

Prepubertal and Early Adolescent Bipolar I Disorder: Review of Diagnostic Validation by Robins and Guze Criteria

Barbara Geller, M.D., and Rebecca Tillman, M.S.

The phenomenology of pediatric bipolar disorder is a controversial topic in the field of child psychiatry. The first National Institute of Mental Health–funded study in the field, Phenomenology and Course of Pediatric Bipolar Disorders, selected a conservative phenotype for credibility in a contentious field. To address the problems of differentiation of mania from attention-deficit/hyperactivity disorder (ADHD) and of the ubiquitous manifestation of irritability across child psychiatry diagnoses, a prepubertal and early adolescent bipolar I disorder phenotype (PEA-BP) was defined by DSM-IV bipolar I disorder (manic or mixed phase) with elation and/or grandiosity as one criterion. This criterion avoided diagnosing mania by symptoms that overlapped with those of ADHD (e.g., hyperactivity, distractibility) and ensured that subjects had at least 1 of the cardinal symptoms of mania (i.e., elation or grandiosity). This definition was analogous to the requirement that DSM-IV major depressive disorder include at least 1 of the cardinal symptoms of depression (i.e., sad mood or anhedonia). Subjects were 93 children with a mean \pm SD age of 10.9 ± 2.6 years. Validation of the phenotype was shown according to Robins and Guze criteria: unique symptoms that did not overlap with those of ADHD, stability of the diagnosis (did not become ADHD or other disorders on follow-up) as shown by a 4-year prospective longitudinal study, significantly higher familial aggregation of bipolar disorder in relatives of PEA-BP versus ADHD and healthy control probands, and family-based linkage disequilibrium of the brain-derived neurotrophic factor Val66 allele in PEA-BP probands. Furthermore, PEA-BP resembled the most severe adult bipolar disorder, manifested by a chronic, ultradian-cycling, mixed manic, psychotic course. A conservatively defined child mania phenotype met the Robins and Guze criteria for establishing diagnostic validity in psychiatric illness. Continuities between PEA-BP and adult bipolar disorder and relationships of PEA-BP to other descriptions of child mania are discussed.

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The area of childhood bipolar disorders appears to have generated far more controversy than other diagnoses.^{1,2} In one way, this is surprising, as there is historical evidence that child manic-depression has been recognized and described in convincing detail.³ Although there is unlikely to be a definitive answer about the basis of this controversy, one speculation is that many behaviors of adults with mania are culturally deemed anathema in children

(e.g., hypersexuality). Another may be developmental, in that healthy children, as opposed to healthy adults, are expected to be carefree, giggly, and grandiose.⁴ Therefore, the differentiation between age-appropriate versus pathologic euphoria and grandiosity may be more challenging for cases in children.⁴

There also seems to be a conception that prepubertal bipolar I disorder is a rare disorder. Epidemiologic studies on the prevalence of prepubertal bipolar I disorder have not yet been conducted, but the clinical prevalence of child mania suggests the disorder is not rare.⁵ In the National Institute of Mental Health (NIMH)–funded study of prepubertal and early adolescent bipolar disorder, Phenomenology and Course of Pediatric Bipolar Disorders (referred to as the “Phenomenology study” elsewhere in this article), 6.3% of consecutive new cases, ascertained from designated pediatric and child psychiatric venues from 1995 to 1998, fit a conservatively defined prepubertal and early adolescent bipolar I disorder phenotype (PEA-BP).⁶ In the consecutive new case ascertainment schema, every new case at the designated venues was screened. For example, a child who presented to a pediatric site with a sore throat was given the same screening as a child who presented to a psychiatric site with hyperactivity. Thus, there

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

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

was no “cherry-picking” of cases. Similarly, in the ongoing, multisite, NIMH-funded Treatment of Early Age Mania (TEAM) study, 7.5% of caseloads at the 5 participating sites had child mania patients (B.G., unpublished data, July 2004). These findings demonstrate that prepubertal bipolar disorder is not a rare disorder.

DIFFERENTIATION OF MANIA FROM ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THE NON-DIAGNOSTIC ROLE OF IRRITABILITY

An area of consensus in the field of pediatric mania is the high prevalence of comorbid attention-deficit/hyperactivity disorder (ADHD).⁷⁻¹⁰ Although rates of comorbid ADHD in child mania in these reports varied by the DSM system used for diagnosis and the use of a severity scale cutoff score,¹⁰ rates of comorbid ADHD across methodologies were nevertheless very high, ranging from 75% to 93%.⁷⁻¹⁰ Overlapping criteria of mania and ADHD add to the difficulty of differential diagnosis.¹¹

Irritable mood is a very sensitive symptom of mania (i.e., detects most cases), but is nonspecific to mania, as irritability also identifies subjects with a range of other child psychiatry diagnoses (e.g., oppositional defiant disorder, conduct disorder). Evidence for irritability as a pervasive symptom across multiple child psychiatric disorders comes from Kim-Cohen and colleagues.¹² These authors found that 25% to 60% of prospectively assessed young adults with a range of adult psychiatric diagnoses had a childhood disorder characterized by irritability and aggression (e.g., oppositional defiant disorder, conduct disorder). Recently, irritability as a dimension that cuts across diagnoses has been the target of treatment studies. For example, 2 double-blind, placebo-controlled trials of risperidone for irritability and aggression in subjects with low IQ¹³ or autism¹⁴ were reported. These double-blind, placebo-controlled trials support the high sensitivity and low specificity of irritability. Notably, 87.1% of PEA-BP subjects had concurrent elated mood and irritability, similar to the rate seen in adult bipolar disorder.^{6,15} Overall, irritability is not a useful differential diagnostic symptom.

DEFINITION OF A PREPUBERTAL AND EARLY ADOLESCENT BIPOLAR I DISORDER PHENOTYPE

To address the problems of comorbid ADHD and irritability, Geller and associates^{6,9} chose the following approach to defining a prepubertal and early adolescent bipolar I disorder phenotype. Subjects were required to fit criteria for current DSM-IV bipolar I disorder (manic or mixed phase) with at least 1 of the cardinal symptoms of mania (i.e., elation and/or grandiosity) as one criterion. Current mania was a criterion because this investigation

was a phenomenology study. The cardinal symptom schema was analogous to the DSM-IV major depressive disorder (MDD) requirement that at least 1 of the cardinal symptoms of depression (i.e., sad mood and/or anhedonia) be met to fit the diagnosis of MDD. Requiring elation and/or grandiosity ensured that all subjects would have at least 1 of the cardinal symptoms of mania and avoided diagnosing mania only by symptoms that overlapped with those of ADHD (e.g., hyperactivity, distractibility). A conservative episode duration of 2 weeks was chosen, and PEA-BP subjects were required to have a Children’s Global Assessment Scale (CGAS)¹⁶ score ≤ 60 , indicating definite clinical impairment.

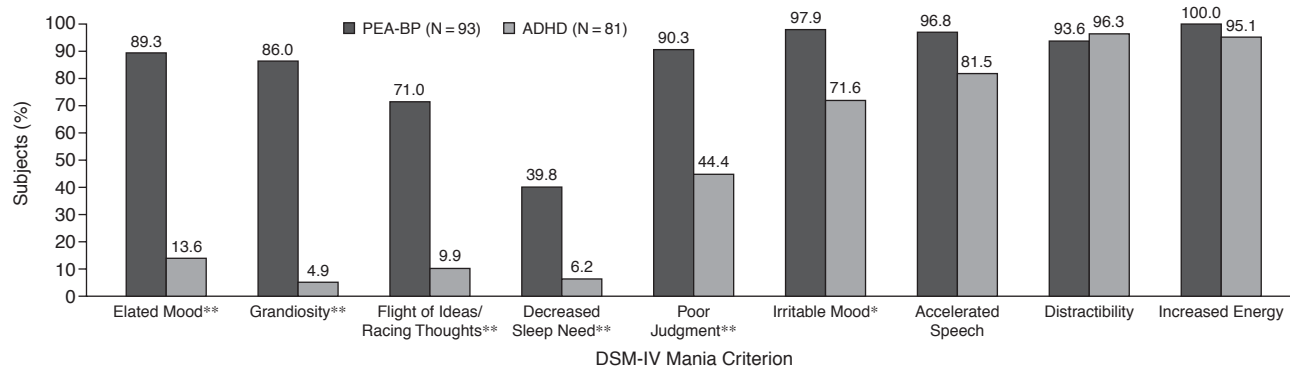
Data on the PEA-BP subjects were obtained during the continuing, NIMH-funded Phenomenology study that was begun in 1995. There were 268 subjects comprising 93 with PEA-BP, 81 with ADHD, and 94 healthy controls. Details of the ascertainment of subjects, assessment, and inclusion and exclusion criteria are described elsewhere.⁶ Subjects with ADHD were required to have hyperactive or combined-type ADHD, because the main differential diagnostic problem was the overlapping hyperactivity symptoms in DSM-IV mania and ADHD. Subjects in the PEA-BP and ADHD groups were obtained through consecutive new case ascertainment from designated pediatric and child psychiatric sites.⁶ In the consecutive new case ascertainment schema, every new case (even those with nonpsychiatric complaints, such as a sore throat) at the designated venues was screened, so that there was no biased case selection. Healthy control subjects were recruited through a random survey that matched healthy controls to PEA-BP subjects by age, sex, socioeconomic status, ethnicity, and zip code.⁶ Experienced research nurses were blind to subjects’ diagnostic group, and separate raters were used for the parent and child in each family to avoid bias.¹⁷

To our knowledge, this investigation was the first systematic phenomenological, longitudinal, family, and molecular genetic study of a sample ascertained for a prepubertal and early adolescent bipolar disorder phenotype.

VALIDATION BY ROBINS AND GUZE (1970) CRITERIA

While various child bipolar disorder phenotypes have been investigated, only PEA-BP has been validated following the Robins and Guze¹⁸ criteria for establishing diagnostic validity in psychiatric illness. These criteria are (1) unique symptoms that do not occur in other disorders, (2) longitudinal diagnostic stability (i.e., do not become another diagnosis on follow-up), (3) higher familial aggregation compared with control groups, and (4) biological markers. Validation of PEA-BP by the Robins and Guze¹⁸ criteria is discussed below.

Figure 1. DSM-IV Mania Criteria That Best and Least Differentiate a Prepubertal and Early Adolescent Bipolar I Disorder Phenotype (PEA-BP) From ADHD^a



^aAdapted with permission from Craney and Geller.¹¹

* $p = .0002$ for symptoms occurring more frequently in the PEA-BP vs. the ADHD group.

** $p < .0001$ for symptoms occurring more frequently in the PEA-BP vs. the ADHD group.

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Validation by Diagnostic Data

Assessment tools. One reason for the paucity of research on prepubertal mania was the lack of an assessment instrument specifically designed to assess mania in children. To address the need for a prepubertal age-specific instrument for assessing mania, Geller and coworkers¹⁹ developed the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) from the KSADS.²⁰ In developing the WASH-U-KSADS, additions to the KSADS included (1) items to specifically assess prepubertal mania manifestations, (2) a section on rapid cycling, (3) items for current and lifetime occurrences of symptoms and syndromes, (4) items for specific timing of onsets and offsets for all symptoms and syndromes, and (5) expanded items for assessment of ADHD and multiple other DSM-IV diagnoses.^{4,6,19,21} The WASH-U-KSADS interview requires that the narrative next to each item justify the severity rating with respect to onset, offset, frequency, duration, intensity, and specific examples. Examples of prepubertal mania manifestations taken from WASH-U-KSADS interview narratives have been previously published.⁴ The WASH-U-KSADS is a semistructured interview designed for use by experienced research clinicians, has excellent reliability (kappa values, 0.82–1.00),²¹ and is now widely used in NIMH-funded studies of prepubertal mania.²²

Parent and child informants. Tillman and colleagues¹⁷ reported that there was poor parent-child concordance for subjects with PEA-BP, evidenced by low kappa statistics, which measure agreement beyond chance. Furthermore, substantial proportions of mania criteria were provided only by the child and not by the parent. Moreover, there were no significant differences between mean kappa values of parent versus child ratings between the ages of 7 and 14 years.¹⁷ Therefore, these findings strongly supported

the need to directly interview children separately from parents. Also, these data were consistent with multiple reports of low mother-child concordance for childhood depression and anxiety.^{23–30}

Symptom distribution. PEA-BP subjects were a mean \pm SD age of 10.9 ± 2.6 years at the baseline assessment and had a mean \pm SD current episode duration of 3.6 ± 2.5 years, so that the mean age at onset of the current episode was 7.3 ± 3.5 years.^{6,9} The mean \pm SD age at onset of the first mania episode in these PEA-BP subjects was 6.8 ± 3.4 years. For 81.7% of the PEA-BP subjects, the baseline episode was the first mania episode.¹⁰

Figure 1 compares rates of mania symptoms in PEA-BP and ADHD subjects. The symptoms that best differentiated PEA-BP and ADHD were elated mood, grandiosity, flight of ideas/racing thoughts, and decreased need for sleep. These differences were not only statistically significant, but also large enough to be clinically meaningful. The symptoms that least differentiated PEA-BP from ADHD were irritable mood, accelerated speech, distractibility, and increased energy. Even though irritability was significantly more common in the PEA-BP group (97.9% vs. 71.6%, $\chi^2 = 13.6$, $p = .0002$), the difference was not clinically meaningful, because irritability had a high prevalence in both groups.^{6,11}

Mixed mania and psychosis. Two definitions of mixed mania were used. The first definition included only syndromal DSM-IV MDD and required overlapping time periods of mania and MDD.⁹ The second definition included overlapping time periods of mania and at least 1 of the depressive disorders MDD, minor depression, or dysthymia.⁵ Rates of mixed mania in the PEA-BP group at baseline were 54.8% (MDD) and 88.2% (MDD, minor depression, or dysthymia).^{5,6}

Psychosis was observed in 60.2% of PEA-BP subjects, with 50.5% of PEA-BP subjects exhibiting grandiose delusions.⁶ Psychosis was defined as malignant, pathologic hallucinations and delusions. In accordance with this definition, benign hallucinations, such as hearing a voice call one's name, were not considered psychotic. In contrast, malignant perceptual distortions, such as hearing a voice telling one to kill oneself, were considered psychotic.⁶

Rapid cycling. In adult psychiatry, rapid cycling is defined as 4 or more episodes per year.^{9,31} Thus, the terms *episode* and *cycle* were essentially used synonymously. Kramlinger and Post³² took this into account in describing ultrarapid (i.e., switching every few days to weeks) and ultradian cycling (i.e., switching every few hours within a day). The Kramlinger and Post³² definitions were later modified by Tillman and Geller.³¹ These authors proposed that *episodes* refer to the duration of an entire period of illness and that *cycles* refer to mood switches during an episode. In this schema, rapid cycling was defined as 4 episodes per year, a phenomenon commonly seen in adult, but not child, bipolar disorder.^{9,31} During an episode, ultrarapid cycling was defined as 5 to 364 cycles per year, and ultradian cycling was 365 or more cycles per year. In ultradian cycling, children cycle multiple times a day, every day or almost every day, for years. As a hypothetical example, an 8-year-old boy who had a bipolar disorder diagnosis for 2 years, during which time he cycled twice daily every day, would be said to have an episode lasting 2 years, characterized by ultradian cycling. With this schema, baseline cycling rates in PEA-BP subjects were 0.0% rapid cycling, 9.7% ultrarapid cycling, and 77.4% ultradian cycling.⁹

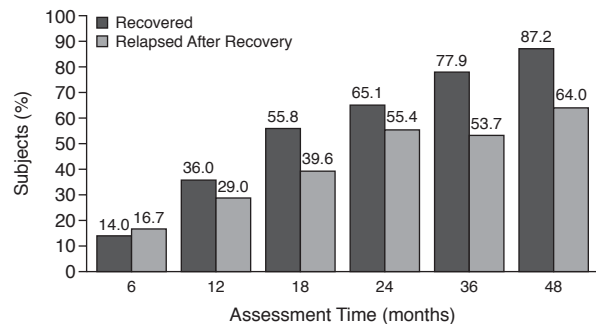
Comment on validation by diagnostic data. These diagnostic data demonstrate that PEA-BP fit the first Robins and Guze¹⁸ criterion of unique symptoms that do not occur in other psychiatric disorders (elation, grandiosity, flight of ideas/racing thoughts, decreased need for sleep). Counterintuitively, PEA-BP resembled the most severe adult bipolar disorder, manifested by a chronic, ultradian-cycling, mixed manic, psychotic course.¹⁵ The most severe adult bipolar disorder reportedly occurs in 20% or fewer of all adult cases,¹⁵ while 77.4% of PEA-BP subjects had ultradian cycling.⁹

Validation by Longitudinal Data: A 4-Year, Prospective, Natural History, Longitudinal Study

Although longitudinal and natural history studies of adult bipolar disorder were available,^{33,34} prior to the Phenomenology study data, there was little systematic study of the natural history of mania in prepubertal children and early adolescents.^{2,5,35-37}

To provide natural history data on childhood mania, PEA-BP subjects were comprehensively assessed using separate, direct parent and child interviews at baseline and at 6-, 12-, 18-, 24-, 36-, and 48-month follow-up points. At

Figure 2. Cumulative Recovery From Baseline Mania Episode and Cumulative Relapse After Recovery From Baseline Mania Episode for 86 Subjects With a Prepubertal and Early Adolescent Bipolar I Disorder Phenotype^a



^aAdapted with permission from Geller et al.⁵ Data are from each assessment point during a 4-year, natural history, prospective follow-up study.

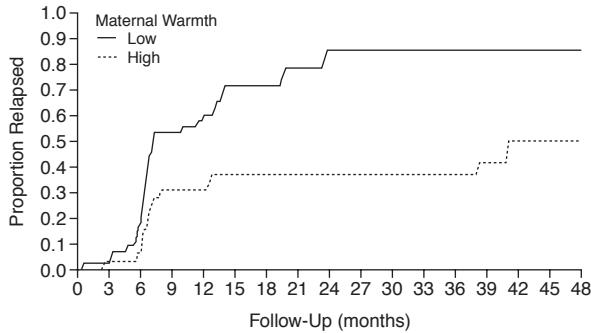
each assessment, onset and offset dates and severity of each symptom were obtained.⁵ Recovery and relapse definitions were adapted from Frank and colleagues.³⁸ Recovery was defined as 8 consecutive weeks without meeting DSM-IV criteria for mania or hypomania, and remission was defined as 2 to 7 weeks without meeting DSM-IV criteria for mania or hypomania. Relapse was defined as at least 2 consecutive weeks of meeting DSM-IV criteria for mania or hypomania with clinical impairment (CGAS score \leq 60). Eighty-six of the 93 PEA-BP subjects who were assessed at baseline were assessed at each follow-up timepoint during the 4-year follow-up (6, 12, 18, 24, 36, and 48 months), for a 4-year retention rate of 92.5%.⁵

Figure 2 shows cumulative rates of recovery from baseline episode and cumulative relapse after recovery from baseline episode at all follow-up assessment points. It can be noted that acutely at 6 months, only 14.0% had recovered from the baseline episode. It was not until the 18-month assessment that 55.8% of the PEA-BP sample had recovered. At the 4-year assessment, mean \pm SD time to recovery from baseline mania episode was 60.2 ± 47.5 weeks, and mean time to relapse after recovery was 40.4 ± 33.4 weeks. Overall, these recovery and relapse rates demonstrated a poor naturalistic prognosis.⁵

PEA-BP subjects experienced any bipolar diagnosis (i.e., mania, hypomania, MDD, minor depression, dysthymia, mixed mania) during $67.1 \pm 28.5\%$ of the 209.4 ± 3.3 weeks of follow-up. The percentage of prospective follow-up weeks spent with mania/hypomania (unipolar or mixed) was $56.9 \pm 28.8\%$, and the percentage spent with MDD, minor depression, or dysthymia (unipolar or mixed) was $47.1 \pm 30.4\%$.⁵

At baseline, PEA-BP subjects reported that the baseline episode had been ongoing for 3.6 ± 2.5 years.⁹ To test the reliability of this baseline history, PEA-BP subjects were examined for prospective episode duration by counting

Figure 3. Proportion of 86 Prepubertal and Early Adolescent Bipolar I Disorder Subjects Who Relapsed, by Low Versus High Maternal Warmth^a



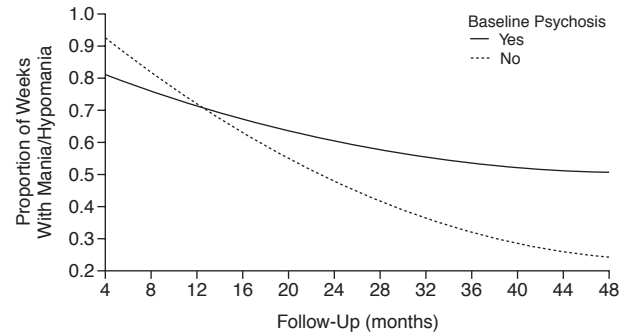
^aAdapted with permission from Geller et al.⁵ Seventy-five of the 86 prepubertal and early adolescent bipolar I disorder subjects with intake episode mania recovered from mania, and 48 subsequently relapsed to mania. Cox proportional hazard modeling for maternal warmth, controlling for gender, age, and mixed mania, was significant ($\chi^2 = 13.6$, $df = 1$, $p = .0002$). The hazard ratio was 3.7 (95% CI = 1.8 to 7.4). The Kaplan-Meier estimate of relapse was 50.3% (95% CI = 28.9% to 71.6%) for the 32 subjects with high maternal warmth and 85.9% (95% CI = 73.9% to 98.0%) for the 43 subjects with low maternal warmth.

the baseline day as the onset day of the manic episode. With this schema, subjects had a prospective episode duration of mania/hypomania of 79.2 ± 66.7 consecutive weeks from the baseline assessment date.⁵ These data provide prospective validation of long episodes of mania in PEA-BP.

Significant predictors of outcome at the 4-year assessment were maternal warmth and psychosis. Maternal warmth was examined because it is a concept akin to expressed emotion, which has been found to be a predictor of outcome in adults with bipolar disorder.³⁹⁻⁴¹ In addition, low maternal warmth was found to predict relapse after recovery at the 2-year follow-up assessment.³⁷ Maternal warmth was assessed with the Psychosocial Schedule for School-Age Children-Revised,⁴² administered separately to parents about their children and to children about themselves by experienced research nurses. As seen in Figure 3, Cox modeling showed that low maternal warmth significantly predicted earlier relapse to mania/hypomania after recovery ($\chi^2 = 13.6$, $df = 1$, $p = .0002$).⁵

Psychosis was examined as a potential predictor, because it had been found to be predictive in studies of adult bipolar disorder.^{34,43} Baseline psychosis predicted a greater proportion of weeks ill over the 4-year follow-up in PEA-BP subjects.⁵ In a mixed model, the interaction of time and baseline psychosis was significant ($F = 2.1$, $df = 11,77$; $p = .028$), indicating that subjects with baseline psychosis spent a greater proportion of weeks ill with mania/hypomania during prospective follow-up. Figure 4 shows that a quadratic model best fit the significant time-by-baseline psychosis interaction ($F = 12.2$, $df = 1,80$; $p = .0008$).⁵

Figure 4. Proportion of Weeks Ill With Mania/Hypomania During 4-Year Prospective Follow-Up of 86 Prepubertal and Early Adolescent Bipolar I Disorder Subjects With Intake Episode Mania by Presence or Absence of Baseline Psychosis^a



^aAdapted with permission from Geller et al.⁵ In a mixed model, controlling for gender, puberty status, and mixed mania, the proportion of weeks ill was significantly higher in the 51 subjects with baseline psychosis than in the 35 nonpsychotic subjects ($F = 12.2$, $df = 1,80$; $p = .0008$).

Comment on validation by longitudinal data. These data support validation by a stable natural history, the second area in the Robins and Guze¹⁸ schema, as subjects remained bipolar and did not develop schizophrenia, ADHD, or other psychiatric disorders during 4-year prospective follow-up. Maternal warmth (akin to expressed emotion) and psychosis as predictors of outcome in PEA-BP were similar to predictors of outcome in adult bipolar disorder studies.^{34,39-41,43}

Validation by Familial Aggregation: A Direct Interview Family Study of PEA-BP

Family, twin, and adoption studies demonstrate a genetic component of adult bipolar disorder.⁴⁴⁻⁴⁷ A recent twin study found heritability of 85% (95% CI = 0.73 to 0.93) using narrow concordance and 89% (95% CI = 0.61 to 1.00) using broad concordance.⁴⁶ By contrast, twin and adoption studies were not available for child bipolar disorder, and there was a paucity of family study data for child bipolar disorder.

To address the need for family studies of child bipolar disorder, the 268 probands in the Phenomenology study were probands in a NIMH-funded, direct interview family study. Methodology of this study met the Merikangas and coworkers⁴⁸ criteria for linkage studies. All probands and relatives over the age of 6 years were interviewed with the WASH-U-KSADS or the Schedule for Affective Disorders and Schizophrenia—Lifetime Bipolar Version, depending on the age of the informant, by experienced raters, different from those in the Phenomenology study. Raters were blinded to all diagnostic information about the probands.

At interim analysis of this ongoing family study, Geller⁴⁹ found that 34.1% of first-degree relatives of PEA-

Figure 5. Transmission of Brain-Derived Neurotrophic Factor (BDNF) Alleles in 53 Complete Biological Trios^a

		Non-Transmitted	
		Val	Met
Transmitted	Val	21	21
	Met	9	3

^aData from Geller et al.⁵⁰ Shaded cells indicate transmission of alleles from heterozygous parents. The BDNF Val66 allele was preferentially transmitted to subjects with a prepubertal and early adolescent bipolar I disorder phenotype (family-based association test: $\chi^2 = 6.0$, $df = 1$, $p = .014$; sib-transmission/disequilibrium test: $p = .014$).

BP probands had bipolar disorder. This rate of familial aggregation was significantly higher than rates in the ADHD (6.9%, $\chi^2 = 18.6$, $p < .0001$) and healthy control families (2.8%, $\chi^2 = 36.4$, $p < .0001$).⁴⁹ These data strongly supported that PEA-BP and ADHD were differentiated by significantly higher familial aggregation of bipolar disorder in the relatives of PEA-BP subjects. In addition, in the PEA-BP group, the mean age at onset of affected parents who had comorbid ADHD was significantly younger than that of affected parents without comorbid ADHD (mean \pm SD = 8.8 ± 4.6 vs. 17.5 ± 5.5 years, $t = 4.2$, $p = .0004$).

Comment on validation by family study of PEA-BP.

These family study data provide validation by the third Robins and Guze¹⁸ familial aggregation criterion.

Validation by Biological Markers:

A Molecular Genetic Study of PEA-BP

Molecular genetic validation of PEA-BP was examined by investigating the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism.⁵⁰ Reasons for studying the potential relationship between BDNF and child mania included the following. Two family-based association studies of adult probands with bipolar disorder reported preferential transmission of the BDNF Val66 allele (at amino acid position 66 in exon 1 of the BDNF gene on chromosome 11p13).^{51,52} Four case-control studies, however, were negative, i.e., did not find a greater prevalence of the Val66 allele in subjects with bipolar disorder.⁵³⁻⁵⁶ To determine if the positive family-based findings from samples with adult bipolar disorder could be replicated in PEA-BP, the BDNF Val66Met polymorphism was investigated.⁵⁰

Family-based transmission was examined in 53 complete, independent, biological trios (probands and both biological parents), among which there were 27 informative trios (that included 30 heterozygous parents).⁵⁰ Frequency of parental Val66 alleles was 79.2%. Proband alleles were

in Hardy-Weinberg equilibrium ($\chi^2 = 0.05$, $df = 2$, $p = .976$). Both transmission/disequilibrium test (TDT) analyses and simulations with Aspex sib-TDT showed preferential transmission of the BDNF Val66 allele (family-based association test: $\chi^2 = 6.0$, $df = 1$, $p = .014$; sib-TDT: $p = .014$) (Figure 5). The Val66 allele was transmitted 21 times and not transmitted 9 times. Exploratory analyses by prepubertal status (16 informative trios; 18 heterozygous parents) were also significant (family-based association test: $\chi^2 = 6.8$, $df = 1$, $p = .009$; sib-TDT: $p = .011$).⁵⁰

Comment on validation by molecular genetic study.

These BDNF findings provide only suggestive validation of the Robins and Guze¹⁸ fourth point, biological evidence. Therefore, further biological validation is warranted. The specificity of preferential transmission of the BDNF Val66 allele for PEA-BP is unclear, as one family-based study of child-onset obsessive-compulsive disorder also reported preferential transmission.⁵⁷ Future research may determine whether preferential transmission of the Val66 allele has implications for continuities between early- and late-onset bipolar disorder.

DISCUSSION

The PEA-BP phenotype was validated by unique symptoms (elation, grandiosity, flight of ideas/racing thoughts, decreased need for sleep) that did not overlap with those of ADHD (e.g., hyperactivity, distractibility).⁶ Longitudinal stability over 4-year prospective follow-up showed that the bipolar diagnosis was stable over time and that subjects did not develop exclusively non-bipolar diagnoses, such as ADHD or schizophrenia.⁵ Familial aggregation was demonstrated by a significantly higher proportion of first-degree relatives with bipolar disorder in PEA-BP versus ADHD or healthy controls.⁴⁹ Finally, a molecular genetic study showed family-based linkage disequilibrium of the BDNF Val66 allele with PEA-BP.⁵⁰ Thus, PEA-BP was validated by Robins and Guze¹⁸ criteria for establishing diagnostic validity in psychiatric illness.

The symptoms that best differentiated PEA-BP from ADHD were elation, grandiosity, flight of ideas/racing thoughts, and decreased need for sleep.⁶ Some major investigative groups in the field, however, have reported lower rates of these differentiating symptoms.⁵⁸ A number of methodological differences may account for differing symptom profiles. These differences included not interviewing children under the age of 12 years, not using an instrument with prepubertal mania-specific items, not using a severity scale, using lay raters rather than experienced clinicians, imposing no cardinal symptom requirement, and ascertainment for ADHD rather than for bipolar disorder.⁵⁸ Thus, methodological differences may account, in part, for the varying prevalence of mania symptoms between investigative groups.

It can be noted that early onset of PEA-BP, characterized by severe symptomatology and high familial aggregation, is consistent with the Childs and Scriver⁵⁹ paradigm of marked severity and higher familial aggregation with earlier onset for multiple medical illnesses. Determining reasons for this paradigm will require further investigation.

Continuities across the age span were supported by the following evidence. Both child- and adult-onset bipolar disorder occurred within the same families. In addition, the BDNF Val66 allele was in family-based linkage disequilibrium in the PEA-BP sample and in 2 family-based studies of adult bipolar disorder. Together, these family and molecular genetic data suggest that there may be common familial-genetic susceptibilities to bipolar disorder across the age span. Other evidence for continuity comes from predictors of outcome that included psychosis and maternal warmth in both the PEA-BP and adult bipolar disorder subjects.

Drug name: risperidone (Risperdal).

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