

Child Bipolar I Disorder

Prospective Continuity With Adult Bipolar I Disorder; Characteristics of Second and Third Episodes; Predictors of 8-Year Outcome

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Context: Child bipolar I disorder (BP-I) is a contentious diagnosis.

Objective: To investigate continuity of child and adult BP-I and characteristics of later episodes.

Design: Inception cohort longitudinal study. Prospective, blinded, controlled, consecutive new case ascertainment.

Setting: University medical school research unit.

Subjects: There were 115 children, enrolled from 1995 through 1998, aged 11.1 (SD, 2.6) years with first episode DSM-IV BP-I, mixed or manic phase, with 1 or both cardinal symptoms (elation or grandiosity) and score of 60 or less on the Children's Global Assessment Scale (CGAS). All DSM-IV severity and duration criteria were fulfilled. Separate interviews were conducted of parents about their children and of children about themselves.

Main Outcome Measures: Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS); Psychosocial Schedule for School Age Children-Revised; CGAS.

Results: Retention was 93.9% (n=108) for completing assessments at every one of the 9 follow-up visits. Subjects spent 60.2% of weeks with any mood episodes and 39.6% of weeks with mania episodes, during 8-year follow-up. During follow-up, 87.8% recovered from mania, but 73.3% relapsed to mania. Even accounting for family psychopathology, low maternal warmth predicted relapse to mania, and more weeks ill with manic episodes was predicted by low maternal warmth and younger baseline age. Largely similar to first episodes, second and third episodes of mania were characterized by psychosis, daily (ultradian) cycling, and long duration (55.2 and 40.0 weeks, respectively), but significantly shorter than first episodes. At 8-year follow-up, 54 subjects were 18.0 years or older. Among subjects 18.0 years or older, 44.4% had manic episodes and 35.2% had substance use disorders.

Conclusions: In grown-up subjects with child BP-I, the 44.4% frequency of manic episodes was 13 to 44 times higher than population prevalences, strongly supporting continuity. The rate of substance use disorders in grown-up child BP-I was similar to that in adult BP-I.

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GIVEN RECENT DATA ON THE enormous increase in clinical visit diagnoses of pediatric bipolar I disorder (BP-I),¹ and given escalating media interest in this area,² there is a cogent need to further establish credibility of DSM-IV mania diagnoses in children. Skepticism about the existence of child BP-I continues, even in the face of data-based work that establishes validity by

long episode duration and daily cycling were reported from studies that used various assessment methods (eg, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological Version [KSADS-E], KSADS-Present and Lifetime Version [KSADS-P/L], and Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia [WASH-U-KSADS]), providing evidence that these characteristics were not method bound.^{4,5,7,8,15-17} This picture is opposed to what has been described as "classic" circumscribed episodes in adults with BP-I. However, both older studies and more recent work suggest that this classic picture may not be the modal presentation in adults with BP-I (eg, see Judd et al¹⁸).

Against this background, key questions remain unanswered: (1) What predicts 8-year outcome? (2) What will be the characteristics of postbaseline episodes?

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Robins and Guze³ criteria.⁴⁻¹¹ One source of the contentiousness has been that child BP-I across most,^{4,5,7,12,13} but not all,¹⁴ investigative groups presents with a chronic picture of long current episode duration (mean, 309.8 days to 4.8 years) and daily cycles (ultradian cycling) during episodes.^{4,5,8,15-17} Both

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(3) Will subjects with child BP-I continue to have BP-I as adults?

To address these questions, this report is on data from a prospective, controlled, blindly rated ongoing National Institute of Mental Health (NIMH)-funded study, "Phenomenology and Course of Pediatric Bipolar Disorders," which began in 1995. As the pioneering study in the field, to address the controversy existing in the mid 1990s, the phenotype was defined as *DSM-IV* BP-I, manic or mixed phase, with at least 1 cardinal symptom (elation and/or grandiosity) as a criterion. This cardinal symptom approach (cardinal symptoms are those limited to a specific *DSM-IV* syndrome) avoided diagnosing mania only by symptoms that overlapped with those of attention-deficit/hyperactivity disorder (ADHD) (eg, distractibility or hyperactivity), the main differential diagnostic problem for child BP-I.^{9,19} The cardinal symptom criterion mimicked the approach to major depressive disorder (MDD) in *DSM-IV*, which requires the cardinal symptom of either depressed mood or anhedonia. Furthermore, a cardinal symptom approach addressed the issue of dimensional irritability/aggression, which is an almost ubiquitous dimension across child psychiatry diagnoses,²⁰⁻²⁴ by not allowing irritable mood as the mood state unless there were also grandiose behaviors. High rates of these cardinal symptoms have been found in most,^{15,16,19} but not all,⁵ studies from other investigative groups.

One question in communicating the adult outcome was when to report the findings. Given that this is the first longitudinal, prospective, controlled, blindly rated study of child BP-I to have adult findings, and given the relevance of predictive validity to the field, it seemed most appropriate to report when approximately half of the sample had reached adult age (≥ 18.0 years), at the 8-year follow-up. Age 18 years was selected because it is the time when many functions associated with adulthood begin in the United States, including serving in the armed forces, voting, and signing one's own consent forms for research.

Family psychopathology was not yet available at the 4-year follow-up. At the 8-year follow-up in this report, parental psychopathology was added to the statistical model because these data are now published.⁸

To our knowledge, this is the first report of adult outcome, of characteristics of second and third episodes, and of predictors of 8-year outcome in a prospective, blindly rated, controlled, consecutively ascertained sample of child BP-I.

METHODS

ASCERTAINMENT

Enrollment in the ongoing NIMH-funded "Phenomenology and Course of Pediatric Bipolar Disorders" study occurred from September 25, 1995, through December 15, 1998. Subjects with child BP-I were obtained from designated outpatient child psychiatric and pediatric sites by consecutive new case ascertainment.⁹ Facilities that agreed to participate in the consecutive new case ascertainment were largely only available to families with health insurance.⁹

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria were 7 to 16 years old, males and females, good physical health, and a diagnosis of current *DSM-IV* BP-I, manic or mixed phase, for 2 weeks or longer with at least 1 cardinal symptom of mania (ie, elation and/or grandiosity). A Children's Global Assessment Scale (CGAS) score of 60 or less was required to establish clinically significant impairment.^{25,26}

Exclusion criteria were IQ less than 70, adopted status, pervasive developmental disorders, schizophrenia, epilepsy or other major medical or neurologic disorder, baseline substance dependency or pregnancy, and manic symptoms only while taking antidepressant, stimulant, or other potential mania-inducing medications. Subjects who developed substance use disorders (SUDs) or became pregnant during the study were continued on the protocol. There were no exclusions for family psychopathology.

Rationales for these criteria were as follows. To increase the likelihood of caseness, the duration criterion was similar to conservative duration in multiple nosologic schemas and was longer than the duration criterion of *DSM-IV*. Data were collected on all lifetime mood episodes (eg, MDD and dysthymia), but current baseline (index) episodes of mania, or mixed mania, were required because this was a phenomenology study of child mania. The introduction notes the rationale for including elation and/or grandiosity as one criterion. For credibility of interview assessments, a lower age of 7.0 years was selected, and an upper age of 16.11 years was chosen so that subjects would still be teenagers at the 2-year follow-up assessment.²⁷ Scores on the CGAS were chosen to ensure definite caseness. At baseline only, presence of SUDs and/or pregnancy was an exclusion criterion to avoid confounding the diagnosis of child BP-I with mental status effects of substance use or gestational state. Because of the prepubertal age of the subjects, however, this did not alter entrance 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 because of concurrent family and molecular genetic studies.^{8,10,11}

NATURAL HISTORY

During this natural history study, treatments were provided by participants' own clinicians in the community and not in any way by the research nurses who conducted the assessments.

ASSESSMENT

The WASH-U-KSADS^{28,29} is a semistructured interview with excellent reliability for mania symptoms, mood diagnoses, daily cycling, and time frames ($\kappa=0.82-1.00$). It was administered by blinded, highly experienced research nurses, 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.³⁰ Before the beginning of the protocol, the research nurses were trained for interrater reliability and their performance was recalibrated annually.^{29,31}

The WASH-U-KSADS was developed from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kiddie-SADS, or KSADS)³² by adding (1) an expanded mania section that included items developed specifically to assess prepubertal mania³³; (2) a section to assess patterns of daily cycles (ultradian cycling)¹⁷; (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. Characteristics of various versions of the original 1978 KSADS (KSADS-

Present State Version [KSADS-P], KSADS-E, Revised KSADS-Present Episode Version [KSADS-R], KSADS-P/L, WASH-U-KSADS) have been detailed in the NIMH Research Roundtable on Prepubertal Bipolar Disorder and elsewhere.^{29,34} To optimize collection of phenomenology data, there are no skip-outs on the WASH-U-KSADS except for impossible situations, eg, circadian quality of mood is not asked if no abnormal mood state was elicited. Time frames were established for children's ratings by using birthdays, holidays, start of school, end of school, and whether present in earlier grades (eg, if subject is in fourth grade, asking whether it was there in third grade) as anchor points. Severity ratings for items were as follows: 1, no pathology; 2, doubtful pathology; 3, mild with no impairment (eg, child with tics who is not teased or ashamed), and 4 or higher, clinically significant pathology (eg, child with tics who refuses to go to school). To fit a rating of 4 or higher, the symptom must be sufficiently frequent (daily or most days for the specified duration in the study), of sufficient duration (≥ 4 hours a day), and of sufficient intensity (must be impairing), and examples must be convincing. Items needed to be rated 4 or higher to count toward a diagnosis of mania or MDD and 3 or higher to count toward hypomania or dysthymia. Examples of the developmental manifestations of mania phenomenology in children have been published.³³ Mother and child responses were combined by using the most severe, in accordance with the methods described by Bird et al.³⁵ Templates to the WASH-U-KSADS to assess DSM-IV SUDs in childhood were also administered.^{36,37} Thus, distinct episodes were from the onset to the offset of a sufficient number of temporally overlapping mania symptoms (including elation and/or grandiose behaviors), at a rating of 4 or higher, to fit DSM-IV criteria, and a CGAS of 60 or lower. These methods may lead to underdiagnosis. Specifically, in a national NIMH-funded study, for which Washington University is the independent evaluator, only 71% of videotaped presumptive subjects with child BP-I, sent from 6 data collection sites that are major child BP-I research centers, were given a BP-I diagnosis by Washington University.

Daily cycling, also called ultradian cycling, is not simply a labile mood. Rather, a cycle required at least 4 hours per day with sufficient symptoms at a rating of 4 or higher (impairing) to support a manic or depressed episode.¹⁷

The CGAS was completed by raters who administered the WASH-U-KSADS. On this scale, 0 is worst, 100 is best, and 60 or lower is definite clinical impairment.³⁶ The Global Assessment Scale, the adult counterpart of the CGAS, was used for subjects aged 19.0 years or older.

The Psychosocial Schedule for School-Age Children-Revised^{38,39} was used to obtain comprehensive measurements of child interaction with parents, siblings, peers, and teachers and of marital relationships. It was administered to mothers about their children, and separately to children about themselves, by the research nurses who administered the WASH-U-KSADS. Psychosocial impairments reported by either informant (ie, mother or child) were used in the analyses.⁴⁰ Socioeconomic status was obtained by the Hollingshead Four Point Index.⁴¹ The Duke Pubertal Status Questionnaire⁴² was used to obtain Tanner stage and was completed by subjects 10.0 years or older at each assessment point until Tanner stage III or greater was obtained.

For symptoms that overlapped between diagnoses (eg, distractibility occurring in overlapping time periods for mania and for ADHD), the investigators did not know a way of discerning toward which diagnosis to count the item. Therefore, symptoms that overlapped with more than 1 diagnosis were counted toward each (if they occurred at a rating of ≥ 4), but each diagnosis was given only if there were sufficient temporally overlapping symptoms to fit DSM-IV criteria. Different methods for how overlapping

symptoms are counted likely accounted for differences in rates of comorbid child BP-I and ADHD.⁴³

Consensus conferences were held after each rating at all time points to establish DSM-IV consensus diagnoses. At these conferences, all assessment instruments, baseline videotapes, school reports, agency records, and pediatrician records were reviewed.

Analyses of treatment data will be presented in a separate report. Hypomanic diagnoses are not included in this report (see the "Comment" section). No DSM-IV diagnostic hierarchies were used. Given the young age of the subjects, the DSM-IV duration criteria for dysthymia was not used.

Parents signed informed consent forms and subjects signed assent forms at baseline. Subjects were recontacted at age 18.0 years. This study was approved by the Human Studies Committee at Washington University in St Louis.

PSYCHOSIS

Psychosis required a pathological delusion or hallucination that did not only occur hypnagogically or hypnopompically, and was assessed with the psychosis section of the WASH-U-KSADS.²⁸ In addition, ratings of 6 or higher on the grandiosity, hopelessness, hypochondriasis, and guilt items signify delusions in these areas.²⁸

FOLLOW-UP METHODS

All baseline instruments were administered to mothers about their children and to children about themselves at the 6-, 12-, and 18-month and 2-, 3-, 4-, 5-, 6-, and 8-year follow-up times. Raters were blind at baseline, and new blinded raters were folded in at year 6.

STATISTICAL ANALYSES

Demography and severity characteristics, types of BP-I episodes, unipolar depression, characteristics of BP-I episodes, and nonmood DSM-IV diagnoses of subjects with BP-I at baseline and between baseline and the 8-year follow-up were compared by paired *t* tests for continuous variables and McNemar test for categorical variables.

Comorbidity with ADHD, conduct disorder/antisocial personality disorder, oppositional defiant disorder, and SUDs were examined because of the high prevalence of disruptive disorders in child BP-I^{19,24} and the high prevalence of SUDs in adult BP-I.⁴⁴ Other comorbidities during follow-up will be examined in a separate publication.

Definitions of recovery and relapse during follow-up were adapted from Frank et al.⁴⁵ Recovery was defined as 8 consecutive weeks without meeting DSM-IV criteria for mania. Remission was defined as 2 to 7 weeks without meeting DSM-IV criteria for mania. Relapse after recovery was defined as 2 consecutive weeks of meeting DSM-IV criteria for mania with a CGAS score of 60 or lower, indicating significant clinical impairment. Relapse refers to new episodes.

Estimates of the rates of recovery from mania and relapse to mania were made by the life-table method. For estimates of recovery, the life table was divided into intervals corresponding to the 9 assessment periods, and for estimates of relapse, the life table was divided into 6-month intervals. Recovery from mania and relapse to mania were modeled by means of Cox proportional hazards modeling.⁴⁶ Potential predictors of recovery and relapse were analyzed in univariate models, and significant predictors at the $P < .05$ level were examined in multivariate models. Baseline variables examined in univariate Cox models were age, sex, CGAS score, ascertainment site (psychiatric or pediatric), age at onset of baseline mania episode, psycho-

sis, grandiose delusions, daily cycling, MDD, dysthymia, ADHD, conduct disorder, maternal warmth and paternal warmth, maternal tension/hostility and paternal tension/hostility, and select diagnoses in first-degree relatives (BP-I, recurrent MDD, BP-I or recurrent MDD, BP-I with ADHD, and SUD).

Measurements of maternal and paternal warmth and of maternal and paternal tension/hostility are included in the Psychosocial Schedule for School Age Children-Revised.³⁸ Impairments reported by either child or parent were included in the analysis. For analysis, a score of 1 (mutual concern and affection, close relationship) on maternal and paternal warmth indicated high warmth, and scores of 2 to 5 indicated low warmth.⁴⁰

Percentage of weeks of the 8-year follow-up spent ill with mania in subjects with BP-I was calculated, and potential predictors were analyzed in univariate general linear models. Variables significant in the univariate models at the $P < .05$ level were further analyzed in a multivariate general linear model. Potential predictors in these general linear models were the same as those stated earlier for the Cox proportional hazards models.

In subjects who had second or third mania episodes during the 8-year follow-up, age at episode onset, CGAS score, duration of the episode, types of BP-I episodes, characteristics of BP-I, and nonmood *DSM-IV* diagnoses were compared between second and third episodes and subjects' own baseline episodes, with the use of paired t tests for continuous variables and McNemar test for categorical variables.

In addition, subjects with BP-I were divided into 2 groups by age at the 8-year follow-up assessment. There were 61 subjects who were younger than 18.0 years and 54 who were 18.0 years or older at the 8-year follow-up. For the 54 subjects 18.0 years or older at the 8-year follow-up, comparisons of demography and severity characteristics, types of BP-I episodes, unipolar depression, characteristics of BP-I, and nonmood *DSM-IV* diagnoses between baseline and the portion of follow-up after reaching age 18.0 years (ie, time between age 18.0 and 8-year follow-up assessment) were made by paired t tests and McNemar test. Percentage of weeks of the 8-year follow-up spent ill with bipolar episodes was calculated separately for subjects younger than 18.0 years and for subjects 18.0 years or older. Comparisons were made between the younger and older subjects by general linear models that covaried for sex, baseline pubertal status, and duration of follow-up. For this analysis, in subjects 18.0 years or older at the 8-year follow-up, percentage of weeks spent ill with bipolar episodes was calculated only for the time subjects were 18.0 years or older, and duration of follow-up was defined as the number of weeks of follow-up after reaching 18.0 years of age.

Bonferroni corrections were made to obtain an overall significance level of $P = .05$ for each group of tests performed. Only independent tests were considered when Bonferroni-corrected P values were determined. The corrected significance levels are noted in the table footnotes.

All analyses were conducted with SAS version 8.2 statistical software (SAS Institute Inc, Cary, North Carolina).

RESULTS

NUMBER, RETENTION OF SAMPLE, AND ETHNICITY

Of the initial 115 children, 108 (93.9%) were seen at every follow-up visit (6, 12, and 18 months and 2, 3, 4, 5, 6, and 8 years). There were no demographic or diagnostic differ-

ences between subjects who dropped out and those who continued. Ethnicity included 101 (87.8%) white subjects, 8 (7.0%) black, 1 (0.9%) Hispanic, 0 Asian, and 5 (4.3%) other.

ASCERTAINMENT

As previously detailed, consecutive new case ascertainment was used to obtain the child BP-I and control ADHD (hyperactive or combined subtypes) cases, from every new case at designated pediatric and psychiatric sites. The recruitment of the healthy control group is detailed elsewhere.⁹ Of the 1468 new cases during the recruitment period, 115 fit the study criteria for child BP-I, manic or mixed phase. As published elsewhere,⁴⁷ in 23 of the 81 (28.4%) original subjects with ADHD the diagnosis switched to BP-I during follow-up. In brief, these subjects with ADHD were from clinics at, or affiliated with, a major academic center, just after public policy changed to children with typical ADHD being seen by general practitioners rather than specialists in child psychiatry.⁴⁸ Zarin et al⁴⁸ reported that ADHD cases seen by psychiatrists had more complex clinical pictures, consistent with our findings. Also consistent with these high switch rates are data showing that ADHD begins before mania in children with mania and comorbid ADHD.⁴³ In subjects whose diagnosis switched from ADHD to BP-I, age at onset of BP-I for this report was the age of switching to BP-I. Because ascertainment for the child BP-I and ADHD groups was the same, these subjects who switched were added to the BP-I group for analyses if the switch occurred during the study baseline age range, 7.0 to 16.11 years old. The mean duration of follow-up after switching to BP-I for the 32 subjects whose diagnosis switched (23 with ADHD and 9 with BP-II) was 309.6 weeks (SD, 124.7 weeks), which was significantly shorter than the 388.0 (SD, 101.4) weeks for the 83 subjects who had BP-I at study inception ($t = 3.5$, $P < .001$). Two subjects who switched from ADHD to child BP-I also had developed SUDs, but they were not excluded because prospective assessment allowed separation of the substance and mood disorders.

COMPARISON OF CHARACTERISTICS AT BASELINE AND ANY TIME DURING 8-YEAR FOLLOW-UP

Table 1 presents characteristics at baseline compared with any time through the 8-year follow-up. The main difference over time is the increase in MDD and psychosis and the development of SUDs.

TIME TO AND PREDICTORS OF RECOVERY AND RELAPSE DURING 8-YEAR FOLLOW-UP

During follow-up, 101 (87.8%) of subjects with BP-I recovered, and 74 (73.3%) of these had relapses after recovery (**Figure 1** and **Figure 2**). Even accounting for family psychopathology, maternal warmth was a significant predictor of relapse after recovery (Figure 2). Mean time to recovery from BP-I was 55.6 weeks (SD, 51.9 weeks), and time to relapse after recovery was 99.0 (81.0) weeks. More weeks ill with BP-I, manic or mixed phase,

Table 1. Characteristics of 115 Children With BP-I at Baseline vs Any Time Through 8-Year Follow-up^a

Demography and Severity	Baseline	Through 8-y Follow-up	t or χ^2
Age, mean (SD), y	11.1 (2.6)	18.1 (2.9)	34.6 ^{b,c}
Age at onset of first (baseline) mania, mean (SD), y	8.3 (3.7)	NA	NA
Duration of first mania episode at baseline, mean (SD), wk	142.7 (139.4)	NA	NA
CGAS score, mean (SD)	43.5 (8.0)	35.5 ^d (10.8)	8.8 ^{b,c}
Sex			
Male	77 (67.0)	77 (67.0)	NA
Female	38 (33.0)	38 (33.0)	
Pubertal status			
Prepubertal	58 (50.4)	2 (1.7)	56.0 ^c
Pubertal	57 (49.6)	113 (98.3) ^e	
Race			
White	101 (87.8)	101 (87.8)	NA
Other	14 (12.2)	14 (12.2)	
BP-I, manic or mixed episodes ^f	115 (100.0)	115 (100.0)	NA
Unipolar mania	17 (14.8)	60 (52.2)	39.3 ^c
Mixed mania	98 (85.2)	102 (88.7)	1.3
Mania and MDD	62 (53.9)	87 (75.7)	17.9 ^c
Mania and dysthymia	36 (31.3)	73 (63.5)	24.9 ^c
Unipolar depression ^f	0	66 (57.4)	NA
Unipolar MDD	0 ^g	48 (41.7)	NA
Unipolar dysthymia	0 ^g	51 (44.3)	NA
Characteristics during BP-I, manic or mixed			
Psychosis	70 (60.9)	84 (73.0)	7.0 ^h
Suicidality	30 (26.1)	40 (34.8)	3.3
Daily cycling	90 (78.3)	100 (87.0)	4.5
Nonmood <i>DSM-IV</i> diagnoses			
Disruptive disorders	111 (96.5)	112 (97.4)	0.3
ADHD	102 (88.7)	108 (93.9)	3.0
Conduct disorder/antisocial	12 (10.4)	22 (19.1)	5.6
Oppositional defiant disorder	87 (75.7)	94 (81.7)	3.8
Substance use disorders	3 (2.6)	39 (33.9)	34.1 ^c
Substance abuse	1 (0.9)	16 (13.9)	13.2 ^c
Substance dependency	2 (1.7) ⁱ	34 (29.6)	32.0 ^c

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP-I, bipolar I disorder; CGAS, Children's Global Assessment Scale; MDD, major depressive disorder; NA, not applicable.

^aValues are number (percentage) unless otherwise indicated. Bonferroni-corrected *P* values were *P* = .02 for BP-I, manic or mixed episodes, *P* = .02 for characteristics during BP-I, manic or mixed, and *P* = .01 for nonmood *DSM-IV* diagnoses.

^bThese are *t* values; all others are χ^2 .

^c*P* < .001.

^dThe CGAS score was the lowest obtained during follow-up.

^eIncludes subjects who were pubertal at baseline and subjects who were prepubertal at baseline but became pubertal during 8-year follow-up.

^fSums of episode categories could be greater than 100% because subjects could have more than 1 category during follow-up.

^gSubjects with BP-I could not have unipolar MDD or unipolar dysthymia at baseline because baseline mania or mixed mania was required.

^h*P* < .01.

ⁱSubstance dependence was an exclusion criterion at baseline. An exception occurred in 2 subjects whose diagnosis switched from ADHD to BP-I during follow-up, as detailed in the text.

was significantly predicted by younger baseline age (*t* = 2.2, *P* = .03) and low maternal warmth (*t* = 2.6, *P* = .01) in a multivariate general linear model that included the significant predictors in univariate models (ie, sex, baseline MDD, baseline psychosis, age at onset of baseline mania episode, paternal warmth, paternal tension/hostility, and parent with BP-I or recurrent MDD) as covariates.

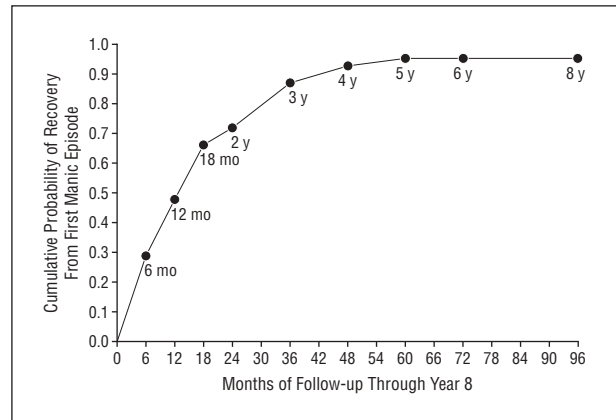


Figure 1. Cumulative probability of recovery from first episode (baseline) of child bipolar I disorder, manic or mixed phase. Life-table estimate of recovery was 95.2% (95% confidence interval, 90.6%-99.8%). The 9 assessment points are indicated.

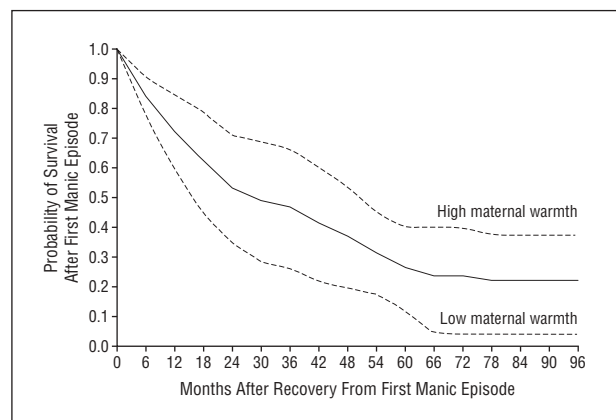


Figure 2. Cumulative probability of survival after recovery from the first episode (baseline) of child bipolar I disorder (BP-I), manic or mixed. The solid curve is the probability of survival for the 101 subjects with BP-I who recovered. Life-table estimate of survival was 22.2% (95% confidence interval [CI], 13.4%-31.0%). For the 52 subjects with high maternal warmth, life-table estimate of survival was 37.3% (95% CI, 23.2%-51.4%). For the 49 subjects with low maternal warmth, life-table estimate of survival was 4.0% (95% CI, 0.0%-11.3%). Cox proportional hazards modeling was significant for maternal warmth (χ^2 = 10.7, *P* = .001), controlling for baseline age, sex, and variables significant in univariate models (baseline Children's Global Assessment Scale score, ascertainment site, baseline major depressive disorder, baseline conduct disorder, maternal tension/hostility, paternal warmth, and parent with BP-I or recurrent major depressive disorder). The hazard ratio was 2.9 (95% CI, 1.5-5.4).

CHARACTERISTICS OF BASELINE (FIRST) COMPARED WITH SECOND AND THIRD BP-I EPISODES

At baseline, 100% of subjects with child BP-I were in their first (and current) BP-I, manic or mixed phase, episode. During the 8-year follow-up, the mean (SD) number of mania or mixed mania episodes was 2.0 (1.0). **Table 2** and **Table 3** compare characteristics of subjects with second or third episodes with their own baselines. Largely similar to first episodes, second and third episodes of mania were characterized by psychosis, daily (ultradian) cycling, and long duration (mean time of 55.2 and 40.0 weeks, respectively) but were significantly shorter than the first episode.

Table 2. Characteristics of Baseline vs Second Episode of Child BP-I, Manic or Mixed Phase, for Subjects Who Had a Second Episode^a

Demography and Severity	Baseline Episode (n=52)	Second Episode (n=52)	t or χ^2
Age at onset of episode, mean (SD), y	7.3 (3.5)	12.8 (2.9)	13.1 ^{b,c}
CGAS score, ^d mean (SD)	39.8 (8.5)	41.4 (9.8)	1.0 ^b
Duration of episode, mean (SD), wk	212.2 (144.6)	55.2 (44.3)	7.9 ^{b,c}
BP-I, manic or mixed episodes	52 (100.0)	52 (100.0)	NA
Unipolar mania	17 (32.7)	16 (30.8)	0.0
Mixed mania	48 (92.3)	42 (80.8)	3.0
Mania and MDD	45 (86.5)	28 (53.8)	10.7 ^e
Mania and dysthymia	21 (40.4)	27 (51.9)	1.5
Characteristics during BP-I, manic or mixed			
Psychosis	38 (73.1)	30 (57.7)	3.6
Suicidality	18 (34.6)	10 (19.2)	3.6
Daily cycling	46 (88.5)	42 (80.8)	1.1
Nonmood <i>DSM-IV</i> diagnoses			
Disruptive disorders	50 (96.2)	47 (90.4)	1.8
ADHD	48 (92.3)	40 (76.9)	5.3
Conduct disorder/antisocial	8 (15.4)	1 (1.9)	5.4
Oppositional defiant disorder	48 (92.3)	32 (61.5)	14.2 ^c
Substance use disorders	0	4 (7.7)	NA
Substance abuse	0	1 (1.9)	NA
Substance dependency	0	4 (7.7)	NA

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP-I, bipolar I disorder; CGAS, Children's Global Assessment Scale; MDD, major depressive disorder; NA, not applicable.

^aOf the 115 subjects, 52 had a second episode with an offset before the 8-year assessment. Comparisons are made between their own baseline and second episode for these 52 subjects. Values are number (percentage) unless otherwise indicated. Bonferroni-corrected *P* values were *P* = .02 for BP-I, manic or mixed episodes, *P* = .02 for characteristics during BP-I, manic or mixed, and *P* = .02 for nonmood *DSM-IV* diagnoses.

^bThese are *t* values; all others are χ^2 .

^c*P* < .001.

^dThe CGAS score was the lowest obtained during baseline and during the second episode.

^e*P* < .01.

CHARACTERISTICS OF SUBJECTS WITH BP-I AFTER REACHING AGE 18.0 YEARS

Twenty-four subjects (44.4%) had mania after they reached age 18.0 years, when their mean age was 20.6 years (SD, 1.8 years) (**Table 4**).

There were no significant differences in the percentage of weeks with mood episodes by age group (<18 years vs \geq 18 years) and, across ages, subjects had mood episodes during a large percentage of weeks (49.4%-65.5%) (**Table 5**).

COMMENT

Notably, even accounting for family psychopathology, maternal warmth predicted outcome. Kim and Miklowitz⁴⁹ reported on the role of high expressed emotion, akin to low maternal warmth, in the course of adult BP-I, similar to the role of low maternal warmth as a predictor in subjects with child BP-I. However, there are data that do not support an effect of high expressed emotion on the

Table 3. Characteristics of Baseline vs Third Episode of Child BP-I, Manic or Mixed Phase, for Subjects Who Had a Third Episode^a

Demography and Severity	Baseline Episode (n=22)	Third Episode (n=22)	t or χ^2
Age at onset of episode, mean (SD), y	6.3 (3.6)	13.6 (3.0)	11.4 ^{b,c}
CGAS score, ^d mean (SD)	38.6 (7.0)	40.0 (9.3)	0.8 ^b
Duration of episode, mean (SD), wk	234.1 (145.3)	40.0 (30.4)	6.6 ^{b,c}
BP-I, manic or mixed episodes	22 (100.0)	22 (100.0)	NA
Unipolar mania	7 (31.8)	3 (13.6)	2.7
Mixed mania	19 (86.4)	20 (90.9)	0.3
Mania and MDD	18 (81.8)	9 (40.9)	9.0 ^e
Mania and dysthymia	8 (36.4)	14 (63.6)	3.0
Characteristics during BP-I, manic or mixed			
Psychosis	19 (86.4)	14 (63.6)	2.3
Suicidality	9 (40.9)	2 (9.1)	5.4
Daily cycling	17 (77.3)	15 (68.2)	0.7
Nonmood <i>DSM-IV</i> diagnoses			
Disruptive disorders	21 (95.5)	20 (90.9)	0.3
ADHD	21 (95.5)	16 (72.7)	3.6
Conduct disorder/antisocial	3 (13.6)	3 (13.6)	0.0
Oppositional defiant disorder	19 (86.4)	14 (63.6)	3.6
Substance use disorders	0	3 (13.6)	NA
Substance abuse	0	1 (4.5)	NA
Substance dependency	0	3 (13.6)	NA

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP-I, bipolar I disorder; CGAS, Children's Global Assessment Scale; MDD, major depressive disorder; NA, not applicable.

^aOf the 115 subjects, 22 had a third episode with an offset before the 8-year assessment. Comparisons are made between their own baseline and third episode for these 22 subjects. Values are number (percentage) unless otherwise indicated. Bonferroni-corrected *P* values were *P* = .02 for BP-I, manic or mixed episodes, *P* = .02 for characteristics during BP-I, manic or mixed, and *P* = .02 for nonmood *DSM-IV* diagnoses.

^bThese are *t* values; all others are χ^2 .

^c*P* < .001.

^dThe CGAS score was the lowest obtained during baseline and during the third episode.

^e*P* < .01.

course of adult BP-I,⁵⁰ so that further research to better define the role of low maternal warmth/high expressed emotion is warranted.

One area of controversy has been the high prevalence of daily cycling (ultradian cycling) during episodes found by several investigative groups.^{4,5,12,15-17} Because a child must have 4 hours or more per day to count as mania and because the mean number of cycles per day was 3.7 (SD, 2.1), these subjects were spending most of the day in a pathological mood episode. The clinical importance of daily cycling is that a euphoric child can very quickly become seriously depressed and suicidal. Daily cycling continued to be highly prevalent when the subjects with child BP-I reached adulthood. Is this just a peculiarity of some samples, or does the detailed questioning about daily cycling on the WASH-U-KSADS increase the likelihood of finding this phenomenon? The WASH-U-KSADS is also being used in the ongoing NIMH-funded "Treatment of Early Age Mania (TEAM)" study. In the TEAM study, daily cycles were found in 98.6% of subjects from 6 national sites,¹² which strongly sup-

Table 4. Characteristics of Subjects With Child BP-I at Baseline vs After Reaching Age 18.0 Years or Older for Subjects Who Reached That Age by Year 8^a

Demography and Severity	After Reaching		t or χ^2
	Baseline (n=54)	Age \geq 18.0 y (n=54)	
Age, mean (SD), y	12.9 (1.9)	20.6 (1.8)	55.5 ^{b,c}
Age at onset of first (baseline) mania, mean (SD), y	9.8 (3.7)	NA	NA
Duration of first mania episode at baseline, mean (SD), wk	162.8 (160.8)	NA	NA
CGAS score, mean (SD)	42.4 (8.3)	33.5 ^d (10.6)	6.5 ^{b,c}
Sex			
Male	30 (55.6)	30 (55.6)	NA
Female	24 (44.4)	24 (44.4)	
Pubertal status			
Prepubertal	13 (24.1)	0	NA
Pubertal	41 (75.9)	54 (100.0)	
Race			
White	46 (85.2)	46 (85.2)	NA
Other	8 (14.8)	8 (14.8)	
BP-I, manic or mixed episodes ^e	54 (100.0)	24 (44.4)	NA
Unipolar mania	8 (14.8)	13 (24.1)	1.5
Mixed mania	46 (85.2)	17 (31.5)	29.0 ^c
Mania and MDD	30 (55.6)	12 (22.2)	13.5 ^c
Mania and dysthymia	16 (29.6)	10 (18.5)	1.6
Unipolar depression ^e	0	16 (29.6)	NA
Unipolar MDD	0 ^f	11 (20.4)	NA
Unipolar dysthymia	0 ^f	9 (16.7)	NA
Characteristics during BP-I, manic or mixed			
Psychosis	20 (83.3)	14 (58.3)	3.0 ^g
Suicidality	7 (29.2)	3 (12.5)	2.7 ^g
Daily cycling	19 (79.2)	16 (66.7)	0.8 ^g
Nonmood <i>DSM-IV</i> diagnoses			
Disruptive disorders	51 (94.4)	32 (59.3)	17.2 ^c
ADHD	44 (81.5)	24 (44.4)	14.3 ^c
Conduct disorder/antisocial	11 (20.4)	10 (18.5)	0.1
Oppositional defiant disorder	38 (70.4)	21 (38.9)	13.8 ^c
Substance use disorders	2 (3.7)	19 (35.2)	15.2 ^c
Substance abuse	1 (1.9)	7 (13.0)	4.5
Substance dependency	1 (1.9) ^h	15 (27.8)	14.0 ^c

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP-I, bipolar I disorder; CGAS, Children's Global Assessment Scale; MDD, major depressive disorder; NA, not applicable.

^aValues are number (percentage) unless otherwise indicated. Bonferroni-corrected *P* values were *P* = .02 for BP-I, manic or mixed episodes, *P* = .02 for characteristics during BP-I, manic or mixed, and *P* = .01 for nonmood *DSM-IV* diagnoses.

^bThese are *t* values; all others are χ^2 .

^c*P* < .001.

^dThe CGAS score was the lowest obtained after age 18.0 years or older.

^eSums of episode categories could be greater than 100% because subjects could have more than 1 category during follow-up.

^fSubjects with BP-I could not have unipolar MDD or unipolar dysthymia at baseline because baseline mania or mixed mania was required.

^gComparison is for the 24 subjects who had mania or mixed mania at age 18.0 years or older.

^hSubstance dependence was an exclusion criterion at baseline. An exception occurred in 1 subject whose diagnosis switched from ADHD to BP-I during follow-up, as detailed in the text.

ports that daily cycles are more likely to be found when they are asked about.

Characteristics of second and third episodes also showed that subjects still had substantial morbidity, including long episode duration, psychosis, and daily cycling. Of note, the score on the CGAS (and the Global

Table 5. Percentage of Weeks During 8-Year Follow-up With Mood Episodes in Subjects With Child BP-I by Age Younger Than 18.0 vs 18.0 Years or Older at 8-Year Follow-up^a

Episode Type	% of Weeks, Mean (SD)		
	Total (N=115)	Age < 18.0 y (n=61)	Age \geq 18.0 y ^b (n=54)
BP-I, manic or mixed	39.6 (27.8)	42.3 (29.2)	34.2 (42.5)
Unipolar mania	8.8 (15.3)	8.5 (15.8)	13.6 (29.9)
Mixed mania	30.7 (27.7)	33.8 (30.7)	20.6 (35.7)
Mania and MDD	17.9 (22.7)	19.7 (26.1)	10.3 (24.7)
Mania and dysthymia	11.8 (16.2)	12.5 (18.0)	10.0 (28.0)
Mania and minor depression	1.1 (4.5)	1.5 (5.8)	0.2 (1.4)
Unipolar depression	20.7 (22.6)	23.2 (25.2)	15.2 (28.5)
Unipolar MDD	8.3 (14.4)	8.4 (16.3)	9.0 (22.5)
Unipolar dysthymia	12.1 (15.0)	14.6 (17.0)	6.1 (17.9)
Unipolar minor depression	0.2 (1.3)	0.2 (1.6)	0.1 (0.7)
Any mood episode	60.2 (28.9)	65.5 (28.6)	49.4 (44.0)

Abbreviations: BP-I, bipolar I disorder; MDD, major depressive disorder.

^aBonferroni-corrected *P* value was *P* < .007. There were no significant differences between subjects with BP-I younger than 18.0 years and those 18.0 years or older after Bonferroni correction.

^bIn subjects with BP-I 18.0 years or older at 8-year follow-up, percentage of weeks represents weeks after reaching age 18.0 years.

Assessment Scale in older subjects) was significantly lower during second and third episodes and in subjects who were 18.0 years or older. This likely reflects how functioning in children may be enhanced by parental behaviors (eg, children are taken to school as opposed to adults, who have to show up for work on their own).

In grown-up subjects with child BP-I, the 44.4% frequency of manic episodes was 13 to 44 times higher than population prevalences,^{51,52} strongly supporting continuity between child and adult BP-I. Subjects with child BP-I who were grown up at the 8-year follow-up constituted approximately half the sample. However, even if all subjects younger than 18.0 years at the 8-year follow-up never had episodes of BP-I as adults, the overall significance of the findings would be similar, because the rate would still be 6 to 22 times higher than population prevalences.^{51,52} In a study of adults with first episodes of *DSM-IV* mania, 20% had a new manic episode during a 2-year follow-up.⁵³ That study used a treated, inpatient population, which is possibly related to the better outcome.

Recent prospective work from Judd et al¹⁸ on the course of adults with BP-I found that subjects were ill with mood symptoms 47.3% of weeks. These findings are similar to those in this report, in which subjects with child BP-I, both those younger than 18.0 years and those 18.0 years or older, were ill with mood episodes 65.5% and 49.4% of weeks, respectively.

In the family study data from this cohort, both child-onset and adult-onset BP-I occurred within the same families,⁸ further bolstering continuity across the age span. In addition, the prevalence of comorbid SUD in the subjects with child BP-I who were 18.0 years or older, 35.2%, was similar to that reported for adults with BP-I, 42.4%.⁴⁴ Given that subjects with child BP-I who reached age 18.0 years

are not yet through the age of risk for SUDs, the 35.2% found may be higher at future follow-up assessment times. It is difficult to compare the rates of ADHD in the subjects with child BP-I who reached adulthood during follow-up with studies of adult BP-I, because ADHD was not systematically assessed in adult BP-I.⁴⁴

Whether there is a relationship between child BP-I symptomatology and concurrent parental mood disorder was not examined in this sample. Given the recent work of Weissman et al³⁴ on the relationship between severity of child depressive symptoms and concurrent maternal depression, similar studies for child BP-I are warranted. There are, however, data that support a less deleterious effect of maternal BP-I than maternal MDD on child-aged offspring.⁵⁵

Limitations of this work are that subjects were largely of higher socioeconomic status (see description in the "Methods" section), so generalization to lower socioeconomic status cannot be known. More frequent assessments and the course of BP-II and BP not otherwise specified are important areas that were not included in this project.

In conclusion, mounting data support the existence of child BP-I, and the severity and chronicity of this disorder argue strongly for large efforts toward understanding the neurobiology and for developing prevention and intervention strategies.

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