ORIGINAL ARTICLE

Four-Year Prospective Outcome and Natural History of Mania in Children With a Prepubertal and Early Adolescent Bipolar Disorder Phenotype

Barbara Geller, MD; Rebecca Tillman, MS; James L. Craney, MPH, JD; Kristine Bolhofner, BS

Background: Diagnosis of child mania has been contentious.

Objective: To investigate natural history and prospective validation of the existence and long-episode duration of mania in children.

Design: Four-year prospective longitudinal study of 86 subjects with intake episode mania who were all assessed at 6, 12, 18, 24, 36, and 48 months. The phenotype was defined as *DSM-IV* bipolar I disorder (manic or mixed) with at least 1 cardinal symptom (elation and/or grandiosity) to ensure differentiation from attention-deficit/hyperactivity disorder. Parent and child informants were separately interviewed, by highly experienced research nurses, using the Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS). A Children's Global Assessment Scale score of 60 or less was needed to establish definite impairment. Treatment was by subjects' community practitioners.

Setting: Research unit in a university medical school.

Participants: Subjects were obtained from psychiatric and pediatric sites by consecutive new case ascertainment, and their baseline age was 10.8±2.7 years. Onset of the baseline episode was 7.4±3.5 years. (Data are given as mean±SD.)

Main Outcome Measures: Episode duration, weeks ill, recovery/relapse rates, and outcome predictors.

Results: Prospective episode duration of manic diagnoses, using onset of mania as baseline date, was 79.2±66.7 consecutive weeks. Any bipolar disorder diagnosis occurred during 67.1%±28.5% of total weeks, during the 209.4±3.3 weeks of follow-up. Subjects spent 56.9%±28.8% of total weeks with mania or hypomania (unipolar or mixed), and 38.7%±28.8% of these were with mania. Major or minor depression and dysthymia (unipolar or mixed) occurred during 47.1%±30.4% of total weeks. Polarity switches occurred 1.1±0.7 times per year. Low maternal warmth predicted faster relapse after recovery from mania (χ^2=13.6, P=.0002), and psychosis predicted more weeks ill with mania or hypomania ($F_{1,80}$=12.2, P=.0008). Pubertal status and sex were not predictive. (Data are given as mean±SD.)

Conclusions: These findings validate the existence, long-episode duration, and chronicity of child mania. Differences from the natural history of adult bipolar disorder are discussed.

Arch Gen Psychiatry. 2004;61:459-467

From the Department of Psychiatry, Washington University in St Louis, St Louis, Mo.

In the approximately 50 years since lithium salts were introduced, there have been several 4- to 5-year prospective follow-up studies[1-6] of older adolescent and adult-onset bipolar disorder (BP). In contrast, to our knowledge, this is the first prospective 4-year follow-up study of a sample systematically ascertained for a prepubertal and early adolescent BP (PEA-BP) phenotype. Because the area of child mania has been highly contentious, an investigation of longitudinal diagnostic validation was clearly warranted.[7-9] Although once thought rare, in the National Institute of Mental Health (NIMH)–funded "Phenomenology and Course of Pediatric Bipolar Disorders," 6.9% of consecutive new cases, ascertained from multiple pediatric and psychiatric facilities, fit PEA-BP by stringent research assessment.[10]

Because this was the first NIMH-funded study of the phenomenology and longitudinal course of child mania, conservative inclusion criteria were selected for credibility in a highly contentious field.[9] Therefore, analogous to the requirement of depressed mood and/or anhedonia for *DSM-IV* major depressive disorder (MDD), the PEA-BP phenotype was defined by elated mood and/or grandiosity as one inclusion criterion.[10-14] This definition

avoided diagnosing mania by criteria (hyperactivity and distractibility) that overlapped with those for attention-deficit/hyperactivity disorder (ADHD) and ensured that subjects had at least 1 of the 2 cardinal features of mania (elated mood and grandiosity). This PEA-BP cardinal symptom phenotype is not uncommon, as evidenced by the first 60 subjects (of the same age as in the PEA-BP sample) enrolled in the ongoing NIMH-funded multisite Treatment of Early Age Mania study. In the Treatment of Early Age Mania study, elated mood or grandiosity was not required to diagnose bipolar I disorder (BP-I). Nevertheless, 98.3% of the subjects had elation, 96.7% had grandiosity, 95.0% had both, and 100.0% had either (B.G., unpublished data, 2004).

In this regard, Biederman et al[15] reported that mania in children is characterized by irritable, rather than elated, mood. These investigators, however, did not interview children younger than 12 years, which has recently been shown to be essential in evaluating child mania.[16] In addition, Biederman et al used lay raters, did not use a scale with prepubertal age-specific items, did not have a severity cutoff, and ascertained for ADHD. These methodological differences between the Biederman et al and the PEA-BP and Treatment of Early Age Mania samples may in part account for the differences in prevalence of mania symptoms. Moreover, the nonspecificity of irritability in child psychiatric disorders has also been demonstrated by recent randomized trials for aggression/irritability in children with autism[17] and a low IQ[18] and by the report[19] that 20% to 60% of young adults with various diagnoses had aggression/irritability diagnoses as children. Thus, irritability is a highly sensitive symptom of child and adolescent mania, but is nonspecific because it occurs in many other diagnoses.

In earlier reports[11-13] on the outcome of the PEA-BP sample, 6-month, 1-year, and 2-year diagnostic stability of mania was found. But, there was a need for 4-year data for the following reasons. Baseline data showed that subjects had been continuously ill with the intake episode of mania for a mean±SD of 3.5±2.5 years. To prospectively validate this history of long-episode duration required prospective data for at least 4 years. Furthermore, to our knowledge, there are no 4-year follow-up data to guide researchers developing intervention and prevention strategies or to aid physicians answering parental inquiries regarding natural history and prognosis.

Contrary to commonly held beliefs that most adults with BP-I had episodic illnesses, recent weekly examination of mood symptoms during a 20-year period supported a complex pattern of varying affective states.[20] Prospective follow-up of the PEA-BP sample provides the opportunity to compare the weekly course in children with that reported for adults.

METHODS

SUBJECTS

Study participants were 86 subjects with PEA-BP and were obtained through consecutive new case ascertainment from multiple child psychiatric and pediatric sites between September 25, 1995, and December 15, 1998, using methods detailed elsewhere.[10] During this naturalistic study, treatments were provided by participants' own clinicians in the community and not in any way by the research nurses who conducted the assessments. Therefore, subjects received treatments exactly as if they were not participating in a longitudinal research study.

ASSESSMENT

The Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS)[21,22] is a semistructured interview with excellent reliability for mania symptoms, mood diagnoses, rapid cycling patterns, and time frames (κ, 0.82-1.00), and is the most widely used instrument in NIMH-funded studies of child mania.[7] It was administered by highly experienced research nurses, blind at baseline, to mothers about their children and separately to children about themselves. Different raters were used for the mother and child within each family to avoid bias from knowing what the other informant had reported.[16] The WASH-U-KSADS was developed from the KSADS[23] by adding the following: (1) an expanded mania section that included items developed specifically to assess prepubertal mania; (2) a section to assess patterns of ultrarapid and ultradian cycling, calibrated as cycles per day that last 4 hours or more per day; (3) items to assess both lifetime and current episodes; (4) items for specific timing of onsets and offsets for all symptoms and syndromes, calibrated by weeks; and (5) sections for ADHD and multiple other *DSM-IV* diagnoses. Skip-outs were minimized to enhance collection of phenomenology data. Establishing time frames for children's ratings was done by using birthdays, holidays, start of school, end of school, and whether present in earlier grades (eg, if the subject is in fourth grade, was it there in third grade?) as anchor points. The WASH-U-KSADS narrative next to each rating is part of this assessment tool (eg, part of the narrative next to a suicidal ideation item read "cut her wrists four times with a kitchen knife and wanted to die to escape her sad feelings"). The data collection guideline is that the narrative must justify the rating with respect to onset, offset, frequency, duration, intensity, and specific examples. Severity ratings for items were as follows: 1, no pathology; 2, doubtful pathology; 3, mild, with no impairment (eg, a child with tics who is not teased or ashamed); and 4 or higher, clinically significant pathology (eg, a child with tics who refuses to go to school). Items needed to be rated 4 or higher to count toward a diagnosis of mania, MDD, or minor depression, and 3 or higher to count toward a diagnosis of hypomania or dysthymia. Examples of the phenomenology of mania criteria in children are published.[24] To score the WASH-U-KSADS items, mother and child responses were combined by using either, in accordance with the methods described by Bird et al.[25] Templates to the WASH-U-KSADS to assess *DSM-IV* substance use disorders (SUDs) in childhood were also given.[26,27]

The Children's Global Assessment Scale (CGAS)[28,29] is a global measure of severity based on psychiatric symptoms and adaptive impairment in family, social, school, and work areas. Ratings were obtained by research nurses who administered the WASH-U-KSADS. On this scale, 0 is the worst, 100 is the best, and 60 or less is definite clinical impairment.[25]

The Psychosocial Schedule for School Age Children–Revised[30] was used to obtain comprehensive measurements of child interaction with parents, siblings, peers, and teachers and of marital relationships, and was administered to mothers about their children and separately to children about themselves by the research nurses who administered the WASH-U-KSADS. The Psychosocial Schedule for School Age Children–Revised has good psychometric properties.[31] Psychosocial impairments reported by either informant (mother or child) were used in the analyses by methods previously detailed.[32]

Socioeconomic status was established by the Hollingshead Four-Factor Index of Social Status.[33] The Duke Pubertal

Status Questionnaire[34] was completed, to obtain Tanner stage, by subjects 10 years or older at baseline.

For symptoms that occurred in more than 1 diagnosis, the investigators did not know a way of discerning which diagnosis to count the item toward. Therefore, symptoms that were concurrent to more than 1 diagnosis were counted toward each, but each diagnosis was only given if there were sufficient symptoms to fit *DSM-IV* criteria. To avoid overdiagnosing ADHD as BP, due to symptoms that occur in both (eg, hyperactivity, distractibility), children only received mania or hypomania diagnoses if elated mood and/or grandiosity was one criterion.

Consensus conferences were held after each rating at all time points to establish *DSM-IV* consensus diagnoses. At these conferences, all assessment instruments, school reports, agency records, and pediatrician records were reviewed. Furthermore, at baseline, videotapes of the WASH-U-KSADS interviews from parent informants and, separately, from child informants were reviewed and discussed.

MIXED, PSYCHOSIS AND CYCLING

Because of the paucity of data on hypomania, minor depression, and dysthymia in children, mixed mania was conservatively defined as mania or hypomania and MDD. This definition was also used by Solomon et al[35] in their article on long-term follow-up of adult unipolar mania. For heuristic purposes, data were also analyzed by using the adult definitions.[20]

Psychosis required a pathologic delusion or hallucination that did not only occur hypnagogically or hypnopompically, and was assessed with the psychosis section of the WASH-U-KSADS.[21] In addition, ratings of 6 on the grandiosity, hopelessness, hypochondriasis, and guilt items signify delusions in these areas.[21]

As recently reported by Tillman and Geller,[36] there is a need to have definitions of cycling and of episodes that are relevant across the age span. Tillman and Geller have proposed that episodes refer to the entire length of illness. In this schema, subjects with 4 episodes per year, who were previously labeled as "rapid cycling," are designated as having 4 episodes per year. Cycling refers to mood changes during an episode. Mood changes that occur every few days are ultrarapid cycling, and mood changes that occur at least once daily are ultradian cycling, using definitions modified from Kramlinger and Post.[37] For example, an 8-year-old boy had mania lasting 2 years during which he had daily cycling. Thus, this child had 1 episode of mania with a duration of 2 years characterized by ultradian cycling (daily cycling for 2 years during 1 episode). Specifically, ultrarapid cycling was defined as 5 to 364 cycles per year, and ultradian (daily) rapid cycling was defined as 365 cycles or more per year.

RESEARCH CLINICIAN TRAINING

Research nurses were trained to interrater reliability and were recalibrated annually.[22] Raters had virtual 100% agreement on diagnostic categories and symptom severity ratings 5 times in a row as both interviewer and observer. In addition, the study site has been a major training site for investigative groups who use the WASH-U-KSADS in other NIMH-funded studies. Training of other investigative teams as of January 9, 2004, included 66 research clinicians from 23 sites, who rated as observers during the follow-up study to obtain interrater reliability with our group.

FOLLOW-UP METHODS

The same instruments were used. At baseline, the WASH-U-KSADS and CGAS instruments were obtained for lifetime and current episodes. At follow-up visits, the WASH-U-KSADS and CGAS instruments were obtained for the period since the prior assessment (eg, at the 6-month follow-up, the time frame was baseline to 6 months). Similar to baseline, the specific dates of onsets and offsets of each symptom and the severity of each symptom for each time frame were obtained.

The number of weeks for every occurrence of each symptom (and the severity at each occurrence) were used to calculate the number of weeks for each diagnosis, for the natural history data analyses.

At this time point, we did not analyze a category equivalent to the "subthreshold but some symptoms" reported in samples of adults[20] because numerous investigators[9,38] report a high prevalence of ADHD in child BP. Based on this, it seemed problematic to designate subjects with interepisode mania symptoms that were similar to those for ADHD (eg, hyperactivity, distractibility) as having subthreshold mania. In addition, the difficulty (for developmental reasons) of differentiating the nonimpairing happiness and expansiveness of normal children from pathologically impairing manic euphoria and grandiosity has been reported.[24]

STUDY INCLUSION AND EXCLUSION CRITERIA

The PEA-BP phenotype was defined as current *DSM-IV* BP-I (manic or mixed phase) for at least 2 weeks, with elation and/or grandiosity as 1 criterion.

Exclusion criteria were as follows: adopted, IQ of less than 70, pervasive developmental disorders, schizophrenia, epilepsy or other major medical or neurological disorder, baseline SUDs or pregnancy, or mania only with medications that may produce manic symptoms (eg, antidepressants).

The rationales for these inclusion and exclusion criteria were as follows: the duration criteria for PEA-BP were similar to conservative durations in multiple nosological schemata and were selected to increase the likelihood of caseness.[7] Baseline (index) episodes of mania were required because this was a phenomenological study, but data were collected on all lifetime episodes. The rationale for including elation and/or grandiosity as one criterion is as previously noted. A younger age of 7 years was chosen because of the credibility of interview assessments, and an older age of 16 years was selected so subjects would still be teenagers at the 2-year follow-up assessment.[13] Scores on the CGAS were selected to ensure definite caseness.[29] At baseline only, SUDs and pregnancy were exclusion criteria to avoid confounding the diagnosis of PEA-BP with mental status effects of substance use or gestational state, but due to the prepubertal age of the subjects, this did not affect enrollment into the study. Subjects continued in the follow-up phase of the study if they developed SUDs or became pregnant after baseline. Adoption was an exclusion criterion due to concurrent family and genetic studies.[39,40]

Characteristics of the PEA-BP sample are provided in **Table 1**.

After complete description of the study was provided to parents and children, written informed consent was obtained from the parents and written assent was obtained from the children.

STATISTICAL ANALYSIS

Analyses included data from the 6-, 12-, 18-, 24-, 36-, and 48-month follow-up points.

Definitions of recovery and relapse during follow-up were adapted from Frank et al.[41] Recovery was defined as 8 consecutive weeks without meeting *DSM-IV* criteria for mania or hypomania. Remission was defined as 2 to 7 weeks without meeting *DSM-IV* criteria for mania or hypomania. Relapse

Table 1. Baseline Characteristics of the 86 Subjects With *DSM-IV* Intake Episode Mania

Characteristic	Value*
Demographics and severity	
Female sex	33 (38.4)
Pubertal	36 (41.9)
Intake age, y	10.8 ± 2.7†
Onset age of intake episode mania, y	7.4 ± 3.5†
Duration of intake episode mania, y	3.5 ± 2.5†
Children's Global Assessment Scale score	43.2 ± 7.8†
DSM-IV mania criteria	
Elated mood	77 (89.5)
Grandiosity	74 (86.0)
Flight of ideas and/or racing thoughts	60 (69.8)
Flight of ideas	49 (57.0)
Racing thoughts	40 (46.5)
Decreased need for sleep	37 (43.0)
Poor judgment	77 (89.5)
Hypersexuality	39 (45.3)
Daredevil acts	57 (66.3)
Silliness, laughing	55 (64.0)
Uninhibited people seeking	55 (64.0)
Irritable mood	84 (97.7)
Accelerated speech	83 (96.5)
Distractibility	80 (93.0)
Increased energy	86 (100)
Other features	
Mixed mania	76 (88.4)
Mania and major depressive disorder	47 (54.7)
Mania and dysthymia	29 (33.7)
Mania and minor depression	0
Total rapid cycling‡	76 (88.4)
Rapid cycling (4 episodes/y)	0
Ultrarapid cycling (cycling every few days during the episode)	9 (10.5)
Ultradian cycling (daily cycling during the episode)	67 (77.9)
No of daily cycles§	3.5 ± 2.0†
Total psychosis	51 (59.3)
Grandiose delusions	44 (51.2)
Suicidality	21 (24.4)
Syndromal comorbid disorders‖	
Attention-deficit/hyperactivity	74 (86.0)
Oppositional defiant	67 (77.9)
Conduct	11 (12.8)
Total anxiety	15 (17.4)
Obsessive-compulsive	6 (7.0)
Generalized anxiety	5 (5.8)
Separation anxiety	4 (4.7)
Social phobia	3 (3.5)
Specific phobia	2 (2.3)
Panic attack	1 (1.2)
Gilles de la Tourette	2 (2.3)
Transient tic	1 (1.2)
Sleep terror	1 (1.2)

*Data are given as number (percentage) of the 86 subjects unless otherwise indicated.

†Data are given as mean ± SD.

‡See "Mixed, Psychosis and Cycling" subsection in the "Methods" section for definitions of rapid cycling categories.

§A cycle was defined as 4 hours per day or more.

‖Subjects met full *DSM-IV* criteria at a severity level of definite impairment. Comorbid disorders not included because no subjects had them were panic, agoraphobia, posttraumatic stress, acute stress, dissociative amnesia, dissociative fugue, dissociative identity, depersonalization, chronic motor or vocal tic, nightmare, sleepwalking, anorexia, bulimia, and substance use.

after recovery was defined as 2 consecutive weeks of meeting *DSM-IV* criteria for mania or hypomania with clinically significant impairment, evidenced by a CGAS score of 60 or less; and partial relapse was similar to full relapse, but lasted only 1 week.

The number of weeks ill with mania, hypomania, major depression, minor depression, dysthymia, or mixed mania was calculated from the severity scores and from the onset and offset dates for each symptom on the WASH-U-KSADS. Diagnostic categories were constituted from a sufficient number of symptoms to fit *DSM-IV* diagnoses.

To examine baseline differences between those subjects who did not experience a recovery from mania during 4 years of follow-up and those subjects who recovered within the first 6 months and remained mania free during follow-up, χ^2 and *t* tests of baseline characteristic differences between the 2 groups were performed.

For predictor analyses, a priori predictors were selected based on the literature.[1-7,20,42-45] These included age, sex, puberty status, CGAS score, psychosis, mixed status (mania plus MDD), rapid cycling, and maternal warmth, which is akin to expressed emotion.[42-44] Details on the construction of categories for maternal warmth and other categories from the Psychosocial Schedule for School Age Children–Revised have been reported.[13] Exploratory analyses were conducted on the following variables: age of onset of first episode, duration of baseline episode, all categories of mixed mania, ascertainment site (pediatric vs psychiatric), comorbid diagnoses (Table 1), maternal tension/hostility, paternal warmth and tension/hostility, and living situation.

The cumulative probability of recovery and relapse was estimated using the Kaplan-Meier (K-M) method.[46] During follow-up, durations of BP diagnoses were calculated as the number of weeks between onset and offset of full *DSM-IV* syndromal criteria. Recovery and relapse were modeled using Cox proportional hazards modeling.[47] Covariates significant in univariate analyses were selected for K-M analyses, controlling for sex, puberty, and mixed mania.

A mixed model using proportion of weeks with BP diagnoses during the 4 years as the outcome measure was constructed with a priori predictors. Covariates significant in the model were examined post hoc, controlling for sex, puberty, and mixed mania. Following the methods of Wolfinger[48] and Littell et al,[49] various underlying covariance structures were tested to select the model with the best fit, which was the unstructured covariance model.

Bonferroni correction was used to limit the possibility of type I errors, resulting in a significance level of $P<.006$ to assess significance for all models. SAS statistical software V8.2 was used for all statistical analyses.[49] Data are given as mean ± SD unless otherwise indicated.

RESULTS

Of the baseline 93 subjects, 86 were interviewed at all follow-up points. Thus, the retention after 4 years of follow-up was 92.5%. The 7 subjects who discontinued the study during the 4 years of follow-up did not differ significantly from those who continued on baseline age, sex, puberty status, age of onset of index episode, duration of index episode, or CGAS score (data not shown). At baseline, 100% of both parent and child informants were separately interviewed. During the 516 follow-up interviews, only 2.3% (n=12) were conducted on a single informant. The socioeconomic status was 4.0±0.9, which is the second highest of 5 classes.[33]

The baseline intake episode of mania was also the first episode of mania for 70 (81.4%) of the 86 subjects. Age of onset for the entire sample (N=86) was 6.9±3.5 years.

PROSPECTIVE MANIA OR HYPOMANIA EPISODE DURATION

Prospective episode duration of manic diagnoses, using onset of mania as baseline date, was 79.2±66.7 consecutive weeks.

RECOVERY AND RELAPSE

The time to recovery was 60.2±47.5 weeks (**Figure 1**). One subject was a remitter. Data analyses with or without this subject were similar, so this subject was included in the analyses. The K-M estimate of the rate of recovery was 87.2% (95% confidence interval, 80.2%-94.3%). The time to relapse after recovery was 40.4±33.4 weeks (Figure 1). The K-M estimate of the rate of relapse was 70.2% (95% confidence interval, 57.4%-83.0%). Only 1 subject experienced a partial relapse, so a separate analysis was not conducted for partial relapse.

There were no significant differences in baseline characteristics between those subjects who did not experience a recovery from mania during 4 years of follow-up (n=11) and those subjects who recovered within the first 6 months and remained free of mania or hypomania during follow-up (n=7) (data not shown). At baseline, 10 subjects had hypomania, but 8 of these developed mania during follow-up and were, therefore, included in the analyses. Data analyses with or without these 2 subjects with hypomania were similar, so these 2 subjects were also included in the analyses.

NUMBER AND PERCENTAGE OF WEEKS WITH MOOD DISORDER DIAGNOSES

These data are presented in **Table 2**. Any BP diagnosis occurred during 67.1%±28.5% of total weeks, during the 209.4±3.3 weeks of follow-up. Subjects spent 56.9%±28.8% of total weeks with mania or hypomania (unipolar or mixed), and 38.7%±28.8% of these weeks were with mania. Major or minor depression and dysthymia (unipolar or mixed) occurred during 47.1%±30.4% of total weeks.

POLARITY SWITCHES

Polarity switches from mania or hypomania to MDD, dysthymia, or minor depression occurred 1.1±0.7 times per year.

PREDICTORS OF RECOVERY AND RELAPSE

The overall mixed model for proportion of weeks ill with mania or hypomania was significant ($\chi^2_{77}=1554.8$, $P<.0001$), with a significant interaction of time × baseline psychosis ($F_{11,77}=2.1$, $P=.028$), indicating that subjects with baseline psychosis spent more weeks ill with mania or hypomania (**Figure 2**). A post hoc analysis indicated that a quadratic model best fit the time × baseline psychosis effect ($F_{1,80}=12.2$, $P=.0008$).

Estimates using K-M analyses showed that low maternal warmth predicted earlier relapse to mania or hypomania (**Figure 3**). No other covariates predicted the outcome of BP diagnoses.

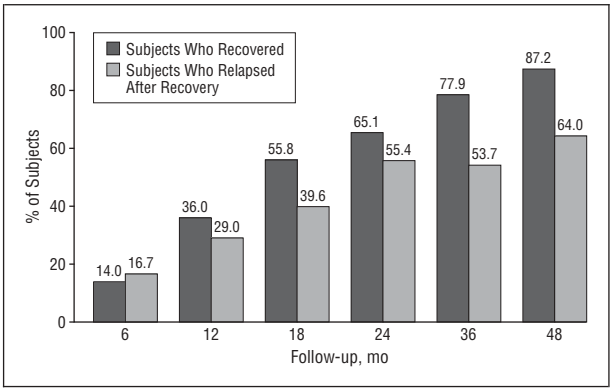

Figure 1. The proportion of subjects who recovered and relapsed after recovery among the 86 subjects with a prepubertal and early adolescent bipolar disorder phenotype during 4 years of prospective follow-up.

COMMENT

Findings from the 4-year prospective follow-up of PEA-BP validate the existence of child mania. Moreover, these data address the controversy over whether PEA-BP can be differentiated from ADHD by demonstrating that these subjects with PEA-BP had persistent mania and did not become diagnosed with only ADHD during follow-up. Whether ADHD in children with pediatric BP is a separate diathesis, a reflection of mania plus normal childhood developmental behaviors (eg, children are naturally more active than adults), shared genetic vulnerabilities, and/or the result of overlapping criteria for both diagnoses is not yet known.[50,51]

Validation of long durations of episodes of child mania or mixed mania was provided by the long time to recovery from mania or mixed mania. Because subjects were obtained by consecutive new case ascertainment, it is likely that this picture is representative of BP children who present clinically. This study does not address, however, the question of whether BP children with shorter episodes are not brought to treatment (ie, are there children with briefer episodes tolerated by families for a few weeks until the episode spontaneously resolves?).

Chronicity of PEA-BP was validated by the percentage of weeks during the 4 years that subjects spent in BP episodes. The chronicity and severity of the clinical picture in child BP-I warrant comment. Subjects with PEA-BP presented with long-episode durations, chronicity, and severity (ultradian rapid cycling, psychosis, and mixed mania). These chronic, severe symptoms have been reported in about 20% of adults,[20,52] but were seen in most PEA-BP subjects (Table 1). In addition to longitudinal validation of PEA-BP, data from a parallel ongoing study[53] of psychopathology in first-degree relatives of PEA-BP probands and 2 control groups (subjects with ADHD and normal controls) evidence high familial aggregation. The clinical picture of marked severity, high familial aggregation, and early onset fits the paradigm reported by Childs and Scriver[54] for many medical illnesses. Future studies of genetic and environmental factors will be needed

Table 2. Total Weeks With Bipolar Disorder Diagnoses During the Prospective 4-Year Follow-up of 86 Subjects With a Prepubertal and Early Adolescent Bipolar Disorder Phenotype

Diagnosis	Time With A Mood Disorder During Follow-up*	
	% of Weeks	No. of Weeks
Total mania or hypomania (unipolar and mixed)	56.9 ± 28.8	119.1 ± 60.2
Mania (unipolar and mixed)	38.7 ± 28.8	81.0 ± 60.3
Hypomania (unipolar and mixed)	18.3 ± 17.9	38.1 ± 37.4
Unipolar mania	9.4 ± 13.2	19.7 ± 27.6
Unipolar hypomania	10.6 ± 14.0	22.1 ± 29.2
Total depression (unipolar and mixed)	47.1 ± 30.4	98.7 ± 63.9
MDD (unipolar and mixed)	32.3 ± 24.4	67.7 ± 51.2
Dysthymia (unipolar and mixed)	14.8 ± 19.5	31.0 ± 40.9
Minor depression (unipolar and mixed)	0.0 ± 0.2	0.0 ± 0.4
Unipolar MDD	5.0 ± 10.1	10.5 ± 21.3
Unipolar dysthymia	5.2 ± 9.9	10.9 ± 20.8
Unipolar minor depression	0.0 ± 0.2	0.0 ± 0.4
Total mixed	36.8 ± 27.9	77.2 ± 58.5
Mania and MDD	23.8 ± 21.1	50.0 ± 44.2
Hypomania and MDD	3.5 ± 7.9	7.2 ± 16.5
Mania and dysthymia	5.4 ± 11.6	11.3 ± 24.3
Cyclothymia	4.2 ± 10.1	8.8 ± 21.1
Any bipolar diagnosis	67.1 ± 28.5	140.6 ± 59.7

Abbreviation: MDD, major depressive disorder.
*Data are given as mean ± SD. The total follow-up was 209.4 ± 3.3 weeks.

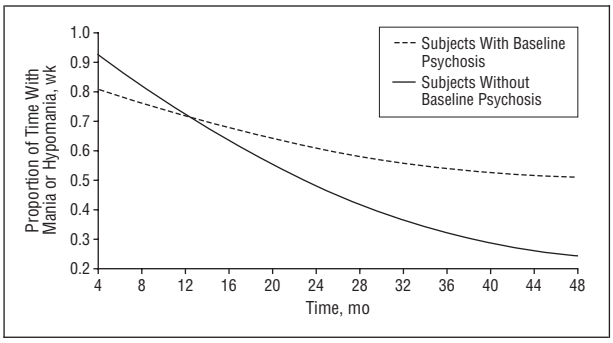

Figure 2. Proportion of weeks ill with mania or hypomania during 4 years of prospective follow-up for the 86 subjects with prepubertal and early adolescent bipolar disorder who had intake episode mania by baseline psychosis. In a mixed model, controlling for sex, pubertal status, and mixed mania, the proportion of weeks ill was significantly higher in the 51 subjects with baseline psychosis than in the 35 subjects without baseline psychosis ($F_{1,80}$=12.2, P=.0008).

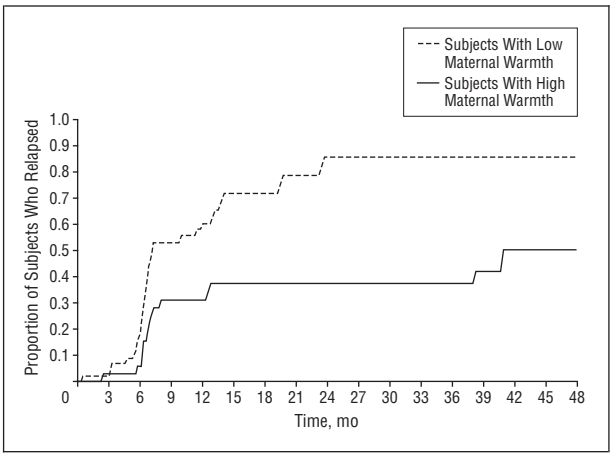

Figure 3. Of the 86 subjects with prepubertal and early adolescent bipolar disorder who had intake episode mania, 75 relapsed after recovery from mania. The result of Cox proportional hazards modeling for maternal warmth, controlling for sex, age, and mixed mania, was significant (χ^2_1=13.6, P=.0002). The hazard ratio was 3.7 (95% confidence interval [CI], 1.8-7.4). The Kaplan-Meier estimate of relapse was 50.3% (95% CI, 28.9%-71.6%) for the 32 subjects with high maternal warmth and 85.9% (95% CI, 73.9%-98.0%) for the 43 subjects with low maternal warmth.

to elucidate the mechanisms of this association of early onset, loaded family psychopathology, and malignant course.

Low maternal warmth as a predictor of relapse, also found at the 2-year follow-up,[13] is consistent with findings in samples of adults with BP that show the predictive effect of impaired expressed emotion, a concept akin to maternal warmth.[42-44] This robust finding can be useful for planning intervention and prevention studies of children with mania and perhaps for those who are high-risk offspring.[55]

Continuity between child- and adult-onset BP is supported by the similarity of mania symptom distribution between PEA-BP and adult-onset cases,[10,14,52] the occurrence of child- and adult-onset BP within the same families,[53] and the occurrence of maternal warmth and psychosis as predictors of outcome of PEA-BP and adult-onset BP.[13,20,42,45]

The long time to recovery and the high number of weeks ill during follow-up emphasize the need for early recognition and for the development of prevention and intervention strategies.

COMPARISON TO NATURAL HISTORY STUDIES OF ADULTS WITH BP

Tohen et al[45] reported recovery rates of 85.5%, 91.6%, and 97.5% at 6 months, 1 year, and 2 years, respec-

tively, in adult subjects with first-episode mania. By comparison, the recovery rates at 6 months, 1 year, and 2 years for the PEA-BP sample were 14.0%, 36.0%, and 65.1% (Figure 1).[11-13] These comparisons support the chronicity of child mania, even in light of methodological differences in the samples (eg, the subjects in the study by Tohen et al were inpatients).

Recently, Judd et al[20] reported 20-year follow-up results of subjects with baseline mood disorders, most of whom had intake mania. Data were not broken down by 4 years, but during the 2 decades, depressive episodes predominated in the adult sample. In contrast to these data from adult mania, there was a higher percentage of weeks with mania or hypomania in the child PEA-BP sample. Speculations on the reasons for this difference include developmental trajectories (ie, mania or hypomania may predominate during the prepubertal and early adolescent age range, and depressive states may become more prevalent with age). Another possibility is that child and adult BP are discontinuous, but this is unlikely because child- and adult-onset BP occur within the same families.[53] A third possibility is that the difference may be methodological, due to differences between the Judd et al study and the PEA-BP sample on credentials of the raters and on use of multiple interviewed informants. The Judd et al study used trained raters compared with the highly experienced research nurses used in the PEA-BP study, which raises the possibility that professionally credentialed clinically experienced raters may be more likely to elicit and/or recognize manic symptoms. In this regard, some epidemiological studies[56] have reported that lay rater–administered interviews identify chronic severe mania, but not less severe cases. With respect to multiple informants, in the Judd et al study, subjects were the only interviewed informants compared with 2 interviewed informants (separate research interviews of mothers about their children and of children about themselves) in the PEA-BP investigation. Child mania symptoms are more likely to be identified if multiple informants are used, as reported for the PEA-BP sample and as reported in studies[16,57-64] of child depression. It is possible that dual informants for adult BP subjects may have elicited more symptoms of mania.

Lack of mixed/cycling as a predictor of child outcome is different from findings in adult BP,[3,20,45] likely due to the higher prevalence of cycling in the PEA-BP sample.

The fewer polarity switches per year in the PEA-BP study compared with the Judd et al[20] study are consistent with the long duration of mania or hypomania episodes in the child BP sample.

LIMITATIONS

During the time this sample was obtained through consecutive new case ascertainment (1995-1998), there was no facility or private practice in St Louis available to obtain consecutive subjects from lower socioeconomic status backgrounds. Therefore, these findings may not generalize to lower socioeconomic status settings.

In addition, due to the paucity of inpatient facilities in St Louis during this study, there were no inpatients in the PEA-BP sample. This is dissimilar to studies[45,65] of BP adults, in which subjects with mania are often hospitalized. By contrast, many severely ill prepubertal and early adolescent children, including those with psychosis, are not inpatients. This is evidenced by the entirely outpatient status of the NIMH-funded PEA-BP and Treatment of Early Age Mania samples, in which pathologic psychosis occurred in 59.3% (Table 1) and 83.3%, respectively.

Since this study was the first phenomenology and longitudinal study of PEA-BP, to our knowledge, we elected to use a conservative phenotype that required *DSM-IV* BP (manic or mixed phase) with elation and/or grandiosity as one inclusion criterion to ensure differentiation from ADHD.[66] Thus, these findings may not generalize to other phenotypes.[7]

FUTURE STUDIES

Several of the predictors of outcome in studies[1,20,67,68] of adults with BP were not examined at the 4-year point because they were not present at baseline (SUD and panic disorder). This is likely due to the young age of the subjects, because panic disorder and SUD usually begin at a later age.[67,68] Future follow-up of the PEA-BP sample will include SUDs and panic disorders as covariates, since these conditions are likely to occur as the PEA-BP sample ages.[68] Separate publications will report the predictive value of community physician–administered treatments. The direct interview family study of these PEA-BP probands and 2 control groups is in the data collection phase and, thus, data are not available for use as predictors of outcome or to determine the relationship of maternal warmth to maternal psychopathology. Later data analyses will examine these issues. More important, later follow-up of the PEA-BP sample will provide data on whether the predominantly manic or hypomanic, long-episode duration, severe, ultradian cycling picture present during childhood continues into later adolescence and adulthood.

Submitted for publication June 27, 2003; final revision received December 2, 2003; accepted December 16, 2003.

This study was supported by grant R01 MH-53063 from the NIMH, Rockville, Md.

We thank Betsy Zimerman, BSN, MA, and Marlene Williams, RN, for contributing to administration and data collection for this study; and Jeanne Frazier, BSN, and Linda Beringer, RN, for contributing to data collection for this study.

Corresponding author: Barbara Geller, MD, Department of Psychiatry, Washington University in St Louis, 660 S Euclid Ave, St Louis, MO 63110 (e-mail: gellerb@medicine.wustl.edu).

REFERENCES

1. Tohen M, Waternaux CM, Tsuang MT, Hunt AT. Four-year follow-up of twenty-four first-episode manic patients. *J Affect Disord.* 1990;19:79-86.
2. Werry JS, McClellan JM. Predicting outcome in child and adolescent (early onset) schizophrenia and bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 1992;31:147-150.
3. Keller MB, Lavori PW, Coryell W, Endicott J, Mueller TI. Bipolar I: a five-year prospective follow-up. *J Nerv Ment Dis.* 1993;181:238-245.

4. Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: a longitudinal follow-up study. *Am J Psychiatry.* 1995;152:379-384.
5. Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry.* 1995;34:724-731.
6. Srinath S, Janardhan Reddy YC, Girimaji SR, Seshadri SP, Subbakrishna DK. A prospective study of bipolar disorder in children and adolescents from India. *Acta Psychiatr Scand.* 1998;98:437-442.
7. National Institute of Mental Health research roundtable on prepubertal bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2001;40:871-878.
8. Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 1997;36:1168-1176.
9. Craney JL, Geller B. A prepubertal and early adolescent bipolar disorder-I phenotype: review of phenomenology and longitudinal course. *Bipolar Disord.* 2003;5:243-256.
10. Geller B, Zimerman B, Williams M, DelBello MP, Bolhofner K, Craney JL, Frazier J, Beringer L, Nickelsburg MJ. *DSM-IV* mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. *J Child Adolesc Psychopharmacol.* 2002;12:11-25.
11. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, Soutullo CA. Six-month stability and outcome of prepubertal and early adolescent bipolar disorder phenotype. *J Child Adolesc Psychopharmacol.* 2000;10:165-173.
12. Geller B, Craney JL, Bolhofner K, DelBello MP, Williams M, Zimerman B. One-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry.* 2001;158:303-305.
13. Geller B, Craney JL, Bolhofner K, Nickelsburg MJ, Williams M, Zimerman B. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry.* 2002;159:927-933.
14. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, Soutullo CA. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2000;10:157-164.
15. Biederman J, Faraone SV, Chu MP, Wozniak J. Further evidence of a bidirectional overlap between juvenile mania and conduct disorder in children. *J Am Acad Child Adolesc Psychiatry.* 1999;38:468-476.
16. Tillman R, Geller B, Craney JL, Bolhofner K, Williams M, Zimerman B. Relationship of parent and child informants to prevalence of mania symptoms in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry.* In press.
17. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A, Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Davies M, Robinson J, McMahon D. Risperidone in children with autism and serious behavioral problems. *N Engl J Med.* 2002;347:314-321.
18. Aman MG, De Smedt G, Derivan A, Lyons B, Findling RL. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry.* 2002;159:1337-1346.
19. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry.* 2003;60:709-717.
20. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry.* 2002;59:530-537.
21. Geller B, Williams M, Zimerman B, Frazier J. *Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS).* St Louis, Mo: Washington University; 1996.
22. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, Soutullo C. Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. *J Am Acad Child Adolesc Psychiatry.* 2001;40:450-455.
23. Puig-Antich J, Ryan N. *The Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kiddie-SADS)–1986.* Pittsburgh, Pa: Western Psychiatric Institute & Clinic; 1986.
24. Geller B, Zimerman B, Williams M, DelBello MP, Frazier J, Beringer L. Phenomenology of prepubertal and early adolescent bipolar disorder: examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. *J Child Adolesc Psychopharmacol.* 2002;12:3-9.
25. Bird HR, Gould MS, Staghezza B. Aggregating data from multiple informants in child psychiatry epidemiological research. *J Am Acad Child Adolesc Psychiatry.* 1992;31:78-85.
26. Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, Heath J. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry.* 1998;37:171-178.
27. Geller B, Cooper TB, Zimerman B, Frazier J, Williams M, Heath J, Warner K. Lithium for prepubertal depressed children with family history predictors of future bipolarity: a double-blind, placebo-controlled study. *J Affect Disord.* 1998;51:165-175.
28. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S. A Children's Global Assessment Scale (CGAS). *Arch Gen Psychiatry.* 1983;40:1228-1231.
29. Bird HR, Canino G, Rubio-Stipec M, Ribera JC. Further measures of the psychometric properties of the Children's Global Assessment Scale. *Arch Gen Psychiatry.* 1987;44:821-824.
30. Puig-Antich J, Lukens E, Brent D. *Psychosocial Schedule for School Age Children–Revised in 1986 and 1987.* Pittsburgh, Pa: Western Psychiatric Institute & Clinic; 1986.
31. Lukens E, Puig-Antich J, Behn J, Goetz R, Tabrizi M, Davies M. Reliability of the Psychosocial Schedule for School Age Children. *J Am Acad Child Psychiatry.* 1983;22:29-39.
32. Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry.* 2000;39:1543-1548.
33. Hollingshead AB. *Four-Factor Index of Social Status.* New Haven, Conn: Department of Sociology, Yale University; 1976.
34. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. *Pediatrics.* 1980;66:918-920.
35. Solomon DA, Leon AC, Endicott J, Coryell WH, Mueller TI, Posternak MA, Keller MB. Unipolar mania over the course of a 20-year follow-up study. *Am J Psychiatry.* 2003;160:2049-2051.
36. Tillman R, Geller B. Definitions of rapid, ultrarapid, and ultradian cycling and of episode duration in pediatric and adult bipolar disorders: a proposal to distinguish episodes from cycles. *J Child Adolesc Psychopharmacol.* 2003;13:267-271.
37. Kramlinger KG, Post RM. Ultra-rapid and ultradian cycling in bipolar affective illness. *Br J Psychiatry.* 1996;168:314-323.
38. Fristad MA, Weller EB, Weller RA. The Mania Rating Scale: can it be used in children? a preliminary report. *J Am Acad Child Adolesc Psychiatry.* 1992;31:252-257.
39. Geller B, Cook EH. Serotonin transporter gene (HTTLPR) is not in linkage disequilibrium with prepubertal and early adolescent bipolarity. *Biol Psychiatry.* 1999;45:1230-1233.
40. Geller B, Cook EH. Ultradian rapid cycling in prepubertal and early adolescent bipolarity is not in transmission disequilibrium with Val/Met COMT alleles. *Biol Psychiatry.* 2000;47:605-609.
41. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry.* 1991;48:851-855.
42. Miklowitz DJ, Goldstein MJ, Nuechterlein KH, Snyder KS, Mintz J. Family factors and the course of bipolar affective disorder. *Arch Gen Psychiatry.* 1988;45:225-231.
43. Honig A, Hofman A, Hilwig M, Noorthoorn E, Ponds R. Psychoeducation and expressed emotion in bipolar disorder: preliminary findings. *Psychiatry Res.* 1995;56:299-301.
44. Ramana R, Bebbington P. Social influences on bipolar affective disorders. *Soc Psychiatry Psychiatr Epidemiol.* 1995;30:152-160.
45. Tohen M, Zarate CA Jr, Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. *Am J Psychiatry.* 2003;160:2099-2107.
46. Cox DR, Oakes D. *Analysis of Survival Data.* Cambridge, Mass: University Printing House; 1984.
47. Cox DR. Regression models and life tables. *J R Stat Soc.* 1972;B34:187-220.
48. Wolfinger RD. An example of using mixed models and PROC MIXED for longitudinal data. *J Biopharm Stat.* 1997;7:481-500.
49. Littell R, Milliken G, Stroup W, Wolfinger R. *SAS System for Mixed Models.* Cary, NC: SAS Institute Inc; 1996:92-105.
50. Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry.* 1997;36:1378-1387.
51. Geller B. Discussion of "attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype?" *J Am Acad Child Adolesc Psychiatry.* 1997;36:1387-1388.
52. Goodwin FK, Jamison KR, eds. *Manic-Depressive Illness.* New York, NY: Oxford University Press Inc; 1990.

53. Geller B. Longitudinal and family study validators of a prepubertal and early adolescent bipolar disorder phenotype. Paper presented at: 41st Annual Meeting of the American College of Neuropsychopharmacology; December 9, 2002; San Juan, Puerto Rico.
54. Childs B, Scriver CR. Age at onset and causes of disease. *Perspect Biol Med.* 1986;29:437-460.
55. DelBello MP, Geller B. Review of studies of child and adolescent offspring of bipolar parents. *Bipolar Disord.* 2001;3:325-334.
56. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of *DSM-III-R* bipolar I disorder in a general population survey. *Psychol Med.* 1997; 27:1079-1089.
57. Herjanic B, Reich W. Development of a structured psychiatric interview for children: agreement between child and parent on individual symptoms. *J Abnorm Child Psychol.* 1982;10:307-324.
58. Angold A, Weissman MM, John K, Merikangas KR, Prusoff BA, Wickramaratne P, Gammon GD, Warner V. Parent and child reports of depressive symptoms in children at low and high risk of depression. *J Child Psychol Psychiatry.* 1987; 28:901-915.
59. Mokros HB, Poznanski E, Grossman JA, Freeman LN. A comparison of child and parent ratings of depression for normal and clinically referred children. *J Child Psychol Psychiatry.* 1987;28:613-624.
60. Weissman MM, Wickramaratne P, Warner V, John K, Prusoff BA, Merikangas KR, Gammon GD. Assessing psychiatric disorders in children: discrepancies between mothers' and children's reports. *Arch Gen Psychiatry.* 1987;44:747-753.
61. Ivens C, Rehm LP. Assessment of childhood depression: correspondence between reports by child, mother, and father. *J Am Acad Child Adolesc Psychiatry.* 1988;27:738-741.
62. Nguyen N, Whittlesey S, Scimeca K, DiGiacomo D, Bui B, Parsons O, Scarborough A, Paddock D. Parent-child agreement in prepubertal depression: findings with a modified assessment method. *J Am Acad Child Adolesc Psychiatry.* 1994; 33:1275-1283.
63. Jensen PS, Rubio-Stipec M, Canino G, Bird HR, Dulcan MK, Schwab-Stone ME, Lahey BB. Parent and child contribution to diagnosis of mental disorder: are both informants always necessary? *J Am Acad Child Adolesc Psychiatry.* 1999;38: 1569-1579.
64. Grills AE, Ollendick TH. Multiple informant agreement and the anxiety disorders interview schedule for parents and children. *J Am Acad Child Adolesc Psychiatry.* 2003;42:30-40.
65. Coryell W, Turvey C, Endicott J, Leon AC, Mueller T, Solomon D, Keller M. Bipolar I affective disorder: predictors of outcome after 15 years. *J Affect Disord.* 1998;50:109-116.
66. Geller B, Craney JL, Bolhofner K, DelBello MP, Axelson D, Luby J, Williams M, Zimerman B, Nickelsburg MJ, Frazier J, Beringer L. Phenomenology and longitudinal course of children with a prepubertal and early adolescent bipolar disorder phenotype. In: Geller B, DelBello MP, eds. *Bipolar Disorder in Childhood and Early Adolescence.* New York, NY: Guilford Press; 2003:25-50.
67. Frank E, Cyranowski JM, Rucci P, Shear MK, Fagiolini A, Thase ME, Cassano GB, Grochocinski VJ, Kostelnik B, Kupfer DJ. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. *Arch Gen Psychiatry.* 2002;59:905-911.
68. Tillman R, Geller B, Bolhofner K, Craney JL, Williams M, Zimerman B. Ages of onset and rates of syndromal and subsyndromal comorbid *DSM-IV* diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry.* 2003;42:1486-1493.