**Schizophrenia Bulletin** vol. 33 no. 3 pp. 703–714, 2007
doi:10.1093/schbul/sbm028
Advance Access publication on May 2, 2007

# Differentiation in the Preonset Phases of Schizophrenia and Mood Disorders: Evidence in Support of a Bipolar Mania Prodrome

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***Objective:*** **The presence and specificity of a bipolar prodrome remains questioned. We aimed to characterize the prodrome prior to a first psychotic and nonpsychotic mania and to examine the phenotypic proximity to the schizophrenia prodrome.** ***Methods:*** **Using a semi-structured interview, the Bipolar Prodrome Symptom Scale-Retrospective, information regarding the mania prodrome was collected from youth with a research diagnosis of bipolar I disorder and onset before 19 years of age, and/or their caregivers. Only newly emerging, at least moderately severe, symptoms were analyzed. Prodromal characteristics were compared between patients with and without subsequent psychotic mania and with published bipolar and schizophrenia prodrome data.** ***Results:*** **In 52 youth (age at first mania: 13.4 ± 3.3 years), the prodrome onset was predominantly "insidious" (>1 year, 51.9%) or "subacute" (1–12 months, 44.2%), while "acute" presentations (<1 month, 3.8%) were rare. The prodrome duration was similar in patients with (1.7 ± 1.8 years, $n = 34$) and without (1.9 ± 1.5 years, $n = 18$) subsequent psychotic mania ($P = .70$). Attenuated positive symptoms emerging late in the prodrome and increased energy/goal-directed activity were significantly more common in patients with later psychotic mania. Mania and schizophrenia prodrome characteristics overlapped considerably. However, subsyndromal unusual ideas were significantly more likely part of the schizophrenia prodrome, while obsessions/compulsions, suicidality, difficulty thinking/communicating clearly, depressed mood, decreased concentration/memory, tiredness/lack of energy, mood lability, and physical agitation were more likely part of the mania prodrome.** ***Conclusions:*** **A lengthy and symptomatic prodrome makes clinical high-risk research a feasible goal for bipolar disorder. The phenotypic overlap with the schizophrenia prodrome necessitates the concurrent study of both illness prodromes.**

*Key words:* bipolar disorder/schizophrenia/prodrome/early identification/prevention

Schizophrenia and bipolar disorder are 2 of the most severe mental disorders that still are associated with insufficient clinical response, a chronic relapsing course, and functional disability in a substantial number of patients.[1–4] Although treatments during the first episode of psychosis and mania have yielded encouraging results,[5,6] follow-up studies have been somewhat disappointing, reconfirming that despite high initial response rates, illness relapse[7–9] and lack of functional recovery[10–12] are relatively frequent. Over the past decade, the schizophrenia field has responded to this situation with a push toward early recognition and intervention during the prepsychotic (ie, prodromal) phase of the illness.[13–19] These efforts were sparked by results from retrospective studies of schizophrenia patients that provided data regarding the trajectory and symptoms of a schizophrenia prodrome.[20,21] Using standardized rating scales for the psychotic prodrome, rates of conversion from the prodromal to the full psychotic state have ranged between 15% and 40% over 1–2 years of follow-up across multinational groups.[22] Pharmacologic and/or nonpharmacologic interventions in patients considered at ultra high risk for the development of psychosis have resulted in the improvement of attenuated psychotic symptoms[23] and a reduced conversion to psychosis.[24–26]

In contrast to schizophrenia, early identification and prevention research in the bipolar prodrome has focused largely on children of bipolar parents.[27–32] Even though these studies have found significant psychopathology and, in particular, high rates of mood disorders in bipolar offspring,[27,31] overall, conversion rates to bipolar disorder have remained either nonexistent[33] or as low as 13%[34] over a period of 5 years. In addition, the vast majority of patients with bipolar disorder do not have a parent with

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that same condition. An exception to these familial high-risk studies are follow-up studies of patients with a major depressive disorder[35–39] or attention deficit-hyperactivity disorder[40,41] that have sought to determine whether specific presentations are predictive of later development of mania. More recently, the rate of conversion to bipolar I disorder from bipolar II disorder or bipolar disorder not otherwise specified has been prospectively examined in youth.[42,43] This is important, as studies have associated longer duration of illness of bipolar disorder with worse outcomes.[44] However, there is a lack of studies that have focused on the identification of patients who are identified based on emerging clinical symptoms that would be indicative of future bipolar I disorder, rather than on the presence of genetic risk or a preceding diagnosis, such as unipolar depression, attention deficit-hyperactivity disorder, or a bipolar spectrum disorder. This dearth of clinical high-risk studies in bipolar disorder can be explained by the fact that the presence and nature of a clinical prodrome is not well established in this condition.

Although controversial, several lines of evidence suggest that in bipolar disorder an identifiable clinical prodrome precedes the full expression of the disorder.[45] At least 3 published studies have reported on the presence of a mixture of general psychopathology, depressive, and subthreshold mania symptom complexes prior to a first mania episode. However, these studies are limited by using either unstructured, retrospective accounts of adults who had developed bipolar disorder many years ago[46,47] or by using information of parents but not the actual patients, who only had a nonverified, clinical diagnosis of bipolar disorder.[48] Moreover, neither symptom severity nor onset patterns were assessed systematically in any of these studies. Although the prevailing opinion is that most patients develop mania within a relatively short period of time, this has recently been questioned by case reports of patients enrolled into psychosis prodrome programs who developed bipolar disorder after 6 months to several years.[49–51] Although prevalence rates of psychotic mania have not been consistent in the literature,[52] psychosis may occur in as many as 53%–97% of adults with bipolar disorder[53–55] and 60%–80% in youth.[56,57] In light of these data, it is somewhat surprising that relatively little attention has been paid to the assessment of a potential bipolar disorder prodrome in studies of subjects considered at clinical high risk for schizophrenia. It is further surprising that rates of bipolar disorder outcomes in these psychosis programs seem to have remained relatively low.[49–51]

To provide more information about the bipolar prodrome, we conducted a structured, retrospective study of early-onset bipolar patients and their caregivers assessing noticeable behavioral and symptomatic changes prior to full mania. We focused on children and adolescents who had their first episode within the past 5 years, as up to two-thirds of patients with bipolar disorder have their first onset of symptoms before age 18.[47,58,59] Moreover, the focus on youth assured a relatively short interval between the first manic episode and the interview and availability of caregivers as informants, improving the reliability of the retrospective recall. In a separate analysis of data from this cohort, we demonstrated that, at least in early-onset bipolar disorder, a lengthy mania prodrome with predominantly slow onset is common, consisting of a mixture of subthreshold depressive symptoms, general psychopathology symptoms, and subthreshold mania symptoms (Correll et al., unpublished data). Contradicting the general notion that, in most cases, mania develops precipitously, these findings suggest that early identification of individuals at clinical high risk for bipolar disorder may be a feasible goal. However, it is of substantial theoretical and practical interest whether specific clinical characteristics differentiate between the bipolar and the schizophrenia prodrome. Therefore, analyzing data from our retrospective data set in bipolar youth and using historical control data from previous retrospective studies of the schizophrenia and bipolar prodrome, we aimed to identify potential temporal and symptomatic differences between (1) the prodrome to a psychotic vs a nonpsychotic first mania episode and (2) the prodrome to a first mania episode compared with a first schizophrenia episode. We hypothesized that in addition to nonspecific depressive and general psychopathology symptoms, certain subthreshold mania symptoms would emerge that differentiate the mania prodrome from the nonaffective psychotic prodrome. We further hypothesized that attenuated psychotic symptoms would emerge late in the mania prodrome and would be specific for the prodrome preceding psychotic mania.

## Methods

### *Subjects*

Included in this retrospective study were 52 youngsters between 7 and 21 years old who had a diagnosis of bipolar I disorder. Subjects were drawn from a prospective study investigating the effects of newly initiated second-generation antipsychotic treatment in 515 youth with psychotic, mood, and disruptive behavior disorders. The study was performed at the inpatient and outpatient child psychiatric services centers of The Zucker Hillside Hospital and was approved by the local Institutional Review Board. All legal guardians and patients aged 18 years or older gave informed written consent and all youngsters aged 9 years and above gave written assent for participation in the study.

### *Procedures*

The research diagnosis of bipolar I disorder was ascertained in 52 youths using the Affective Disorders module

of the Schedule for Affective Disorders and Schizophrenia for School-Age Children[60] ($n = 33$) or the Washington University in St Louis Schedule for Affective Disorders and Schizophrenia ($n = 19$).[61] Two patients were excluded because they either fulfilled criteria for bipolar II disorder or for bipolar disorder not otherwise specified. Comorbid diagnoses were made using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria, based on information from the patients' charts and previous providers as well as information obtained during the interview with the patient and/or guardian. Patients with a confirmed bipolar I disorder and/or their caregivers independently underwent a newly developed semi-structured interview, the Bipolar Prodrome Symptom Scale-Retrospective (BPSS-R) (available from the first author upon request). The BPSS-R was developed based on an extension downward of the *DSM-IV* criteria and available rating scales for bipolar disorder and major depressive disorder. In addition, the BPSS-R development was informed by a review of existing literature regarding risk factors and early symptoms of bipolar disorder, published scales and interviews for the assessment of the psychotic prodrome and character traits, input from experts in the areas of the schizophrenia prodrome and bipolar disorder, and open questioning of youths with bipolar disorder and their caregivers regarding emerging subthreshold symptoms prior to the onset of a first syndromal bipolar manic, mixed, and depressive episode.

The BPSS-R systematically assesses the onset pattern, duration, severity and frequency of 36 symptoms, and signs that emerge or worsen prior to the first major depressive and/or first manic episode. It covers all *DSM-IV* symptoms of depression and mania and provides specific probes and anchors for more precise ratings. Prodromal symptom severity is rated on an ordinal scale with zero = absent, 1 = mild (ie, clearly noticeable, may affect functioning somewhat), 2 = moderate (ie, clearly noticeable, clearly affecting functioning), and 3 = severe (ie, noticeable, but not affecting functioning). Symptom frequency is rated on an ordinal scale with zero = absent, 1 = infrequent (ie, less than once a week), 2 = moderately frequent (ie, a couple of times a week), 3 = very frequent (ie, present more than 50% of the time), and 4 = static lifetime or character trait (which is not considered part of the dynamic prodrome). In addition to symptoms present during the mania prodrome, the BPSS also assesses presence of the same symptoms during the first manic episode. This includes structured probes for suprathreshold psychotic symptoms, which usually stand out due to their severity and qualitatively different nature. Whenever possible, both patient and one parent/legal guardian were interviewed. To increase reliability of the information, patient interviews were only conducted in youths who were at least 12 years old and/or who had reached a Clinical Global Impression severity score of "moderate" or lower at the time of the interview. These thresholds were set a priori, excluding 4 prepubertal youth from in-person interviews. All interviews were conducted in person by the first author, a board certified child, and adolescent psychiatrist or by medical trainees at the MD or medical student level who were trained and closely supervised by the first author. Reliability data were not collected for the retroactive version of the BPSS.

### *Description of Retrospective Comparison Studies of the Mania Prodrome and the Schizophrenia Prodrome*

To compare characteristics of a mania prodrome with those of a schizophrenia prodrome, results from this study were compared and contrasted, whenever possible, with studies that also reported on retrospectively ascertained bipolar or schizophrenia prodrome characteristics. To identify such studies, a PubMed/Medline search was conducted using the search terms "bipolar," "mania," "schizophrenia," or "psychosis" and "prodrome," "risk," or "conversion." Using this methodology, 5 studies were identified that reported on onset patterns or prevalence rates of specific symptoms during the bipolar prodrome or the schizophrenia prodrome.

In a retrospective, medical record study, Egeland et al[46] reviewed the social history information for presence of symptoms prior to first mania in 58 Amish adults with a postpubertal diagnosis of bipolar disorder (32 males, 26 females). Information was systematically coded but had been obtained as part of an unstructured interview during a first hospital admission that did not target any specific symptoms. Lish et al[47] conducted a 154-item mailed survey of 500 members of the National Depressive and Manic-Depressive Association with self-reported diagnoses of bipolar disorder (37% male, most common age group: 35–44 years old [32%]). Questions focused on illness onset and course, impact on quality of life and role functioning, and the onset and nature of treatment.

Hafner et al[21] studied the schizophrenia prodrome in 232 patients, aged 12–29 years, with a first episode of schizophrenia. Subjects were assessed using a newly developed structured interview, the Instrument for the Retrospective Assessment of the Onset of Schizophrenia, which assessed prodromal, negative, and positive symptoms, as well as environmental and individual social changes. The 10 most frequently first noticed symptoms were reported. Assessment of timing of the prodrome was performed by means of a visual time grid and using anchor events. Onset was coded from the time when negative or nonspecific symptoms remained present until the first psychotic break or from the time of first occurrence of any attenuated positive symptoms. In the study by Jackson et al,[62] prodromal schizophrenia symptoms were investigated in 313 first-episode psychosis patients, aged 14–46 years, using the Royal Park Multidiagnostic Instrument for Psychosis. Finally, Gourzis et al[63]

assessed 100 patients (mean age: 25.6 years), recently diagnosed with schizophrenia, along with 100 healthy controls. Patients were evaluated using the DSM-III-R prodromal symptoms ratings, present and retrospective Global Assessment of Functioning scoring, and the identification of less specific initial prodromal symptoms, such as concentration difficulties, sleep disturbances, irritability, suicidality, and compulsive behavior. Prodromal symptoms were categorized as negative, positive prepsychotic, and positive disorganization.

To provide an indirect account of the symptomatic overlap or delineation between the bipolar and the schizophrenia prodrome, pooled data from the retrospective studies that reported on bipolar prodrome symptom prevalences[46,47](this study) were compared with prevalence rates from one or all retrospective schizophrenia prodrome studies.[21,62,63] Prevalence rates were pooled without weighting whenever more than one study provided data.

### *Data Analysis*

Although with the BPSS-R, data were collected for both first depressive and manic episode prodrome, this report focuses only on the prodrome to the first syndromal mania. Consistent with the thresholds used in the schizophrenia prodrome literature[64–66] and in order to capture clinically relevant prodromal mania symptoms, only symptoms of at least moderate severity were considered for the analyses. Furthermore, consistent with the dynamic character of an illness prodrome, symptoms and signs were excluded from the analyses that were considered part of an unchanged lifetime or character trait. The mania prodrome duration and onset pattern were calculated starting from the first noticeable symptomatic change of at least moderate severity over baseline preceding a syndromal mania episode. Because Hafner et al[21] counted depression as part of the schizophrenia prodrome, we also calculated the duration and onset pattern of the mania prodrome using the beginning of a first syndromal depressive episode as the prodrome onset, whenever depression was the first mood polarity. Whenever results were available from independent interviews of both the patient and parent, data were combined into one aggregate set for each patient. When patient and caregiver responses differed, we counted the positive response, the higher symptom rating, and the earlier symptom onset to enter into the aggregate data set. This was done based on the assumption, employed by the WASH-U-KSADS and other instruments that assess data from patients and second informants, that patients and informants are more likely to forget, minimize, or underreport symptoms, rather than to overreport. In addition, previous studies have found that patients are better at identifying and characterizing internalizing symptoms, whereas parents are better at identifying and characterizing externalizing symptoms.[67]

Following the definitions by Hafner et al,[21] we defined "insidious" onset as a prodrome duration of more than 1 year, subacute onset as a prodrome duration of between 1 month and 1 year, and acute onset as a prodrome duration of less than 1 month. To analyze the study cohort and prodrome, we used descriptive statistical methods. Whenever not indicated otherwise, data are presented at means ± SDs. For the duration of the prodrome, 95% confidence intervals (CIs) were calculated. For comparisons of categorical and continuous variables, chi-square tests and *t*-tests or Fisher's exact test were used, where appropriate. Because the methodologies and populations of the comparison studies of the bipolar and the schizophrenia prodrome were heterogeneous across studies, odds ratios (ORs) with 95% CIs were only calculated in cases where the prodromal symptom prevalence rates differed by at least 100% across the bipolar mania and the schizophrenia prodrome. Data were analyzed using JMP 5.0.1, 1989-2003, SAS Institute Inc. Significance levels were set at $P < .05$ and all analyses were 2-tailed. We did not correct for multiple comparisons, as this was a first and preliminary study aimed at generating hypotheses and facilitating future research.

## Results

### *Study Population*

Table 1 summarizes the demographic characteristics of the 52 children and adolescents with bipolar I disorder comprising the study sample. For 28 patients (53.9%), interviews were conducted both in the patient and caregiver, for 17 (32.7%) only the caregiver was interviewed, and 7 interviews (13.5%) were conducted with the adolescent only. Patients had a mean age at the time of the first mania episode of 13.4 ± 3.3 years, 51.9% were female, 64.7% were White, and 29.4% had a first-degree family member with bipolar disorder. The mean lag between the first manic episode and the interview was 2.8 ± 2.0 years. All patients were interviewed within 5 years of their first manic episode. In 61.3% of the patients, the syndromal mood episode consisted of mania, with postpubertal onset in 73.1%. Psychosis occurred in 13 of 20 patients (65.0%) in whom a major depressive episode preceded mania. Comorbidities included oppositional defiant disorder (53.9%), attention deficit-hyperactivity disorder (32.7%), substance use disorders (23.1%), anxiety-spectrum disorders (19.2%), and learning disorders (7.7%).

Patients who experienced psychosis as part their first mania differed from those without psychosis only regarding a higher age of onset of the first mania (14.2 ± 3.1 vs 11.9 ± 3.4 years, $P = .014$) and a lower prevalence of comorbid attention deficit-hyperactivity disorder (14.7% vs 66.7%, $P = .0001$). While patients with psychotic mania also had a higher prevalence rate of psychosis during a full depressive episode preceding mania

**Table 1.** Demographic and Clinical Characteristics of 52 Youth with Early-Onset Bipolar I Disorder

| Characteristic | Total ($N$ = 52) | Mania With Psychosis ($n$ = 34) | Mania Without Psychosis ($n$ = 18) | $P$ Value |
|---|---|---|---|---|
| Age at time of interview (years ± SD) | 16.2 ± 2.8 | 16.6 ± 2.6 | 15.5 ± 3.2 | .20 |
| Age at first manic episode (years ± SD) | 13.4 ± 3.3 | 14.2 ± 3.1 | 11.9 ± 3.4 | **.014** |
| Female sex ($N$, %) | 27 (51.9%) | 18 (52.9%) | 9 (50.0%) | .84 |
| Ethnicity/race[a] | | | | .72 |
| White ($N$, %) | 33 (64.7%) | 20 (60.6%) | 13 (72.2%) | |
| African American ($N$, %) | 8 (15.7%) | 5 (15.1%) | 3 (16.7%) | |
| Hispanic ($N$, %) | 4 (7.8%) | 3 (9.1%) | 1 (5.6%) | |
| Asian ($N$, %) | 6 (11.8%) | 5 (15.1%) | 1 (5.6%) | |
| Family history of bipolar disorder | | | | |
| First-degree family member[a,b] ($N$, %) | 15 (29.4%) | 8 (23.5%) | 7 (41.2%) | .19 |
| Bipolar I disorder characteristics | | | | |
| Prepubertal onset mania ($N$, %) | 14 (26.9%) | 7 (20.6%) | 7 (38.9%) | .16 |
| Major depression as first mood episode ($N$, %) | 20 (38.5%) | 13 (38.2%) | 7 (38.9%) | .96 |
| Major depression as first mood episode with psychosis ($N$, %) | 13 (25.0%) | 11 (32.3%) | 2 (11.1%) | .092 |
| Comorbidities | | | | |
| Oppositional defiant disorder | 25 (53.9%) | 15 (44.1%) | 10 (55.7%) | .43 |
| Attention deficit-hyperactivity disorder | 17 (32.7%) | 5 (14.7%) | 12 (66.7%) | **.0001** |
| Substance use disorders | 12 (23.1%) | 7 (20.6%) | 5 (27.8%) | .56 |
| Anxiety disorders/OCD/PTSD[c] | 10 (19.2%) | 7 (20.6%) | 3 (16.7%) | .73 |
| Learning disorder | 4 (7.7%) | 3 (8.8%) | 1 (5.6%) | .67 |

[a]Based on 51 patients with available information.
[b]Four first-degree family members with bipolar disorder were interviewed as informants.
[c]Generalized Anxiety Disorder (GAD): $n$ = 2; Obsessive Compulsive Disorder (OCD): $n$ = 4; not otherwise specified (NOS): $n$ = 2; Post-traumatic Stress Disorder (PTSD): $n$ = 2.

(32.2% vs 11.1%), this did not reach statistical significance ($P$ = .092).

### *Mania Prodrome Duration and Trajectories*

Table 2 summarizes the mean duration and onset pattern of the mania prodrome, with added reference values from the retrospective study by Hafner et al[21] for the schizophrenia prodrome. The mania prodrome duration requiring the presence of at least one newly emerging symptom of at least moderate severity was 1.8 ± 1.7 (95% CI: 1.3–2.2) years for the entire sample, without differences depending on psychosis status during subsequent mania ($P$ = .70). Using syndromal depression as an alternative onset threshold in those patients with a major depressive episode as the first mood polarity, the mean mania prodrome duration increased by 6 months to 2.3 ± 2.1 (95% CI: 1.7–2.8) years. Using either a prodromal mania symptom of at least moderate severity or syndromal depression as an alternative mania prodrome onset threshold, the predominant mania onset patterns were insidious (ie, >1 year) (51.9% and 63.4%, respectively) or subacute (ie, >1 month to 1 year) (44.2% or 28.8%, respectively). Acute onset of prodromal symptoms within less than 1 month of a full manic episode was rare (3.8% and 7.8%, respectively). The onset pattern did not differ between the prepsychotic and nonpsychotic mania prodrome. The initial symptom presentation of the clinical mania prodrome included attenuated positive symptoms in 28.9% of patients, which was less common in patients with subsequent nonpsychotic mania (11.1% vs 38.2%, $P$ = .055).

Furthermore, neither sex, age, or pubertal status nor possibly reduced reliability of recalled information due to a period between first mania and the interview of more than 6 months vs ≤6 months ago was significantly related to the reported mania prodrome duration and prodromal trajectories. For the mania prodrome duration, significance levels for these potential moderating variables ranged from $P$ = .15 to $P$ = .46, when excluding syndromal depression from the mania prodrome, and from $P$ = .17 to $P$ = .93, when including syndromal depression. With the exception of a trend level for more frequently occurring insidious mania onset when including syndromal depression as part of the mania prodrome in females compared with males, significance levels ranged from $P$ = .78 to $P$ = .99, when excluding syndromal depression from the mania prodrome, and from $P$ = .22 to $P$ = .61, when including syndromal depression.

### *Symptoms and Signs of the Mania Prodrome*

Table 3 summarizes the frequency of the systematically assessed symptoms of at least moderate severity that

**Table 2.** Prodrome Onset Patterns Prior to a First Mania Episode With or Without Psychosis and in First Episode Schizophrenia

| Prodrome Characteristic | At Least One Moderately Severe Mania Prodrome Symptom ($N = 52$) | Mania With Psychosis ($N = 34$) | Mania Without Psychosis ($N = 18$) | $P$ Value | First Depression Counted as Mania Prodrome ($N = 52$) | Prodrome to First Episode Schizophrenia[21] ($N = 232$) |
|---|---|---|---|---|---|---|
| Prodrome duration (years ± SD, 95% CI) | 1.8 ± 1.7 (1.3–2.2) | 1.7 ± 1.8 (1.1–2.3) | 1.9 ± 1.5 (1.2–2.6) | .70 | 2.3 ± 2.1 (1.7–2.8) | 5.0 |
| Prodrome onset ($N$, %) | | | | .22 | | |
| Insidious[a] (>1 y) | 27 (51.9) | 15 (44.1) | 12 (66.7) | | 33 (63.4) | 157 (67.7) |
| Subacute[a] (>1 mo–1 y) | 23 (44.2) | 18 (52.9) | 5 (27.8) | | 15 (28.8) | 34 (14.7) |
| Acute[a] (<1 mo) | 2 (3.8) | 1 (2.9) | 1 (5.6) | | 4 (7.8) | 41 (17.7) |
| Initial symptom attenuated positive symptom | 15 (28.9) | 13 (38.2) | 2 (11.1) | .055[b] | NA[c] | 62 (26.7) |

[a]Definitions according to Hafner et al.[21]
[b]Fisher's exact test.
[c]Could not be calculated, as presence of attenuated positive symptoms was not assessed as part of a major depressive episode.

newly emerged prior to a first manic episode. The most frequent prodromal symptoms that were present in at least 50% of patients in either of the 2 subgroups (ie, psychotic or nonpsychotic mania prodrome) consisted of nonspecific psychopathology (ie, drop in school/work functioning, mood swings, anger outbursts/tantrums, social isolation, and oppositionality), subthreshold mania symptoms (eg, irritability/anger, racing thoughts, and increased energy/goal–directed activity), subthreshold symptoms that cut across criteria for mania and depression (ie, inattention and psychomotor agitation), and subthreshold depressive symptoms (ie, depressed mood and anhedonia).

Expectedly, patients with subsequent psychosis during the first manic episode were significantly more likely to have attenuated psychotic symptoms as part of the mania prodrome than those without subsequent psychotic mania ($P$-values ranging between .029 and .0041). Symptoms included subthreshold grandiosity, suspiciousness, other unusual thought content, and hallucinations. By contrast, the measured proxy for attenuated thought disorder (ie, difficulty thinking or communicating clearly) was not different between the 2 groups. The only additional symptom unrelated to psychosis that differed significantly between prepsychotic and nonpsychotic mania was increased energy/goal–directed activity, which was significantly more common in patients with subsequent psychotic mania ($P = .0036$).

Attenuated positive symptoms captured by the BPSS-R were present as part of the mania prodrome in 34 (65.4%) patients. Difficulty thinking/communicating clearly (40.4%) and unusual thought content (36.5%) were more common than perceptual disturbances (23.1%) (table 4). Among perceptual disturbances, attenuated auditory hallucinations predominated (19.2%), followed by attenuated visual hallucinations (13.5%). Regarding symptom onset, attenuated positive psychotic symptoms, particularly different types of thought content disorder, occurred late in the prodrome (mean duration: 1.4–2.8 months, median duration: 0.6–1.5 months). While still considerably shorter than the overall mania prodrome duration, the different types of perceptual disturbances and difficulties with thinking/communication were present longer before full mania than predelusional thoughts (mean duration: 7.6–8.8 months, median duration: 2–3 months).

### *Comparison of Symptom Prevalence Rates During the Mania and the Schizophrenia Prodrome*

In table 5, prodromal symptom prevalence rates are displayed from this study as well as from published studies that retrospectively assessed prodromal symptoms prior to a first episode of bipolar disorder or schizophrenia. Data are only displayed where information from at least 2 studies were available and ORs were only calculated whenever the prevalence rates differed by at least 100% in patients with the bipolar mania prodrome and the schizophrenia prodrome. The mania and the schizophrenia prodrome consist of a mixture of subthreshold manic, depressive and general psychopathology symptoms. However, rates across studies assessing the prodrome to the same disorder varied, at times, considerably. As part of the mania prodrome, decreased school/work performance (65.4%) and decreased concentration/memory (51.9%) were the most prevalent symptoms, followed by increased energy/goal-directed activity (48.3%), depressed mood (46.7%), social isolation (44.2%), and anger outbursts (43.8%). During the schizophrenia prodrome, social isolation (55.7%), strange or unusual ideas (53.3%), and decreased school/work performance (44.2%) were most prevalent. Compared with the schizophrenia

**Table 3.** Symptoms and Signs During the Bipolar Mania Prodrome (*n*, %)

| Bipolar Prodrome Symptom/Sign (≥Moderate Severity) | Mania With Psychosis (*n* = 34) | Mania Without Psychosis (*n* = 18) | *P* Value |
|---|---|---|---|
| Subsyndromal manic symptoms | | | |
| Irritability or easily angered | 21 (61.8) | 11 (61.1) | .96 |
| Racing thoughts | 22 (64.7) | 9 (50.0) | .30 |
| Increased energy or goal-directed activity | 22 (64.7) | 4 (22.2) | **.0036** |
| Overly talkative | 16 (47.1) | 6 (33.3) | .34 |
| Reckless or dangerous behavior | 16 (47.1) | 5 (27.8) | .18 |
| Decreased need for sleep | 14 (41.2) | 6 (33.3) | .58 |
| Overly cheerful or happy | 13 (38.2) | 5 (27.8) | .45 |
| Overly self confident | 8 (23.5) | 4 (22.2) | .91 |
| Increased sexual energy | 8 (23.5) | 2 (11.1) | .28 |
| Risky sexual behavior | 1 (2.9) | 2 (11.1) | .23 |
| Subsyndromal manic or depressive symptoms | | | |
| Decreased concentration/attention/memory | 20 (58.8) | 7 (38.9) | .17 |
| Physically agitated | 19 (55.9) | 6 (33.3) | .12 |
| Subsyndromal manic or psychotic symptoms | | | |
| Grandiose ideas | 8 (23.5) | 0 (0.0) | **.021** |
| Subsyndromal psychotic symptoms | | | |
| Strange or unusual (nongrandiose) ideas | 10 (29.4) | 0 (0.0) | **.010** |
| Suspiciousness | 12 (35.3) | 0 (0.0) | **.0041** |
| Hallucinatory experiences | 11 (32.3) | 1 (5.6) | **.029** |
| Subsyndromal manic or psychotic or depressive symptoms | | | |
| Difficulty thinking or communicating clearly | 13 (38.2) | 8 (44.4) | .66 |
| Subsyndromal depressive symptoms | | | |
| Depressed mood | 18 (52.9) | 10 (55.6) | .86 |
| Anhedonia | 17 (50.0) | 4 (22.2) | .052 |
| Insomnia | 14 (41.2) | 5 (27.8) | .34 |
| Feeling worthless or guilty | 13 (38.2) | 4 (22.2) | .24 |
| Thinking about suicide | 10 (29.4) | 6 (33.3) | .77 |
| Tiredness or lack of energy | 9 (26.5) | 4 (22.2) | .74 |
| Weight loss or decrease in appetite | 10 (29.4) | 2 (11.1) | .14 |
| Physically slowed down | 4 (11.8) | 4 (22.2) | .32 |
| Weight gain or increase in appetite | 4 (11.8) | 3 (16.7) | .62 |
| Attempting suicide | 4 (11.8) | 2 (11.1) | .94 |
| Hypersomnia | 1 (2.9) | 2 (11.1) | .23 |
| General psychopathology | | | |
| Decreased school or work functioning | 24 (70.62) | 10 (55.6) | .28 |
| Frequent mood swings/lability | 21 (61.8) | 9 (50.0) | .41 |
| Anger or losing temper a lot | 15 (44.1) | 10 (55.6) | .43 |
| Social isolation | 13 (38.2) | 10 (55.6) | .23 |
| Anxiety or nervousness | 16 (47.1) | 6 (33.3) | .30 |
| Oppositionality | 10 (29.4) | 9 (50.0) | .14 |
| Obsessions or compulsions | 10 (29.4) | 4 (22.2) | .58 |
| Ambivalence | 9 (26.5) | 2 (11.1) | .20 |

prodrome, prevalence rates during the mania prodrome were at least twice as high for decreased concentration/memory (51.9% vs 25.4%; OR: 3.6, 1.9–6.9), physical agitation (40.0% vs 17.2%; OR: 2.8, 2.1–3.9), depressed mood (46.7% vs 16.2%; OR: 3.7, 2.8–4.9), suicidal thoughts (30.8% vs 7.0%; OR: 6.3, 2.5–16.9), tiredness/lack of energy (31.4% vs 12.1%; OR: 3.5, 2.0–6.4), difficulty thinking/communicating clearly (29.8% vs 9.0%; OR: 2.9, 1.8–4.6), and obsessions/compulsions (26.9% vs 5.0%; OR: 7.3, 2.7–20.1). On the other hand, strange or unusual ideas were more prevalent during the schizophrenia prodrome (53.3% vs 18.0%, OR: 5.3, 3.9–7.1).

## Discussion

The main results from this study of 52 patients with onset of bipolar disorder before adulthood were as follows: (1) the first episode of mania is preceded by a relatively lengthy and symptomatic clinical prodrome, (2) the mania prodrome duration/illness onset is predominantly insidious or subacute, (3) the prepsychotic mania prodrome differs very little from the nonpsychotic mania prodrome (except for a greater likelihood of attenuated positive symptoms proximal to the first manic episode), and (4) the mania prodrome and the schizophrenia prodrome

**Table 4.** Attenuated Positive Symptom Duration Prior to a First Manic Episode

| Prodromal Symptom | Total ($N$ = 52) | Mean Prodrome Duration (months ± SD, 95% CI) | Median Prodrome Duration |
|---|---|---|---|
| ≥1 Symptom, ≥moderate severity | 52 (100.0) | 18.8 ± 19.2 (13.4 to 24.2) | 12.0 |
| Attenuated positive symptom | 34 (65.4) | | |
| Perceptual abnormality[a] | 12 (23.1) | 7.6 ± 15.4 (2.2 to 17.4) | 2.0 |
| Auditory | 10 (19.2) | 8.8 ± 16.8 (0.0 to 20.8) | 2.0 |
| Visual | 7 (13.5) | 4.3 ± 5.0 (0.0 to 8.9) | 2.0 |
| Olfactory | 1 (1.9) | 0.5 | — |
| Tactile | 1 (1.9) | 2.0 | — |
| Missing information | 1 (1.9) | — | — |
| Unusual thought content[a] | 19 (36.5) | | |
| Nongrandiose unusual thoughts | 10 (19.2) | 1.4 ± 1.6 (0.3 to 2.6) | 0.62 |
| Grandiose unusual thoughts | 8 (15.4) | 1.9 ± 1.7 (0.4 to 3.4) | 1.5 |
| Suspiciousness | 12 (23.1) | 2.8 ± 4.8 (0.0 to 5.9) | 0.75 |
| Difficulty thinking or communicating clearly | 21 (40.4) | 6.6 ± 12.9 (0.8 to 12.5) | 3.0 |

[a]$N$ in subcategory may be greater than the total number of patients due to presence of multiple abnormalities per subject.

overlap substantially regarding onset patterns and symptom expression.

The finding of a symptomatic and relatively lengthy mania prodrome has implications for prevention programs for bipolar disorder as well as for schizophrenia. The predominance of insidious or subacute illness onset and prodrome durations of 1.8 or 2.3 years (depending on whether or not the first major depressive episode was counted into the mania prodrome) provide the basis for the development of early identification programs in bipolar disorder.[5] Although the mean prodrome duration was shorter than the 5.0 years reported for the schizophrenia prodrome,[21] the predominant illness onset pattern included a prodrome of more than 1 year in our sample, similar to the patterns described for the schizophrenia prodrome.[21] When major depression was counted as part of the mania prodrome, insidious onset rates were comparable for bipolar disorder (63.4%) and schizophrenia (67.7%).[21] Thus, while potentially shorter than the schizophrenia prodrome, the mania prodrome duration appears to be sufficiently long to enable clinical high-risk programs for bipolar disorder that would complement existing studies in patients identified by presence of a first-degree family member with bipolar disorder.[27–29,31,32] Such complementary approach is of importance, as more than 70% of patients in this study would not have been identified by the familial high-risk approach.

On the other hand, our findings of substantial onset type and phenotypic overlap between the prepsychotic and nonpsychotic mania prodrome and between the mania and the schizophrenia prodrome also suggest that schizophrenia and psychosis prevention programs need to broaden their respective methodologies. Assessment tools that capture clinical and endophenotypic characteristics of bipolar disorder risk[45] should be added when assessing individuals considered at clinical high risk for schizophrenia. The reverse should be implemented in high-risk bipolar disorder studies. In order to enable the sufficiently accurate identification of individuals at risk for schizophrenia or bipolar disorder, the specificity and prognostic power of individual prodromal symptoms or symptom constellations are highly relevant. Despite similarities between the mania and schizophrenia prodrome, several potential differences emerged. First, subthreshold delusions and hallucinations seem to occur late in the mania prodrome, occurring before syndromal mania at a median time of 0.75–3.0 months compared with 12.0 months for the overall mania prodrome. By contrast, attenuated positive symptoms are used as the initial symptom to identify patient at risk for nonaffective psychosis.[65,68] Second, in the pooled comparison of studies using retrospective methodologies for the assessment of the prodrome preceding a first episode of mania or schizophrenia, several symptoms occurred more frequently prior to a mania episode (OR: 2.8–7.3). These prodromal symptoms include certain depressive symptoms (ie, depressed mood, suicidality, and decreased energy/tiredness), subthreshold mania-like symptoms (ie, decreased concentration, psychomotor agitation, and difficulties thinking/communicating clearly), as well as general psychopathology (ie, obsessions/compulsions and mood swings/lability). By contrast, strange/unusual thoughts were more likely part of the schizophrenia prodrome (OR: 5.3). However, it is important to note that these relative frequencies of preillness symptomatology were ascertained by comparing rates from studies that used very different methodologies, leading to wide variations even within the mania or schizophrenia prodrome for some symptoms. In addition to the lack of a direct comparison within the same study, the lack of control groups does not permit an evaluation of the prognostic specificity of individual prodromal symptoms.

Regarding the prediction of subsequent psychosis, it is also of interest that attention deficit-hyperactivity

**Table 5.** Retrospectively Studied Prodromal Symptoms Preceding First Mania or Schizophrenia Episode[a]

| Prodromal Symptom/Sign | Studies of the Prodrome Prior to First Manic Episode | | | | Studies of the Prodrome Prior to First Psychotic Episode in Schizophrenia | | | | OR (95% CI)[c] |
|---|---|---|---|---|---|---|---|---|---|
| | Lish[47] ($N$ = 500) | Egeland[46] ($N$ = 58) | This Study[b] ($N$ = 52) | Mean Across Studies | Hafner et al.[21] ($N$ = 232) | Jackson et al[62] ($N$ = 313) | Gourzis et al[63] ($N$ = 100) | Mean Across Studies | |
| Subsyndromal manic | | | | | | | | | |
| Irritability or easily angered | 9.4% | 32.8% | 61.5% | 34.6% | | | 39.0% | 39.0% | |
| Increased energy or activity | | 46.6% | 50.0% | 48.3% | | | | | |
| Overly self-confident/ grandiose | | 17.2% | 23.1% | 20.1% | | | | | |
| Subsyndromal manic or depressive | | | | | | | | | |
| Decrease in concentration/ attention/memory | | | 51.9% | 51.9% | 15.9% | | 35.0% | 25.4% | 3.6[d] (1.9–6.9) |
| Physically agitated | 32.0% | | 48.1% | 40.0% | 18.5% | | 16.0% | 17.2% | 2.8[d] (2.1–3.9) |
| Subsyndromal psychotic | | | | | | | | | |
| Strange or unusual ideas | 9.2% | | 26.9% | 18.0% | | 53.3% | | 53.3% | 5.3[e] (3.9–7.1) |
| Suspiciousness | 9.2% | | 23.1% | 16.1% | 9.9% | | 34.0% | 21.9% | |
| Hallucinatory experiences | | | 23.1% | 23.1% | | 23.7% | 35.0% | 29.3% | |
| Subsyndromal depressive | | | | | | | | | |
| Depressed mood | 32.8% | 53.4% | 53.8% | 46.7% | 18.5% | | 14.0% | 16.2% | 3.7[d] (2.8–4.9) |
| Anhedonia | | | 40.4% | 40.4% | | 23.7% | 43.0% | 33.3% | |
| Insomnia | 24.2% | 25.9% | 36.5% | 28.9% | | | 21.0% | 21.0% | |
| Feeling worthless or guilty | | 22.4% | 32.7% | 27.5% | | | | | |
| Thinking about suicide | | | 30.8% | 30.8% | | | 7.0% | 7.0% | 6.3[d] (2.5–16.0) |
| Tiredness or lack of energy | | 37.9% | 25.0% | 31.4% | 12.1% | | | 12.1% | 3.5[d] (2.0–6.4) |
| Subsyndromal manic/depressive/ psychotic | | | | | | | | | |
| Difficulty thinking or communicating clearly | | | 40.4% | 40.4% | | 29.0% | 7.0% | 18.0% | 4.0[d] (1.9–8.1) |
| General psychopathology | | | | | | | | | |
| Decrease in school or work functioning | | | 65.4% | 65.4% | 11.2% | 62.5% | 59.0% | 44.2% | |
| Frequent mood swings/lability | 12.8% | 19.0% | 57.7% | 29.8% | | | 9.0% | 9.0% | 2.9[d] (1.8–4.6) |
| Anger or losing temper a lot | | 39.6% | 48.1% | 43.8% | | | | | |
| Social isolation | | | 44.2% | 44.2% | 20.7% | 75.5% | 71.0% | 55.7% | |
| Anxiety or nervousness | | 22.4% | 43.1% | 32.7% | 18.1% | | 32.0% | 25.0% | |
| Oppositionality | | 27.5% | 36.5% | 32.0% | | | | | |
| Obsessions or compulsions | | | 26.9% | 26.9% | | | 5.0% | 5.0% | 7.3[d] (2.7–20.1) |
| Blunted or inappropriate affect | | | | | | 33.3% | 38.0% | 35.6% | |
| Impaired personal hygiene | | | | | | 22.3% | 12.0% | 17.1% | |
| Markedly peculiar behavior | | | | | | 25.6% | 9.0% | 17.3% | |
| Somatic symptoms | | 19.0% | | 19% | | | 14.0% | 14.0% | |

[a]Prodromal symptoms listed that were reported in at least 2 studies.
[b]Systematically assessed prodromal symptoms of at least moderate severity.
[c]ORs only calculated for variables where differences in prevalence rates between the 2 diagnostic groups were at least 100% or greater.
[d]OR greater for bipolar prodrome.
[e]OR greater for schizophrenia prodrome.

disorder was relatively infrequent in patients with psychotic mania. We are not aware of previous studies that compared the rates of attention deficit-hyperactivity disorder in psychotic and nonpsychotic mania. While this finding could be an artifact, as comorbidities were only assessed clinically, the relative absence of attention deficit-hyperactivity disorder in psychotic mania could also point to a clinical subtype of bipolar disorder that is closer to the adult-onset type. This is suggested by the fact that patients with a first episode of psychotic mania had a later illness onset and were more likely to have episodes of increased energy or goal-directed activity, which may be seen as a more specific mania symptom. Further, although not statistically significant, patients with psychotic mania had an almost 3-fold higher prevalence of psychotic depression as a first mood polarity compared with nonpsychotic mania. Because we did not systematically collect data regarding the characteristics of a major depressive episode that followed the first mania later on in the course of the illness, we were unable to examine this further in our data set. However, if confirmed in other samples, genetic and endophenotypic studies should also focus on psychosis as a phenotype, independent of mood polarity and primary diagnosis, such as schizophrenia, bipolar disorder, or unipolar depression.

Several limitations have to be taken into consideration when interpreting the results from this study. These include its retrospective nature and small sample size, focus on patients with preadult-onset bipolar disorder who were also in clinical need for second-generation antipsychotic treatment, the lack of a clinical or healthy control group, lack of structured diagnostic interviews for presence and onset of psychiatric comorbidities, use of a not yet validated interview for the elicitation and rating of prodromal mania symptoms, as well as the methodological and demographic differences in the studies that reported on the bipolar and the schizophrenia prodrome that were used for preliminary comparisons of the 2 conditions. Furthermore, there has been considerable debate about the validity of pediatric bipolar disorder.[69] Although we utilized unmodified *DSM-IV* criteria for bipolar I disorder, it is possible that the symptom expression[70–72] and, thus, prodromal patterns differ between pediatric-onset bipolar disorder and adult-onset bipolar disorder. While the factors mentioned above may reduce the generalizability of our findings, this is the first study that systematically assessed the nature and onset pattern of the manic prodrome in individuals with a research diagnosis of bipolar I disorder, that assessed the severity of prodromal symptoms to create clinically meaningful thresholds of prodromal symptoms and signs, and that utilized information from both patients and caregivers. Furthermore, despite methodological challenges, this study provides first data regarding the indirect comparison between characteristics of the schizophrenia prodrome and the mania prodrome.

In summary, these results of a sufficiently lengthy and symptomatic mania prodrome indicate that clinical high-risk and early identification studies should be attempted in bipolar disorder. Because there seems to be substantial overlap between the mania and schizophrenia prodrome and because the prodrome preceding a psychotic mania also contains attenuated positive symptoms, these results further suggest that bipolar disorder and early psychosis identification programs should simultaneously measure clinical precursors and biological underpinnings of both conditions. The nonspecificity of many of the identified symptoms poses a problem regarding the ability to utilize clinical symptoms as predictors and inclusion criteria for patients at clinical high risk for bipolar disorder. Therefore, prospective studies of at-risk individuals are needed to determine whether specific symptom clusters, either alone or in combination with endophenotypic markers,[45] have sufficient predictive power to enable the clinical identification of patients at ultra high risk for bipolar disorder. Until such long-term studies are completed, large retrospective studies are needed to confirm and extend our preliminary findings of a substantial phenotypic overlap and potentially isolated differences between the schizophrenia and bipolar prodrome. Such studies should use the same methodology to assess patients with research-based diagnoses of bipolar disorder and schizophrenia with pediatric as well as adult onset. Importantly, these studies should also include clinical control groups in order to test the specificity of prodromal risk markers and to identify predictors of conversion to either schizophrenia or bipolar disorder. While clearly more research needs to be conducted, it is hoped that the combination of clinical, genetic, and endophenotypic approaches will ultimately yield sufficiently predictive prodromal and biological risk profiles that will enable the timely identification and preventive interventions in individuals at risk for bipolar disorder and nonaffective psychotic disorders.

## Acknowledgments

Supported in part by "Characterization of the Schizophrenia Prodrome" MH61523-06 (B.A.C., PhD), and The Zucker Hillside Hospital NIMH Advanced Center for Intervention and Services Research for the Study of Schizophrenia MH 074543-01 (J.M.K., MD). Financial disclosures: Dr Corrrell serves as a consultant, advisor, and/or lecturer for AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Intra-Cellular Therapeutics, Janssen Pharmaceutica, Otsuka and Solvay Pharmaceuticals. Dr Kane serves as a consultant, advisor, and/or lecturer for Abbott, AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Janssen Pharmaceutica, Lundbeck, Otsuka and Wyeth. Dr Cornblatt serves as consultant for Bristol-Meyers Squibb, Janssen Pharmaceutica and Solvay Pharmaceuticals.

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