-I		Bipolar-II		Bipolar NOS		Analyses		
	N	%	N	%	N	%	N	%	df	χ^2	p
Rate of Recovery	336/413	81.4	207/244[a]	84.8	21/28[a,b]	75.0	108/141[b]	76.6	2	4.80	0.09
Rate of Recurrence	210/336	62.5	135/207 [a]	65.2	17/21[a]	81.0	58/108 [b]	53.7	2	7.27	0.03
Median time to recovery from the index episode, † wk	123.7		78.3 [a]		76.9[a]		180.0 [b]		2	14.12	0.001
Median time to recurrence, ‡ wk	71.0		69.0 [a]		45.0[a]		82.0 [b]		2	7.73	0.02

Different superscripts indicate significant pair-wise differences at $p \leq 0.05$

†The index episode was defined as the most recent or current episode from the data of intake. To ascertain the real duration of illness, time to recovery was calculated from the onset of the index episode. Therefore, for some subjects the duration of episode exceed the length of prospective follow-up.

‡Time to recurrence was calculated from the time subjects fulfilled criteria for recovery until they met full criteria for a new episode.

Recurrence: the recurrence requires either a one week of PSR 5 for Mania/Hypomania OR two consecutive weeks of PSR ≥ 5 for Depression.

Table 3

Weekly Symptomatic Status and Changes in Mood Polarity by Bipolar Subtype

	All Sample (n=413)		Bipolar-I (n=244)		Bipolar-II (n=28)		Bipolar-NOS (n=141)		Analyses		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	df	χ^2	p
Asymptomatic (%)	41.2	31.6	44.0[a]	30.6	45.0[a,b]	33.6	35.6[b]	32.4	2	8.08	0.02
Syndromal (%)	16.6	21.9	17.8[a]	19.8	24.6[a]	28.0	12.8[b]	23.3	2	31.74	0.001
Mania	0.9	4.1	1.6[a]	5.3	0.0[b]	0.0	0.0[b]	0.0	2	61.49	0.001
Hypomania	1.8	6.1	2.7	[a] 7.7	1.4[a]	2.7	0.3[b]	1.5	2	30.22	0.001
Mixed/Cycling	7.9	16.1	8.1[a]	13.3	10.8[a,b]	22.1	7.0[b]	19.0	2	15.40	0.001
MDD	6.0	13.1	5.5[a]	11.1	12.4[b]	19.4	5.5[a]	14.3	2	13.47	0.001
Subsyndromal (%)	41.8	28.8	38.2[a]	25.4	30.4[a]	26.0	50.2[b]	32.8	2	16.24	0.001
Mania	14.1	18.9	14.1[a]	17.1	7.0[b]	10.9	15.6[a,b]	22.5	2	6.14	0.05
Mixed	15.4	22.2	13.2	18.6	8.9	16.5	20.6	27.4	2	4.78	0.09
Depression	12.2	16.9	10.9	14.2	14.5	21.2	14.1	20.0	2	0.41	0.8
Psychosis (delusions and/or hallucinations)	3.1	12.9	3.4[a]	12.1	5.5[a,b]	20.5	2.3[b]	12.3	2	11.99	0.002
	Changes in Mood Polarity, times per year [†]										
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
	12.1	15.0	11.0	13.8	10.3	16.3	14.3	16.7	2	2.46	0.3

	All Sample (n=413)		Bipolar-I (n=244)		Bipolar-II (n=28)		Bipolar-NOS (n=141)		Analyses		
	N	%	N	%	N	%	N	%			
≤1	129	31.2	72	29.5	10	35.7	47	33.3	2	0.89	0.6
>5	211	51.1	123	50.4	10	35.7	78	55.3	2	3.70	0.2
>10	160	38.7	87	35.7[a]	7	25.0[a]	66	46.8[b]	2	7.07	0.03
>20	98	23.7	51	20.9	5	17.9	42	29.8	2	4.47	0.1

Different superscripts indicate significant pair-wise differences at $p \leq 0.05$

[†] Indicates switch between depression (psychiatric Status Rating, ≥3) and mania/hypomania (Psychiatric Status Rating, ≥3) or vice versa with or without intervening weeks at the asymptomatic status.