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Course of Subthreshold Bipolar Disorder in Youth: Diagnostic Progression From Bipolar Disorder Not Otherwise Specified

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Abstract

Objective—To determine the rate of diagnostic conversion from an operationalized diagnosis of Bipolar Disorder Not Otherwise Specified (BP-NOS) to Bipolar I or Bipolar II Disorders (BP-I/II) in youth over prospective follow-up and to identify factors associated with conversion.

Method—Subjects were 140 children and adolescents recruited from clinical referrals or advertisement who met operationalized criteria for BP-NOS at intake and participated in at least one follow-up evaluation (91% of initial cohort). Diagnoses were assessed at follow-up interviews using the Longitudinal Interval Follow-Up Evaluation. The mean duration of follow-up was 5 years and the mean interval between assessments was 8.2 months.

Results—Diagnostic conversion to BP-I/II occurred in 63 subjects (45%): 32 (23%) to BP-I (9 of whom had initially converted to BP-II) and 31 to only BP-II (22%). Median time from intake to

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conversion was 58 weeks. First or second-degree family history of mania or hypomania was the strongest baseline predictor of diagnostic conversion ($p=.006$). Over follow-up, conversion was associated with greater intensity of hypomanic symptoms and with greater exposure to specialized, intensive outpatient psychosocial treatments. There was no association between conversion and exposure to treatment with particular medication classes.

Conclusions—Children and adolescents referred with mood symptoms that meet operationalized criteria for BP-NOS, particularly those with a family history of BP, frequently progress to BP-I or BP-II disorders. Efforts to identify these youth and effectively intervene may have the potential to curtail the progression of mood disorders in this high-risk population.

Keywords

Mood Disorders - Bipolar; Child Psychiatry; Adolescents; Diagnosis; Classification

Introduction

Several reports have noted the presence of subthreshold manic-like states in youth that do not meet DSM-IV criteria for Bipolar I (BP-I) or Bipolar II (BP-II) Disorders.^{1–4} These subthreshold presentations are associated with substantial impairment and require intensive treatment and many of these youth receive a diagnosis of Bipolar Disorder Not Otherwise Specified (BP-NOS).^{5–7} The American Academy of Child and Adolescent Psychiatry Practice Parameters recommends assigning a diagnosis of BP-NOS to children and adolescents when they either: (1) do not meet DSM-IV duration criteria for a Manic, Mixed, or Hypomanic episode, or (2) do not present with distinct mood episodes.¹ However, it is unclear whether both of these subthreshold BP phenotypes are on a continuum with syndromic bipolar illness, or if particular clinical factors predict eventual progression to Bipolar I or II Disorders.

Criteria for subthreshold BP (see Table 1) vary considerably among research studies, which may contribute to the heterogeneity of findings. The prevalence of subthreshold BP in epidemiological samples of adolescents ranges from 1.2%–13.3%.^{8–12} Prospective, longitudinal data in youth with subthreshold BP is limited. In one study of a community sample, 2% of adolescents with subthreshold BP were found to have converted to BP-I when re-interviewed during young adulthood, whereas a substantially greater number, 41%, had developed a Major Depressive Episode.¹³ In contrast, findings from a different epidemiological study of subjects aged 14–24 years at intake, indicated that subjects with a history of Major Depressive Disorder (MDD) and subthreshold BP at baseline were more likely to progress to BP-I over follow-up than MDD subjects without bipolar features (7.2% vs. 1.7%).¹⁰ Additional analyses restricted to the 14–17 year olds in this sample found that while subthreshold hypomania was very common in adolescence, new incidence of subthreshold BP was rare after age 22.¹⁴ A recent secondary analysis of a psychosocial treatment study of children with mood disorders found that of 25 participants with MDD or Dysthymic Disorder plus transient symptoms of mania, 3 progressed to BP-I and 5 to BP-II over 18 months of follow-up.¹⁵

Of relevance to the issue of subthreshold BP in youth is a rich literature on similar phenomena in adults.^{16,17} Several epidemiological studies report that subthreshold BP is highly prevalent and impairing among adults.^{10,18–20} Furthermore, subthreshold (hypo)manic symptoms were associated with higher rates of developing BP over follow-up in a Dutch adult epidemiological sample, and in a large clinical sample of adults with MDD in the United States.^{21,22} In line with these observations, some investigators have called into question the duration criteria for a Hypomanic Episode (≥ 4 days), given data showing that

episodes lasting only 1–3 days differ little from those of longer duration.^{18,23,24} Some authors have posited that (hypo)manic symptomatology in adults exists on a continuum that precludes clear diagnostic separation of BP from unipolar depression.^{25–27}

The Course and Outcome of Bipolar Youth (COBY) study, funded by the National Institute of Mental Health, is a longitudinal study being conducted at Brown University, University of California Los Angeles, and University of Pittsburgh. Its aims are to examine the presentation and prospective longitudinal course of pediatric-onset bipolar disorders, including an operationalized diagnosis of subthreshold BP – labeled BP-NOS in COBY. As reported previously,⁵ COBY subjects received a BP-NOS diagnosis primarily because the duration of their (hypo)manic-like episodes did not meet DSM-IV criteria. COBY subjects with BP-NOS did not differ from those with BP-I in age of onset, duration of illness, lifetime occurrence of comorbid diagnoses, suicidal ideation, major depression, or family history.⁵ A recent 4-year longitudinal follow-up of the COBY sample²⁸ indicated that subjects with BP-NOS took longer to recover (defined as 8 consecutive weeks of no or minimal mood symptoms) from their index mood episode (either depression or COBY-defined BP-NOS) compared to those with BP-I, and spent fewer weeks free of clinically significant mood symptoms during prospective follow-up. Furthermore, 38% of the youth with BP-NOS progressed to a diagnosis of BP-I or BP-II.

In this report we describe the course of BP-NOS in detail and examine factors associated with diagnostic progression to BP-I and II, while extending the findings of transition to BP-I and BP-II to an average of 5 years of follow-up. As we were not aware of prior literature that identified factors associated with diagnostic conversion, we hypothesized variables *a priori* that were clinically plausible to be associated with progression from BP-NOS to BP-I/II. These included developmental factors (younger age of illness onset and longer duration of illness at intake); measures of illness severity assessed at intake (higher severity of manic symptoms, depressive symptoms and functional impairment in the month leading up to intake); putative markers of lifetime illness severity (a history of Major Depressive or Hypomanic Episode, psychosis, and psychiatric hospitalization); diagnostic specificity (a history of manic symptoms that do not overlap with other DSM-IV disorders) and genetic vulnerability (family history of mania, hypomania, and/or depression). We further hypothesized that a greater hazard of conversion would be associated with the following time varying factors measured over longitudinal follow-up: greater proportion of time with mood symptoms, greater intensity of hypomanic and depressive symptoms, the presence of psychosis, and higher rates of comorbid psychiatric disorders. We performed two sets of exploratory analyses: (1) whether exposure to treatment during follow-up was associated with diagnostic conversion, and (2) whether duration of longest episode and total cumulative days meeting BP-NOS criteria were associated with a higher hazard of conversion. The second exploratory analysis was performed only with subjects from the Pittsburgh site, where this information was included in the subject's research and clinical records. Lastly, we performed sensitivity analyses by repeating all of the analyses after excluding subjects who had a lifetime history of a Hypomanic Episode at intake.

CASE REPORT

G. entered the COBY study at age 7. He had a history of chronic irritability, sadness, aggression, tantrums, defiance, inattention, separation anxiety and ongoing decreased need for sleep since he was a toddler. At age 4, he had a 2-week period of depressed mood, anhedonia, fatigue, hypersomnia, and markedly increased appetite, during which he made many self-critical comments and complained that no one loved him. The depression relented but would return periodically for a few days at a time. In addition, he started having brief periods of unusually silly and elevated moods that would last from a couple of hours to most

of the day. During these times, G. was very hyperactive, energetic, had rapid, pressured speech and his inattention was far worse than usual. These would occur 1 to 2 days a week, and were a clear change in his behavior but did not cause major impairment. However the irritability and aggression that were present chronically, worsened over time to the point where he would physically attack family members. This escalated to the point of punching and biting his mother while she drove and attempting to jump out of a moving car, which precipitated his first psychiatric hospitalization at age 4¾ years. No medication treatment was initiated until G. started risperidone when in outpatient treatment at age 5. His explosive tantrums and decreased need for sleep improved, though he continued to have predominantly irritable mood interspersed occasionally with brief 1–2 day periods of depression and euphoric hypomania... As G. grew older, his inattentive symptoms worsened to the point where he met criteria for Attention-Deficit Hyperactivity Disorder, inattentive type and his anxiety became more pervasive and generalized. Treatment with stimulants and SSRIs ameliorated these symptoms to some extent, though he stopped taking them at age 10. At age 11, his course of illness worsened to the point where he exhibited for the first time an episode of manic symptoms that lasted several days, with a substantial intensification of irritable, explosive mood, flight of ideas, pressured speech, psychomotor agitation, grandiosity, mild paranoid ideation and disinhibited behavior. During this time, he threatened peers and staff at school and screamed homicidal threats toward his family, prompting neighbors to call the police, who then brought him for admission to the psychiatric hospital. Given that G. had a distinct period of intensification of his irritability with four accompanying manic symptoms, mild psychosis and an inpatient hospitalization caused by consequences of the irritable mania, his diagnosis was changed at this point to Bipolar I Disorder.

Methods

Subjects

The methods for COBY have been described in detail elsewhere.^{5,29} In brief, we recruited youth ages 7 to 17 years 11 months with DSM-IV defined BP-I, BP-II or operationally defined BP-NOS. The COBY study defined the *minimum* inclusion threshold for the BP-NOS group as failure to meet DSM-IV criteria for BP-I or BP-II but having a distinct period(s) of abnormally elevated, expansive or irritable mood, plus: (1) at least two DSM-IV manic symptoms (three if the mood is irritable only) that were clearly associated with the onset of abnormal mood; (2) a clear change in functioning associated with the onset of these affective symptoms; (3) the presence of the elated and/or irritable mood and manic symptoms for a significant part of the day (a *minimum* of 4 hours, though this did not necessarily need to be expressed consecutively); and (4) a *minimum* of four days (not necessarily consecutive) meeting criteria 1–3 over the subject's lifetime. These analyses include the 140 youth with BP-NOS who had at least one follow-up evaluation (91% of the original sample). The subjects fulfilled BP-NOS criteria for the following reasons: (1) 15% had a history of a Hypomanic Episode but without a Major Depressive Episode; (2) 83% met full symptom criteria but not duration criteria for a Manic, Mixed, or Hypomanic Episode; and (3) 2% were one symptom short of full criteria for a Manic/Mixed/Hypomanic Episode. The requirement of distinct episodes of mood change with associated manic/hypomanic symptoms differs from the criteria for *Severe Mood Dysregulation (SMD)* as defined by Leibenluft and colleagues, which requires chronic, non-episodic irritable mood and symptoms of hyperarousal found in ADHD.³⁰

Subjects were recruited from outpatient clinics (76%), inpatient units (5%), advertisement (13%), and referrals from other mental health professionals (6%). At the time that data were censored for these analyses, subjects had been followed an average of 259 ± 100 weeks

(mean $\pm$ SD; median 267 weeks; range 26 – 434 weeks), with a mean of 7.4 follow-up assessments (range 1 – 15) and an average interval between assessments of 8.2 months.

Procedures

Each university's Institutional Review Board approved the study. Informed consent was obtained from the parents or guardian and assent from the children and adolescent subjects. Subjects were assessed by semi-structured interviews of the youth and a parent/primary caregiver (about the subject) by a trained research clinician. Non-mood psychiatric disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS-P/L)³¹ with mood symptoms assessed by the mood disorder sections of the KSADS-P (Present Episode, 4th revision)³² plus additional items from the KSADS-Mania Rating Scale (KSADS-MRS).³³ Copies of the KSADS-MRS are available at www.wpic.pitt.edu/research. Mood symptom severity was determined using the 12-item KSADS depression rating score (total score range 0–61) and KSADS-MRS (total score range 0–63) for the most severe week in the month prior to the intake assessment and for the most severe week lifetime.³⁴ For reference, prior studies indicate that KSADS-MRS scores of 12–17 correspond approximately to a mild overall severity of manic symptoms, 18–25 to a moderate level, and ≥ 26 to marked or worse severity of symptoms.³³ As per the KSADS instructions, mood symptoms that are also in common with other psychiatric disorders (i.e. distractibility) are not rated as present in the mood sections unless they intensify with the onset of abnormal mood. The age of onset for BP-NOS was considered to be when the subject first met DSM-IV criteria for a Major Depressive Episode or COBY criteria for BP-NOS.

The subject's primary caretaker was interviewed at intake about his/her personal psychiatric history using the Schedule for Clinical Interview for DSM-IV (SCID).³⁵ The primary caretaker was interviewed about the psychiatric status of the subject's first- and second-degree relatives using an enhanced version of the Family History Screen (FHS).³⁶ When a relative screened positive for a diagnosis on the FHS, the interviewer reviewed the individual symptom criteria, duration of symptoms and impairment, so that a diagnosis was assigned only if the relative met DSM-IV criteria.

Longitudinal changes in psychiatric symptomatology were assessed using the Longitudinal Interval Follow-up Evaluation (LIFE), a semi-structured interview, and tracked on a week-by-week basis using this instrument's Psychiatric Status Rating (PSR) scales for each diagnosis (see eAppendix 1 for additional methodological details).^{37,38} The PSR scores are numeric values that are linked to DSM-IV criteria. The clinical status of the subject at the time of the last assessment, including depressive symptoms, manic symptoms and comorbid illnesses, is reviewed with subject and parent caregiver informant. The interviewer then inquires about change points in the course of illness (times when symptoms improved or worsened), and assesses the intensity of the symptomatology by reviewing the DSM-IV criteria for the relevant diagnosis. Important events that occurred during the assessment interval, such as start of school, holidays, vacations, are used to help with determining when the change in symptom intensity occurred. In addition, the LIFE uses screening questions for depression, mania and all major DSM-IV disorders that the interviewer uses to prompt the subject and informant to recall symptomatology during the assessment interval. Any endorsement of depressed mood, anhedonia or irritability triggers the interviewer to explore all DSM-IV symptom criteria for Major Depression and any endorsement of elevated, expansive or irritable mood prompts the interviewer to explore all DSM-IV symptom criteria for a Manic, Mixed or Hypomanic Episodes, and for COBY BP-NOS. Mood symptoms that are also in common with other psychiatric disorders were not counted on the Mood PSR ratings unless they started or intensified with the onset of abnormal mood. In addition to the LIFE assessment, the KSADS-MRS and KSADS-P Depression scales

inquires separately about each individual depressive and manic symptom for the most symptomatic week in the past month, which then informs the completion of the PSR for the past month. The results are then translated into ratings for *each week* of the follow-up period on the PSR line for the diagnosis. For mood disorders, the PSR scores range from 1–2 for no or minimal symptoms, 3–4 for varying levels of clinically relevant subthreshold symptoms, and 5–6 for full criteria. Manic symptomatology that did not meet full DSM-IV criteria for a Manic or Mixed Episode was rated on the 5-point Hypomania PSR diagnostic line. For example a score of 4 would be used for when the subject fell short of full criteria for a Hypomanic Episode, but had major symptoms (e.g., a subject has elated mood plus 2 associated symptoms plus change in level of functioning for ≥ 4 days; or the subject met full symptom criteria for hypomania, but had a duration of only 2–3 days). A score of 3 on the Hypomania PSR line was given when subjects had considerably less psychopathology than full criteria with no more than moderate impairment in functioning, but still has obvious evidence of manic symptoms (e.g., a subject had elation and 3 associated symptoms but duration of less than one day; or a subject had elation plus 1–2 symptoms that lasted several days). Weekly scores for each PSR diagnostic line were determined after interviewing subjects and parent/caregiver informant, as well as reviewing available medical records.

All interviews were performed by trained research clinicians with a Bachelors, Masters, or PhD degrees in mental health related fields. At intake, all interviews were presented for a case conference to one of the principal investigators, who reviewed all available information before reaching a consensus diagnosis. Over follow-up, more than 65% of cases were also presented to one of the principal investigators. Interviewers were not blind to subjects' prior diagnoses.

An exploratory analyses was performed examining the association of diagnostic conversion to duration of longest episode and total cumulative days meeting BP-NOS criteria. Duration and number of episodes were originally recorded using a grid adapted from the Mania/Hypomania/Mixed State duration table of the KSADS-P Mania section. However, the complexity of this grid resulted in problems with reliability of data coding and the data could not be used. In order to perform the analysis, simplified ordinal categories classifying these factors were constructed from a retrospective review of the medical and research records of the 71 subjects from the Pittsburgh site, where this data was routinely documented. One of the authors, DAA (blind to conversion status) reviewed the records and was able to determine the categories for the longest duration of episode (consecutive days) with manic/hypomanic symptoms meeting COBY BP-NOS criteria and estimated total number of days lifetime meeting COBY BP-NOS criteria in 68 of the 71 subjects.

Reliability of the diagnostic assessments was assessed using audiotapes of randomly selected interviews. The kappa (κ) coefficient of the reliability of differentiating BP-NOS from BP-I/II and no Bipolar Disorder at the intake assessment, based on ratings of 13 different interviews by an average of 6 raters per interview (range 5–7), was $\kappa = 0.74$. The reliability of the PSR for diagnosing mood episodes over a follow-up interval was based on ratings from 36 different interviews by an average of 7.6 raters (range 4–10) per interview. The level of agreement among raters that a Manic, Mixed, or Hypomanic Episode occurred during follow-up was $\kappa = 0.62$ and $\kappa = 0.62$ for the occurrence of a Major Depressive Episode. Kendall's W statistic of the reliability for the LIFE assessment of the percentage of weeks of follow-up in euthymic, full syndromal, and subsyndromal mood states was ≥ 0.75 .

The LIFE was also used to record exposure to all psychotropic medications and psychosocial treatments on a week-by-week basis. Medications were grouped by class (e.g. lithium, valproate, carbamazepine and antipsychotics were considered *Antimanic Medications*) and weekly exposure was considered a dichotomous variable (yes/no) for each

class. Psychosocial treatments were examined as a dichotomous variable (yes/no) together, as well as divided into three categories of intensity that were coded separately for each week: inpatient hospitalization/residential treatment, specialized intensive services (e.g. in-home services, partial hospitalization), and standard outpatient services.

Statistical Analyses

Descriptive data on individual manic symptoms was taken from the KSADS-MRS. As the MRS assessed the most symptomatic week in the month prior to each follow-up evaluation, we only included subjects that had evidence of at least subthreshold manic symptoms (Hypomania PSR ≥ 3) in a month prior to one of their evaluations. The maximum rating over all of the follow-up assessments for each individual symptom was used.

Analyses that examined factors at intake associated with conversion to BPI/II used multi-stage survival analyses with diagnostic conversion to either BP-I or BP-II as the event of interest. Univariate analyses of these factors were performed using the log-rank test or Cox proportional hazard regressions. Demographic factors and clinical factors at intake that were hypothesized to be associated with conversion were analyzed initially. Individual demographic and hypothesized clinical factors that showed potential association with conversion ($p \leq .25$) were entered into a forward stepwise Cox regression with $p > .10$ as removal criterion. Exploratory univariate survival analyses were performed with clinical factors measured at intake that were not hypothesized *a priori*. Any exploratory variable showing potential ($p < .10$) association was entered with factors retained in the initial multivariate model into a final stepwise Cox regression.

A Cox proportional hazards regression analysis with time-varying covariates was used to identify factors during prospective follow-up which were associated with hazard of diagnostic conversion. We summarized the time-varying covariates over 8-week blocks, starting with the week prior to conversion. For example if a participant had a manic episode at week 81 (converting to BP-I), then they would have 10 timepoint measurements of the time-varying covariates. For the covariate *% weeks without significant mood symptoms*, if the participant did not have mood symptoms during the first 8 weeks of follow-up, then the value would be 100% for the timepoint 1 measurement of the covariate. Since the participant did not convert at week 9, this measurement would not be associated with conversion. If they were without mood symptoms for weeks 9–14, but had subthreshold symptoms on weeks 15 and 16, then the value would be 75% (6 out of 8 weeks without mood symptoms) for the timepoint 2 measurement, which again would not be associated with conversion. This would continue up to weeks 73–80, which would be the timepoint 10 measurement and would be linked with conversion. In essence, the regression is examining whether the covariate is associated with conversion, by comparing its value over the 8-weeks prior to conversion with those measured earlier in the course of follow-up of converters and over the entire follow-up for the non-converters. Given that these covariates were summarized over 8-week time intervals, converting subjects were included only if they had a minimum of 8 weeks of follow-up prior to conversion. Univariate analyses of these factors were performed first; factors that showed potential association with conversion ($p < .10$) were entered into a stepwise Cox regression analysis with $p < 0.10$ as removal criteria.

In addition, we performed exploratory analyses using Cox proportional hazards regressions in the Pittsburgh subsample to examine whether duration of longest episode of manic symptomatology meeting COBY BP-NOS criteria and total number of days lifetime meeting COBY BP-NOS were associated with hazard of diagnostic conversion.

Course of illness before and after conversion was examined using Wilcoxon Sign-Rank test in converting subjects that had sufficient follow-up prior to the week of conversion (defined as 8 weeks).

We performed sensitivity analyses by excluding the 21 subjects who met COBY BP-NOS criteria because they had a lifetime history of a Hypomanic Episode but no Major Depressive Episode. For survival analyses, the converting event was set to be the first time the subject met DSM-IV criteria for a Hypomanic, Manic or Mixed Episode.

Results

Of the 140 youth who had at least one follow-up visit, 107 (76%) had at least one DSM-IV Mood Episode over follow-up: 82 (57%) had a Major Depressive Episode, 36 (26%) had a Manic or Mixed Episode, and 54 (39%) had a Hypomanic Episode. Diagnostic conversion to BP-I or II occurred in 63 subjects (45%): 32 (23%) to BP-I (9 of whom converted to BP-II prior to BP-I) and 31 (22%) to only BP-II. The average time from intake to any diagnostic conversion was 98.0 ± 93.9 weeks (BP-I: 80.2 ± 89.5 ; BP-II: 117.0 ± 94.6) and median time to conversion was 58 weeks (BP-I 39.5; BP-II 117.5).

Significant manic symptoms (Hypomania PSR ≥ 3) were present in the month prior to at least one follow-up assessment in 119 subjects (85%). The maximum KSADS-MRS score over follow-up for these subjects was a mean of 24.6 ± 7.0 . Elated/elevated mood was present at an intensity level of *moderate* or greater for a least one follow-up assessment in 66% of these subjects; it was rated at a *mild* intensity in an additional 26% (see Figure 1). Of the 119 symptomatic subjects, 91% had a least two of the five symptoms selected as specific to mania (*elated mood, decreased need for sleep, grandiosity, increased goal-directed activity, and hypersexuality*) rated at an intensity of *mild* or greater, and 61% had two or more rated at a *moderate* intensity or greater.

Factors Measured at Intake that Predicted Diagnostic Conversion

Demographics (Table 2)—No demographic factor was associated with rate of diagnostic conversion, though being *White* and *Living With Both Biological Parents* met the $p < 0.25$ threshold for inclusion in multivariate models.

Hypothesized Factors (Table 3)—In the univariate analyses examining the hypothesized factors, only a *Positive Family History of Mania or Hypomania in at Least One 1st or 2nd Degree Relative* ($\chi^2 = 7.4$; $p = 0.006$ – see Figure 2) was a significant predictor of conversion to BP-I or II. As shown in Table 3, seven other factors met the threshold for inclusion in the multivariate analyses.

Multivariate Analyses—Entry of these ten potential factors into a stepwise Cox regression resulted in retention of five factors: *Family History of Mania/Hypomania* (Hazard Ratio (HR)=3.08; 95% Confidence Interval (CI) 1.77–5.38; $p < 0.0001$); *Psychiatric Hospitalization* (HR=2.48; 95% CI 1.43–4.32; $p = 0.001$); *History of Psychosis* (HR 0.29; 95% CI 0.12–0.72; $p = 0.007$); *White race* (HR=2.70; 95% CI 1.15–6.33; $p = 0.02$); and *Intake MRS Score* (HR=1.03; 95% CI 1.00–1.06; $p = 0.02$).

Other Intake Factors—In the exploratory univariate analyses of other clinical factors, only *Family History of Substance Use Disorder* and *Suicide Attempt* had significant associations with increased hazard of conversion, with *Family History of Conduct Disorder* and *Anxiety Disorder* also meeting the $p < 0.10$ criterion for entry into the multivariate analysis (see Table S1, available online). However, none of these variables were significant when combined with those from the initial multivariate stepwise Cox regression. The

subanalysis of the 68 subjects from the Pittsburgh site found that neither the duration of longest episode ($\chi^2 = 1.2$; $p = 0.28$) nor cumulative number of days meeting BP-NOS criteria ($\chi^2 = 0.1$; $p = 0.74$) were associated with conversion to BP-I or II.

Factors Assessed During Follow-up Predicting Diagnostic Conversion (Table 4)

An increased hazard of diagnostic conversion was significantly associated with greater proportion of the pre-conversion follow-up interval with mixed manic and depressive symptoms that did not meet diagnostic threshold for a mood episode, higher peak intensity of hypomanic symptomatology (as measured on the PSR), and a smaller proportion of follow-up time free of mood symptoms. The percentage of weeks with psychotic symptoms present was sufficiently positively associated with increased hazard of conversion to meet the $p < 0.10$ criteria for inclusion in the multivariate analysis. The hazard to convert was associated with greater proportion of time exposed to any psychosocial treatments, in particular with specialized, intensive non-inpatient psychosocial treatments (e.g. in-home services, partial hospitalization), but there was no association with time exposed to antimanic, antidepressant, or stimulant medications, nor was it associated with the presence of comorbid disorders. The multivariate analysis showed that higher maximum scores on the Hypomania PSR (HR=1.45; 95% CI 1.13 – 1.85; $p = .003$) and greater proportion of time exposed to specialized intensive non-inpatient psychosocial treatment (HR=1.009; 95% CI 1.003 – 1.016; $p = .006$) pre-conversion remained significantly associated with a higher hazard of conversion. Percentage of weeks with psychotic symptoms was retained in the model but was not statistically significant ($p = 0.06$).

Course of Illness after Diagnostic Conversion

The 63 converting subjects were followed for a median time of 197 weeks (range 9 – 401 weeks) *after* they converted to BP-I or BP-II. From the time of conversion, they spent a median of 4.5% (mean 10.9%) of the subsequent observational period meeting criteria for a Manic, Mixed, or Hypomanic Episode; 80.4% had at least one week post-conversion that fulfilled criteria for a Manic, Mixed, or Hypomanic Episode, and 71.5% had two or more weeks. Converting subjects spent a median of 3.9% of post-conversion weeks of follow-up meeting criteria for a Major Depressive Episode and 60.3% had two or more weeks fulfilling criteria for Major Depression. Converting subjects spent a median of 32.1% of follow-up weeks with no or minimal mood symptoms.

For the 54 converting subjects who had a least 8 weeks of follow-up prior to conversion, there was no significant difference ($Z = 1.5$, $p = 0.15$) in the percentage of follow-up weeks with no or minimal mood symptoms prior to conversion (median = 30%) as compared to after conversion (median = 38%). There was no difference in the percentage of weeks meeting criteria for Major Depression pre-conversion vs. post-conversion (median pre = 14% vs. post = 10%; $Z = -0.2$, $p = 0.25$) or in percentage of weeks with subsyndromal mood symptoms prior to conversion vs. after conversion (median pre = 55% vs. post = 42%; $Z = 1.4$, $p = 0.18$).

Analyses excluding subjects with history of a Hypomanic Episode at intake assessment

There were 119 subjects who did not have a lifetime history of a Hypomanic Episode at intake. Of these, 52 (44%) met full criteria for a Manic/Mixed Episode ($n = 29$, 24%) or for a Hypomanic Episode ($n = 23$, 19%) over follow-up. There was no difference in the conversion rate to BP-I or BP-II in the 119 subjects without history of a Hypomanic Episode at intake compared to the 21 subjects who did (44% vs. 52%; $\chi^2 = 0.5$; $p = 0.46$). In addition, there was no difference in conversion rates to BP-I between subjects without history of a Hypomanic Episode at intake as compared to those who did (24% vs. 14%; $\chi^2 = 1.0$; $p = 0.31$).

Univariate Cox Regression analysis of the intake factors identified three that were associated with a new onset of a Manic, Mixed or Hypomanic Episode: *Family History of Mania/Hypomania* ($\chi^2 = 5.8$; $p = 0.02$); *Family History of Depression* ($\chi^2 = 3.9$; $p = 0.05$); and *Negative Lifetime History of Psychotic Symptoms* ($\chi^2 = 3.9$; $p = 0.05$). *Lifetime History of Psychiatric Hospitalization*, *Intake MRS score*, and *White Race* were not significantly associated but met the $p < .25$ criteria for inclusion in the multivariate analysis. The results of the multivariate analyses were nearly identical to that using the full sample, with the same 5 factors retained in the same order of significance. In the analyses of the Pittsburgh subsample, neither the duration of the longest episode of manic/hypomanic symptoms, nor the cumulative number of days lifetime meeting COBY BP-NOS criteria were associated with onset of a Manic, Mixed or Hypomanic Episode over follow-up (see Table 5).

In the analysis of factors occurring over follow-up, *Maximum Hypomania PSR score* ($\chi^2 = 5.2$; $p = 0.02$), lower *% of weeks with no significant mood symptoms* ($\chi^2 = 4.9$; $p = 0.03$) and greater exposure to *Specialized Intensive Outpatient Psychosocial Treatment* ($\chi^2 = 4.4$; $p = 0.04$) were significantly associated with onset of a Manic/Mixed/Hypomanic Episode, with higher *% of weeks with subthreshold mood symptoms* and higher *% of weeks with psychotic symptoms* meeting the $p < .25$ threshold. Only lower *% of weeks with no significant mood symptoms* ($\chi^2 = 5.7$; $p = 0.02$) and greater exposure to *Specialized Intensive Outpatient Psychosocial Treatment* ($\chi^2 = 5.5$; $p = 0.02$) remained significant in the multivariate model.

After the week of conversion, 73% of the 52 converting subjects spent at least 4 additional weeks over follow-up meeting criteria for a Manic, Mixed or Hypomanic Episode (see Figure S1, available online). A majority of the subjects (56%) also spent at least 4 weeks meeting criteria for Major Depression after conversion (see Figure S2, available online). Only 27% of the subjects were free of significant mood symptoms for more than half of the post-conversion follow-up period (see Figure S3, available online).

Discussion

This study found that 45% of youth with distinct, but subthreshold episodes of manic symptoms meeting COBY BP-NOS criteria, progressed to BP type I or type II illness during an average of 5 years of prospective follow-up. Morbidity from manic symptomatology following onset of the transition from subthreshold to full syndromic illness was significant, as these subjects spent a median of 4.5% of weeks in a Manic, Mixed, or Hypomanic Episode, and 71% of converters met episode criteria for two or more weeks post-conversion. The only individual clinical factor assessed at intake that predicted diagnostic conversion in the univariate analysis was a *Family History of Mania or Hypomania*; specifically after 5 years of follow-up, 58% of BP-NOS subjects with a positive family history of BP converted to BP-I or II as compared to 36% whose family history was negative. Multivariate analyses identified four additional factors, that when taken together with a family history of BP, were associated with conversion: *White race*, *Lifetime History of Psychiatric Hospitalization*, *Severity of Manic Symptoms at intake (MRS score)*, and a *Negative Lifetime History of Psychotic Symptoms*. However, as the effect sizes of these additional factors were small, their significance is deemed to be limited.

With regard to the analysis of time varying covariates assessed longitudinally, we found that peak severity of hypomanic symptomatology prior to conversion was significantly associated with a higher hazard rate of conversion. Similar results were found in the sensitivity analyses that removed the 15% of COBY BP-NOS subjects who had a lifetime history of a Hypomanic Episode at intake. The one exception was that onset of a Manic, Mixed or Hypomanic Episode over follow-up was associated with a lower percentage of follow-up weeks free of significant mood symptoms prior to conversion, instead of peak

severity of hypomanic symptoms. Overall, these results indicate that the BP-NOS subjects who showed progression of illness had a higher burden of mood symptoms prior to conversion than those who did not progress. That we observed a higher amount of psychosocial treatment in the converters is in accord with the clinical findings suggesting greater overall symptom morbidity.

Significant manic symptomatology was present in the month leading up to a prospective follow-up assessment in most (85%) subjects. Similar to what was found at the intake assessment, multiple symptoms specific to mania were present in nearly all of these subjects and greater than 90% had *Elated/Elevated Mood*. Also similar to what was found at intake, the BP-NOS subjects continued to have high rates of comorbid disorders, indicating a substantial burden of non-mood psychopathology.

In many ways, these analyses are notable for the lack of association between diagnostic progression to BP-I or BP-II and a wide variety of clinical variables. Therefore, we could not identify clinical profiles that would strongly predict diagnostic conversion. Surprisingly, though 41% of COBY BP-NOS subjects had a history of a Major Depressive Episode at intake, this was not predictive of diagnostic conversion in both the primary analysis and in the sensitivity analysis. History of a Hypomanic Episode at intake also was not associated with conversion to BP-I or II. Diagnostic progression occurred regardless of exposure to antimanic treatment, whereas greater exposure to psychosocial intervention anticipated conversion. It is important to note in this regard that our analyses only examined treatment exposure to different medication classes as a dichotomous factor and did not examine dose intensity of different medications. The association with conversion and psychosocial treatment was driven entirely by a greater hazard of conversion in subjects exposed to specialized intensive non-inpatient psychosocial treatments. In regards to this seemingly paradoxical finding, we hypothesize that greater affective morbidity among subjects who eventually convert could be “driving” treatment seeking for these intensive services.

Limitations of the study are important to consider. Diagnosis at intake was based on a semi-structured interview using information obtained via the retrospective recall of the subjects and their caretakers; accuracy of recall could be an issue. Similar uncertainties apply to the longitudinal follow-up interviews, though the interval between assessments was 8 months on average. Follow-up interviewers were not blind to prior diagnoses and not explicitly blinded to the family history information collected at the intake assessment. This has the potential to introduce bias that could increase the association between diagnostic progression and family history. Diagnostic reliability was substantial, but not to the level of “near perfect”.³⁹ In addition, the reliability assessment procedure did not measure information variance (i.e. independent interviewers may elicit different information from the same subject), which could be an unknown source of diagnostic unreliability. Two important factors (longest duration of episode and total lifetime days of manic/hypomanic symptoms) were measured retrospectively and in only a subset of subjects. The “typical” duration of manic/hypomanic periods for each subject was not assessed. Family history of 1st and 2nd degree relatives (other than the primary caregiver) was not obtained through direct interview. Given that COBY subjects were ascertained from multiple sources, the findings may not generalize to either community or different clinical settings. Lastly, since the vast majority of subjects in COBY had received treatment prior to intake and most continued to receive treatment over the follow-up, these results may not generalize to untreated samples.

Although the criteria for subthreshold BP was less stringent than COBY, the study by Nadkarni and Fristad had similar rates of conversion to BP-I or BP-II over 18 months of follow-up.¹⁵ However the rate of diagnostic progression in COBY is in strong contrast to that of the subthreshold BP subjects in the Lewinsohn et al. study.¹³ This may in part be due

to different diagnostic thresholds, as the Lewinsohn study required only a distinct period of abnormally elated and/or irritable mood for inclusion in the subthreshold BP group. It also may be related to differences in ascertainment (referred vs. community), assessment procedures (caregiver informant included for COBY subjects vs. subject only) and/or assessment frequency (average of 8 months vs. an interval of 6 years). Family history was not assessed in the Lewinsohn study, so we cannot compare the rate of familial BP to the high rate (51%) of positive history of Bipolar Disorder in either a 1st or 2nd degree relative in the COBY sample.

Family history was a potent predictor of diagnostic conversion from MDD to BP-I or II in the Collaborative Depression Study, though the other factors associated with conversion, such as number of manic symptoms at baseline, psychosis and age of onset, were not significant in the COBY BP-NOS sample.²² In this regard, it is important to note that even with a family history of bipolarity, many COBY BP-NOS subjects did not progress to BP-I or II. However, given that the onset of BP-I/BP-II frequently occurs after 25 years of age⁴⁰ and that the average follow-up duration was five years, the long-term stability of this phenotype remains to be fully determined.

The COBY BP-NOS phenotype differs from the proposed Disruptive Mood Dysregulation Disorder diagnosis for the DSM-5, whose core features are chronic irritability with recurrent severe temper outbursts, and from SMD, which includes these elements plus ADHD-like symptoms of hyperarousal.⁴¹ Though a large majority of COBY subjects with BP-NOS have chronic psychopathology in the context of comorbid non-affective disorders and subsyndromal mood disturbances, they must by definition also have distinct periods of manic or hypomanic symptomatology that represent a departure from their customary functioning. Therefore results from this study do not necessarily apply to non-episodic presentations of manic symptoms that have been labeled BP-NOS in the literature.

These findings have potential implications for diagnostic classification. That many of the COBY youth who presented clinically with “subthreshold” Bipolar Disorder progressed to full syndromal BP-I or II, raises questions about the current diagnostic criteria for BP illness. Combined with the data from the adult literature, it is possible that BP includes a phenotype of recurrent brief episodes of manic symptoms and further research into the appropriateness of the duration criteria for manic and hypomanic episodes is clearly warranted. Whether or not the typical initial presentation of pediatric BP is recurrent subthreshold episodes progressing to full syndromal disorder is an important question that cannot be answered by this study. Cyclothymia and subthreshold presentations of BP are common in the child and adolescent offspring of bipolar parents.^{42–45} A recent study reported that children of BP parents have a 13 times higher odds of meeting criteria for COBY-defined BP-NOS as compared to community controls.⁴⁴ In addition, BP-NOS (7.2%) was much more commonly diagnosed in the offspring of BP parents than BP-I (2.1%) or BP-II (1.3%).⁴⁴ Longitudinal follow-up will determine whether the rate of diagnostic progression from subthreshold BP to BP-I/II in a genetically high-risk sample is similar to that of COBY.

Clinical implications of these findings need to be considered with caution. The diagnostic criteria for COBY BP-NOS were intentionally set to be broad for research purposes. We chose to operationalize a minimum time threshold for distinct (hypo)manic symptomatology to be **present for a significant part of the day** in order to avoid classification of transient phenomena as BP-NOS. The four-hour (not necessarily consecutive throughout the day) **minimum** threshold was taken from the KSADS-P *Elated Mood* item. In practice, it has functioned reasonably well, as informants (many of whom did not see the child for much of the day) seemed comfortable estimating whether observable symptomatology was present

for greater than or less than four hours. One could argue that *most of the day* would be a better threshold and based on our clinical experience, many of the COBY BP-NOS subjects with “1-day” episodes would have met this criterion. Those that did not meet the “most of the day” standard often had irritability and/or depressive features for much of the remaining time, so they had mood symptoms most of the day, just not distinctly (hypo)manic symptoms. The results of the Pittsburgh subanalysis (taken with the limitations noted above) indicate that most of the COBY subjects far exceeded the four lifetime days diagnostic threshold. Though we did not find phenomenological factors that predicted diagnostic progression, it is reasonable to suggest that clinical applications of the COBY BP-NOS criteria should use a higher threshold for lifetime days (e.g. at least 7 days) and that the 4-hour minimum threshold should be used in conjunction with the presence of other mood symptoms for most of the day. Diagnostic confidence in identifying a bipolar syndrome may increase with longer (e.g. 2 days) and more recurrent episodes and with the presence of symptoms specific to mania (elated mood, decreased need for sleep, grandiosity, etc.), but these are, at present, possibilities that require further empirical study..

Treatment guidelines for COBY BP-NOS do not exist, and one controlled treatment study of subthreshold BP youth failed to show a benefit of active medication over placebo.⁴⁶ However, the fact that over half of the youth presenting clinically with COBY BP-NOS who have a family history of BP are likely to progress to BP-I/II, should be taken into consideration when weighing the risks and benefits of different treatment options. Future efforts to identify these high-risk youth and studies designed specifically to evaluate effective interventions may have the potential to reduce affective morbidity and curtail the progression of illness to full diagnostic threshold Bipolar Disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Manic Symptoms Present over Follow-Up*

*From KSADS Mania Rating Scale items for the most symptomatic week during the month prior to follow-up assessment(s). Maximum intensity rating used over all follow-ups for each symptom. Subjects include those who had at least subthreshold manic symptoms during the month prior to a follow-up assessment (n = 119).

Abbreviations: ↓ = Decreased; ↑ = Increased

Figure 2.
Survival Analysis of Conversion to Bipolar I or II Disorders by Family History of Mania/
Hypomania
Abbreviations: BP-I/II – Bipolar I or II Disorders

Table 1**Diagnostic Criteria for Subthreshold Bipolar Disorder in Cited Studies**

Author	Subject Age Range (years)	Primary Criteria	Additional Specifiers
Carlson and Kashani, 1988 ¹²	14–16	4 or more manic symptoms of at least 2 days duration	Symptoms occur during unusual excitement, mood lability or increased energy causing inability to sleep
Findling et al., 2005 ⁴	5–17	Unmodified DSM-IV Criteria for BP-NOS	Spontaneous, dysfunctional mood episodes that did not meet for any other mood disorder
Findling et al., 2007 ⁴⁴	5–17	DSM-IV BP-NOS criteria plus at least one distinct period of abnormally elated mood within past 2 months with YMRS > 12	As above, plus biological parent with Bipolar Disorder required
Kessler et al., 2009 ⁸	13–17	Either (1) Recurrent Subthreshold Hypomania with or without MDE; or (2) Recurrent Hypomanic Episodes without MDE	Subthreshold Hypomania criteria same as DSM-IV Hypomanic Episode but 1 less Criterion B symptom required
Lewinsohn et al., 1995 ⁹	14–18	Distinct period of abnormally elevated, expansive or irritable mood	Cyclothymia and BP-II subjects excluded; Hypomania without MDE included
Nadkarni et al., 2010 ¹⁵	8–11	(1) One of either elated mood or criterion B symptoms; (2) can be differentiated from ADHD; (3) 1–3 episodes lasting ≥ 4 hours or ≥ 2 lasting 2–4 hours; (4) functional impairment	MDE or Dysthymic Disorder
Stringaris et al., 2010 ¹¹	8–19	Distinct episodes of elevated / expansive mood plus ≥3 criterion B manic symptoms and impairment in functioning	Duration > 1 hour and less than 4 days
Tijssen et al., 2010 ¹⁴	14–17	(Hypo)manic symptom(s) on at least 4 consecutive days occurring in the presence of unusual happiness, excitement or irritability	Two thresholds set: ≥1 symptom and ≥4 symptoms
Zimmerman et al., 2009 ¹⁰	14–24	Either (1) elated or expansive mood causing trouble or observable change in functioning; or (2) unusually irritable mood with at 3 accompanying manic symptoms, but symptoms not necessarily observable by others	Minimum duration of 4 days; MDE required
Angst, 1998 ²³	22–35	DSM-IV criteria for Hypomanic Episode except duration 1–3 days	-----
Judd et al., 2003 ¹⁹	≥18	At least 2 manic symptoms lifetime occurring while mood is happy, excited, or high	Symptom must be present for at least 1 week; Mood must cause impairment
Merikangas et al., 2007 ²⁰	≥18	Either (1) Recurrent Subthreshold Hypomania with or without MDE; or (2) Recurrent Hypomanic Episodes without MDE	Subthreshold Hypomania criteria same as DSM-IV Hypomanic Episode but only 2 Criterion B symptoms required
Regeer et al., 2006 ²¹	18–64	Abnormally elevated, expansive, or irritable mood plus at least one manic symptom	Duration at least 2 days

Note: BP-NOS = bipolar disorder not otherwise specified; MDE = Major Depressive Episode; YMRS = Young Mania Rating Scale

Table 2

Demographic Factors at Intake (Converters to Bipolar- I or II vs. Non-Converters)

	Conversion (n=63)	Non-Conversion (n=77)	Chi-sq	p-value
Age	11.9 ± 3.3	11.8 ± 3.2	0.0	0.95
Sex (Male) %	66.7	57.1	1.3	0.26
Race (White) %	88.9	76.6	2.7	0.10
SES	3.3 ± 1.1	3.4 ± 1.1	0.0	0.97
Living with both natural parents %	50.8	39.0	1.5	0.23
Pubertal Status (Tanner Stages)			0.8	0.67
I	37.7	31.6		
II–III	28.3	28.1		
IV–V	34.0	40.3		
Site			0.4	0.81
Brown	44.5	37.7		
UCLA	7.9	11.7		
UPMC	47.6	50.6		

Note: SES = Socioeconomic Status; UCLA = University of California, Los Angeles; UPMC = University of Pittsburgh Medical Center

Table 3

Clinical Factors at Intake Hypothesized to be Associated with Conversion to Bipolar I or II

	Converters (n=63)	Non- Converters (n=77)	Chi-sq	p-value
<i>Developmental Factors</i>				
Age Onset of Mood Symptoms (years)	7.9 ± 3.5	7.9 ± 3.4	0.1	0.71
Duration of Illness (years from onset of 1 st mood episode)	4.3 ± 3.1	4.1 ± 2.8	0.1	0.75
<i>Severity of Illness at Intake – Worst Week in the Past Month</i>				
Mania Rating Scale	23.2 ± 10.2	20.9 ± 10.4	1.5	0.22
Depression Rating Scale	14.2 ± 8.2	13.8 ± 9.2	0.2	0.65
Children's Global Assessment Scale	56.8 ± 12.0	57.2 ± 10.2	0.6	0.45
<i>Severity of Illness over Lifetime</i>				
Lifetime History of Major Depressive Episode (%)	44.4	39.0	0.6	0.42
Lifetime History of Hypomanic Episode (%)	17.5	13.0	1.7	0.19
Psychotic Symptoms (% lifetime)	11.1	15.6	2.7	0.10
Lifetime History of Psychiatric Hospitalization (%)	36.5	23.4	3.0	0.08
<i>Five Manic Specific Symptoms: Presence during most severe week lifetime or past month</i>				
Elated Mood (%)	85.4	83.9	0.7	0.80
Grandiosity (%)	56.1	68.9	1.4	0.23
Decreased Need for Sleep (%)	68.3	58.1	1.1	0.28
Increased Goal-Directed Activity (%)	47.5	62.9	2.3	0.13
Hypersexuality (%)	24.4	32.3	0.4	0.52
Total number of specific manic symptoms (mean ± SD)	2.8 ± 1.0	3.0 ± 1.2	0.9	0.35
<i>Family History (% with 1st or 2nd degree relative)</i>				
Family History of Mania/Hypomania	63.5	40.3	7.4	0.006
Family History of Depression	90.5	77.9	3.7	0.05

Note: Kaplan-Meier Survival (for categorical factors) and Cox Regression (for scalar variables) analyses performed.

Table 4
Cox Regression Analysis of Time-Varying Covariates Assessed over Follow-Up

	Converters (n=54)		Non-Converters (n=77) During entire follow-up interval	Statistics		
	8 week period immediately before conversion	Period greater than 8 weeks before conversion		Chi-square	p-value	Hazard Ratio
% Weeks in Mood State (mean ± SD)						
No significant mood symptoms	30.3 ± 41.5	27.7 ± 31.0	47.0 ± 31.0	4.055	0.044	0.993
Subthreshold Depression	12.3 ± 27.4	12.1 ± 21.7	17.9 ± 20.1	0.128	0.720	
Subthreshold Manic Symptoms	15.0 ± 31.7	21.4 ± 27.8	12.4 ± 16.5	0.045	0.832	
Subthreshold Mixed Symptoms	30.8 ± 42.9	22.5 ± 28.8	16.9 ± 22.5	5.642	0.018	1.008
Full Threshold Major Depression	10.2 ± 28.7	15.0 ± 27.2	5.8 ± 8.9	0.255	0.614	
Full Threshold Hypomania	1.4 ± 7.5	1.2 ± 4.2	0.1 ± 0.3	0.959	0.328	
Maximum PSR Score (1–6, mean ± SD)						
Depression	2.8 ± 1.4	3.0 ± 1.2	2.6 ± 0.9	0.737	0.391	
Hypomania	3.0 ± 1.3	2.9 ± 0.8	2.2 ± 0.8	9.824	0.002	1.480
% Weeks in Psychosis (mean ± SD)						
Psychosis	5.6 ± 23.1	5.3 ± 19.5	0.7 ± 5.4	3.090	0.079	
Comorbid Disorders (% weeks meeting full diagnostic criteria, mean ± SD)						
Any Comorbid Disorder	73.4 ± 44.1	69.1 ± 39.5	67.0 ± 33.4	0.984	0.321	
ADHD	51.9 ± 50.4	54.7 ± 46.1	44.3 ± 39.3	0.611	0.434	
ODD/CD	38.9 ± 49.2	39.6 ± 43.6	30.9 ± 35.8	0.727	0.394	
Anxiety	26.9 ± 44.0	27.7 ± 38.7	20.9 ± 35.2	1.619	0.203	
Substance Use Disorder	11.1 ± 31.7	9.2 ± 25.9	5.5 ± 16.8	1.537	0.215	
Medication Treatment						
% Weeks Receiving Medication over follow-up (mean ± SD)						
Any Psychotropic Medication	70.1 ± 44.7	75.2 ± 37.0	65.4 ± 35.2	0.005	0.943	
Antimanic	48.1 ± 49.4	56.3 ± 42.3	48.7 ± 38.7	0.237	0.627	
Antidepressant	24.8 ± 42.1	27.6 ± 38.0	18.4 ± 29.1	0.195	0.659	
Stimulants	28.2 ± 45.0	24.4 ± 39.1	24.4 ± 34.9	0.539	0.463	
Psychosocial Treatment						

	Converters (n=54)		Non-Converters (n=77) During entire follow-up interval	Statistics		
	8 week period immediately before conversion	Period greater than 8 weeks before conversion		Chi-square	p-value	Hazard Ratio
% Weeks Receiving Treatment over follow-up (mean ± SD)						
Any Psychosocial Treatment	53.9 ± 40.0	51.1 ± 33.3	39.6 ± 25.8	4.060	0.044	1.007
Inpatient/Residential Treatment	4.6 ± 19.6	4.7 ± 12.5	2.7 ± 7.2	0.076	0.784	
Specialized Outpatient Services ^a	25.9 ± 43.2	22.5 ± 36.1	9.4 ± 16.4	8.545	0.004	1.010
Standard Outpatient Services	36.6 ± 34.9	34.6 ± 27.8	31.1 ± 23.7	0.852	0.356	

Note: ADHD = Attention-Deficit Hyperactivity Disorder; CD = Conduct Disorder; ODD = Oppositional Defiant Disorder; PSR = Psychiatric Status Rating.

^aPartial Hospitalization, Wrap-Around Services, Intensive Outpatient Services, In-home family-based services

Table 5

Longest Duration of Episode and Total Days of Manic/Hypomanic Symptoms

	Manic, Mixed, or Hypomanic Episode over Follow-Up (n=23)	No Episode over Follow-Up (n=34)	Chi-sq	p-value
Longest Duration (number of consecutive days) meeting COBY BP-NOS Criteria (% subjects)				
1 day	43.5%	51.5%	0.20	0.89
2 days	21.7%	21.2%		
3–4 days	34.8%	27.3%		
Cumulative number of days lifetime meeting COBY BP-NOS Criteria (% subjects)				
7 – 20 days	22.7%	9.4%	0.03	0.96
21–100 days	27.3%	50.0%		
> 100 days	50.0%	40.6%		

Note: Pittsburgh subsample with no history of Hypomanic Episode at intake assessment. BP-NOS = Bipolar Disorder Not Otherwise Specified; COBY = Course and Outcome of Bipolar Youth.