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

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Objective: To determine the rate of diagnostic conversion from an operationalized diagnosis of bipolar disorder not otherwise specified (BP-NOS) to bipolar I disorder (BP-I) or bipolar II disorder (BP-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 or BP-II occurred in 63 subjects (45%): 32 (23%) to BP-I (nine of whom had initially converted to BP-II) and 31 to only BP-II (22%). Median time from intake to 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. Efforts to identify these youth and effectively intervene may have the potential to curtail the progression of mood disorders in this high-risk population. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(10):1001–1016. **Key words:** bipolar mood disorders, child psychiatry, diagnosis and classification

Several reports have noted the presence of subthreshold manic-like states in youth who do not meet *DSM-IV* criteria for bipolar I disorder (BP-I) or bipolar II disorder (BP-II).[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 whether particular clinical factors predict eventual progression to BP-I or BP-II.

This article is discussed in an editorial by Dr. Ellen Leibenluft on page 972.

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Criteria for subthreshold BP (Table 1[4,8-19]) 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% to 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 reinterviewed during young adulthood, whereas a substantially greater number (41%) had developed a major depressive episode.[20] In contrast, findings from a different epidemiological study of subjects aged 14 to 24 years at intake, indicated that those 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 were MDD subjects without bipolar features (7.2% versus 1.7%).[10] Additional analyses restricted to the 14- to 17- year-olds in this sample found that whereas subthreshold hypomania was very common in adolescence, new incidence of subthreshold BP was rare after age 22 years.[15] 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 five to BP-II over 18 months of follow-up.[14]

Of relevance to the issue of subthreshold BP in youth is a rich literature on similar phenomena in adults.[21,22] Several epidemiological studies report that subthreshold BP is highly prevalent and impairing among adults.[10,17,18,23] 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.[19,24] 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 to 3 days differ little from those of longer duration.[16,23,25] Some authors have posited that (hypo)manic symptomatology in adults exists on a continuum that precludes clear diagnostic separation of BP from unipolar depression.[26-28]

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 sample[29] 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 with 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 or BP-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