Further Evidence for Robust Familiality of Pediatric Bipolar I Disorder: Results From a Very Large Controlled Family Study of Pediatric Bipolar I Disorder and a Meta-Analysis

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ABSTRACT

Objective: To determine the risk for bipolar I disorder in first-degree relatives of children with DSM-IV bipolar I disorder via meta-analysis and expanded controlled study.

Data Sources and Extraction: Meta-Analysis. We searched the PubMed database for scientific articles published in the world literature in the English language through 2011. The keywords searched were bipolar disorder, first-degree relatives, family study, control. All online abstracts were reviewed and relevant full manuscripts were collected and reviewed. Citations were also examined for other potential relevant articles. We included only controlled family studies that examined rates of bipolar I disorder in all first-degree relatives (parents and siblings) of pediatric bipolar I probands and included only studies that had age- and sex-matched controls. Family history studies were excluded. Also excluded were studies that were not in English, did not report the rates of all first-degree relatives, and reported only bipolar spectrum rates. We also excluded family studies that included only adult probands. We conducted a meta-analysis of the 5 controlled family studies of pediatric bipolar I probands that met our search criteria using the random effects model of DerSimonian and Laird.

Method: Family Study. We greatly expanded our previous sample of DSM-IV bipolar I probands using structured diagnostic interviews. Our new study included 239 children satisfying full DSM-IV diagnostic criteria for bipolar I disorder (n = 687 first-degree relatives), 162 ADHD controls (without bipolar I disorder) probands (n = 511 first-degree relatives), and 136 healthy control (without ADHD or bipolar I disorder) probands (n = 411 first-degree relatives). We used the Kaplan-Meier cumulative failure function to calculate survival curves and cumulative, lifetime risk in relatives. Cox proportional hazard models were used to calculate the risk of bipolar I disorder in relatives.

Results: The pooled odds ratio for bipolar I disorder in relatives was estimated to be 6.96 (95% confidence interval [CI], 4.8 to 10.1). We also found first-degree relatives of bipolar I probands to be significantly more likely than first-degree relatives of both ADHD (hazards ratio [HR] = 2.73; 95% CI, 1.66 to 4.50; P < .001) and control probands (HR = 2.71; 1.57 to 4.66; P < .001) to have bipolar I disorder.

Conclusions: Our results document an increased familial risk for bipolar I disorder in relatives of pediatric probands with DSM-IV bipolar I disorder.

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METHOD

Meta Analysis

We searched the PubMed database for scientific articles published in the world literature in the English language. The keywords searched were bipolar disorder, first-degree relatives, family study, control. All online abstracts were reviewed and relevant full manuscripts were collected and reviewed. Citations were also examined for other potential relevant articles. We included only controlled family studies that examined rates of bipolar I disorder in all first-degree relatives (parents and siblings) of pediatric bipolar I probands and included only studies that had age- and sex-matched controls. Family history studies were excluded. Also excluded were studies that were not in English, did not report the rates of all first-degree relatives, and reported only bipolar spectrum rates. We also excluded family studies that included only adult probands.

Family Study

Subjects. This study represents a large expansion of our previous sample of 157 families of pediatric probands with bipolar I disorder diagnosis ascertained through NIMH grants. The expanded sample was possible through the support of a philanthropic grant to increase the sample size using the same methodology (all of these funding sources are noted in the acknowledgments section).

As previously described, families were recruited and assessed at the Clinical and Research Program in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital based on the presence of a diagnosis of bipolar I disorder in proband youth 6–17 years of age of both sexes. Comparators were youth with ADHD and controls without ADHD or bipolar disorder of similar age and sex along with their first-degree relatives. All studies used the same assessment methodology regardless of the disorder used to classify probands as cases. All study procedures were reviewed and approved by the subcommittee for human subjects of our institution. All subjects' parents or guardians signed written informed consent forms and children older than 7 years of age signed age-appropriate written assent forms.

For this study, we recruited an additional 82 probands and their 200 first-degree relatives for a total of 239 bipolar I probands and their 687 first-degree relatives. From 522 families participating in our case-control ADHD family studies, we randomly selected 162 nonbipolar ADHD (511 first-degree relatives) and 136 nonbipolar, non-ADHD control probands (411 first-degree relatives) so that the age and gender distribution was similar to that of the bipolar I probands. ADHD probands with comorbid bipolar disorder were not included in the present analyses.

Ascertainment method. Potential bipolar I probands were ascertained from our clinical service, referrals from local clinicians, or self-referral in response to advertisements. To avoid biasing our sample toward familial cases of bipolar disorder, all probands were ascertained blind to the diagnostic status of their relatives. Subjects were administered a phone screen, reviewing symptoms of DSM-IV bipolar I disorder and, if criteria were met, were scheduled for a face-to-face structured diagnostic interview in order to confirm the diagnosis of bipolar disorder using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) mania module. We have published data on the convergence of these clinical interviews with our structured interview diagnosis on the first 69 cases. We report 97% agreement between the structured interview and clinical diagnosis in this analysis of 69 children.

As previously reported, ADHD cases were identified from either a major academic medical center, where we selected ADHD subjects from referrals to a pediatric psychopharmacology program, or from a health maintenance organization, in which ADHD subjects were selected from pediatric clinic outpatients. Controls were ascertained from outpatients referred for routine physical examinations to pediatric medical clinics at each setting, identified from their computerized records as not having ADHD. Screening procedures were similar to those described for the recruitment of the bipolar probands with the exception that we queried about ADHD (and not bipolar disorder) in the initial telephone screening and each proband was not assessed clinically. No co-occurring disorders in probands or relatives were excluded.

Diagnostic procedures. Psychiatric assessments of subjects younger than 18 years were made with the K-SADS-E (epidemiologic version), and assessments of adult family members were made with the Structured Clinical Interview for DSM-IV (SCID), supplemented with modules from the K-SADS-E to cover childhood disorders. Diagnoses were based on independent interviews with mothers and direct interviews with children older than 12 years of age. Data were combined such that endorsement of a diagnosis by either report resulted in a positive diagnosis.

Interviews with both the K-SADS-E and SCID were conducted by extensively trained and supervised psychometricians with undergraduate degrees in psychology. This training involved several weeks of classroom instruction.
of interview mechanics, diagnostic criteria, and coding algorithms. They also observed interviews by experienced raters and clinicians and were observed while conducting interviews during the final training period. In addition, all diagnoses were reviewed by a sign-off committee of experienced board-certified child and adolescent psychiatrists or clinical psychologists. The committee members were blind to the subjects’ ascertainment status, ascertainment site, and data collected from other family members. We computed κ coefficients of agreement by having experienced clinicians diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 interviews, the median κ coefficient between raters and clinicians was 0.99. For individual diagnoses, the κ values were ADHD (0.88), conduct disorder (1.0), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (0.95), substance use disorder (1.0), and tics/Tourette’s (0.89). The median agreement between individual clinicians and the clinical review committee was 0.87 and for individual diagnoses was ADHD (1.0), conduct disorder (1.0), major depression (1.0), bipolar (0.78), separation anxiety (0.89), agoraphobia (0.80), panic (0.77), substance use disorder (1.0), and tics/Tourette’s (0.68).

Children and adolescents were diagnosed with bipolar I disorder according to DSM-IV criteria. The DSM-IV requires subjects to meet criterion A for a distinct period of extreme and persistently elevated, expansive or irritable mood lasting at least 1 week, plus criterion B, manifested by 3 (4 if the mood is irritable only) of 7 symptoms during the period of mood disturbance. To ensure that the B criterion symptoms were concurrent with A criterion mood disturbance, subjects were directed to focus on the worst or most impairing episode of mood disturbance while being assessed for the presence of the confirmatory B criterion symptoms. That is, the subject was asked to consider the time during which the screen was at its worst for the purpose of determining whether the remaining symptoms were also evident at the same time as the screening item. Also recorded was the onset of first episode, the number of episodes, offset of last episode, and total duration of illness. Any subject meeting criteria for bipolar II disorder or bipolar disorder not otherwise specified was not included in this study. To gauge a distinct episode, our interviewers asked for “a distinct period (of at least 1 week) of extreme and persistently elevated, expansive or irritable mood” and further required that the irritability endorsed in this module is “super” and “extreme.”

**Statistical analysis.** Our meta-analysis used the random effects model of DerSimonian and Laird\(^\text{16}\) as implemented in Stata 12.0. We used the I\(^2\) index to assess the heterogeneity of effect sizes.\(^\text{17}\) Its value lies between 0 and 100 and estimates the percentage of variation among effect sizes that can be attributed to heterogeneity. A significant\(^\text{12}\) suggests that the effect sizes analyzed are not estimating the same population effect size.

For our family study, differences in demographics and clinical characteristics were assessed using ANOVA for continuous outcomes, Pearson χ\(^2\) for binary outcomes, and Kruskal-Wallis for socioeconomic status (SES). The Kaplan-Meier cumulative failure function was used to calculate survival curves and cumulative lifetime risk in relatives. The cumulative failure function was calculated based on the ages at onset for the individual disorders for affected subjects and the age at the time of interview for unaffected subjects. The individual disorders were assessed during the structured diagnostic interview. Cox proportional hazard models were used to calculate the risk of bipolar disorder as well as other psychiatric disorders in relatives. All diagnoses reported represent lifetime rates. Data are expressed as mean ± SD unless otherwise specified. All tests were 2-tailed, and our α level was set at .05 for all analyses, unless otherwise noted. We calculated all statistics using STATA, version 12.0.
RESULTS

Our literature search identified 5 manuscripts that met our inclusion and exclusion criteria. The meta-analysis of these studies is presented in Figure 1. In the figure, the small dot gives the estimated odds ratio, the size of the square surrounding the dot is proportional to the sample size, and the horizontal line gives the 95% confidence interval. Odds ratios greater than 1 indicate greater transmission of bipolar I disorder compared to relatives of ADHD probands. As Figure 1 shows, all studies reported significant differences in the rates of bipolar I disorder in the first-degree relatives of pediatric bipolar I probands when compared with relatives of controls. The pooled odds ratio of risk for bipolar I disorder to relatives of pediatric bipolar I probands was estimated to be 6.96 (95% CI, 4.8 to 10.1). There was no statistically significant heterogeneity among studies ($I^2 = 0\%$, $P = .62$) suggesting that each study was estimating a common odds ratio.

Expanded Sample Family Study Results

Clinical and demographic characteristics are presented in Table 1. We found statistically significant differences in the ethnic and sociodemographic composition between groups. The control families had the highest SES and the bipolar I families had the most ethnic diversity. As a result, all subsequent analyses were adjusted for SES and ethnicity.

Risk for Bipolar I Disorder in First-Degree Relatives

The age-dependent cumulative, lifetime prevalence risk of bipolar I disorder in relatives is illustrated in Figure 2. First-degree relatives of bipolar I probands were significantly more likely than first-degree relatives of both ADHD (hazard ratio [HR] = 2.73; 95% confidence interval [CI], 1.66 to 4.50; $P < .001$) and control probands (HR = 2.71; 95% CI, 1.57 to 4.66; $P < .001$) to have bipolar I disorder (Figure 2). In contrast, relatives of ADHD probands were not at an increased risk for bipolar I disorder compared to relatives of control probands (HR = 0.99; 95% CI, 0.51 to 1.92; $P = .98$). These findings remained significant after controlling for psychiatric comorbidity in probands (disruptive behavior disorders/antisocial personality disorder, major depression, multiple ($\geq 2$) anxiety disorders, and substance [drug or alcohol] use disorders).

DISCUSSION

To the best of our knowledge, this study represents the largest controlled, blinded, direct interview family study of pediatric bipolar disorder to date. This new expanded sample increased by over 50% ($N = 239$) our previous report of 157

| Table 1. Clinical and Demographic Characteristics (N = 2,146)$^a$ |
|-----------------|-----------------|-----------------|-----------------|
| **Proband**     | **Bipolar I**   | **ADHD**        | **Control**     |
| **Families**    | **Families**    | **Families**    | **Statistic**   |
| **Age, y**      | $n = 239$       | $n = 162$       | $n = 136$       |
| **Gender, n (%)** | **Male**       | **Male**         | **Male**         |
| **Past GAF score** | **Current GAF score** | **Current GAF score** | **Chance** |
| **Parents**     | $n = 444$       | $n = 323$       | $n = 269$       |
| **Age, y**      | $n = 243$       | $n = 188$       | $n = 142$       |
| **Race/ethnicity, n (%)** | **White** | **White** | **White** |
| **Siblings**    | $n = 926$       | $n = 673$       | $n = 547$       |

$a$Values expressed as mean ± SD unless otherwise noted.

$^b$For socioeconomic status, 1 = most advantaged, 5 = most disadvantaged.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAF = Global Assessment of Functioning.

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bipolar I probands. In this much expanded sample of pediatric bipolar I probands, we replicated our initial findings documenting that rates of bipolar I disorder were significantly greater in the first-degree relatives of pediatric probands with bipolar I disorder than in the first-degree relatives of ADHD and control probands. These results, coupled with those of the meta-analysis of the extant literature, provide strong support for the familiality of bipolar I disorder, which provides further support for the validity of pediatric bipolar I disorder as a diagnostic entity.

As shown in the meta-analysis, our findings documenting high level of familiality of pediatric bipolar I disorder are consistent with the prior pediatric literature on the subject. They are also consistent with family studies of adult bipolar I probands that document high levels of heritability of bipolar disorder in adults that range from 59%–87%.22

In our meta-analysis, the studies that met our criteria (direct interview, controlled, all first-degree relatives included) reported odd ratios indicating that the risk for bipolar I disorder to relatives of bipolar I probands is 4 to 14 times greater than the risk to relatives of nonbipolar probands. In addition to finding significant familial transmission in all prior studies, we found no evidence of heterogeneity in the magnitude of familial transmission. This finding can be seen in Figure 1, which shows that the confidence intervals for the odds ratios overlap among the different studies. This lack of differences between studies suggests that the familial transmission of bipolar disorder cannot be accounted for by the diagnostic traditions of a single group of investigators. While all research groups employ standardized structured diagnostic techniques, they differ in the interviews they employ, which may lead to differences in sample characteristics. For example, there are differing approaches to diagnosing bipolar disorder in the presence of ADHD23 due to concerns about overlapping symptoms and the use of irritability as a mood criterion for diagnosing bipolar I disorder in youth.24

As in our previous report, the familial transmission of bipolar I disorder in this expanded sample was statistically significant even when controlling for psychiatric comorbidity in the probands. Aside from the Geller et al21 study, which controlled for the presence of ADHD, other family studies did not report findings adjusted for psychiatric comorbidity. This finding further supports the hypothesis that bipolar I disorder is not an alternate expression of a different disorder. The lack of difference between the ADHD and control families in the prevalence of bipolar I disorder is consistent with our prior work suggesting that, in the absence of comorbid bipolar disorder, ADHD does not share susceptibility genes with bipolar disorder.20,25,26

Our family study results and those of the meta-analysis add to an emerging literature over the last 2 decades that provides compelling support for the validity of pediatric bipolar disorder as a diagnostic entity. Clinical studies have documented the unique diagnostic features associated with this disorder across different clinical and research centers in this country and abroad, reporting high levels of severe and persistent irritability and associated morbidity and disability.3,27–30 Large-scale follow-up studies have documented persistence of pediatric bipolar disorder into adolescent and young adult years.30–32 A recent comprehensive review of the extant pharmacologic literature of pediatric bipolar disorder treatments comprises close to 3,000 bipolar youth who had participated in clinical trials. That review documented the safety and efficacy of antimanic treatments for pediatric bipolar disorders.33 Emerging neuroimaging and genetic studies have also begun to describe neurobiological correlates of pediatric bipolar disorder as well.34–38

Our findings should be considered in the context of methodological limitations. Although we used lay interviewers with undergraduate degrees in psychology, rather than clinician raters, these raters were extensively trained to high levels of interrater reliability. Although we did not administer structured diagnostic interviews directly to children younger than age 12, the diagnosis of bipolar I disorder in probands was corroborated by clinical assessment by an expert child and adolescent psychiatrist.13 Although we relied for comparison on existing samples of ADHD and non-ADHD families, these were recruited from the same catchment area and were assessed using the same assessment methods. Because this sample was clinically referred and primarily white, these results may not generalize to nonreferred children or to families of other ethnic groups.

Despite these limitations, results from this large family study and meta-analysis provide compelling evidence for the familiality of pediatric bipolar I disorder and, thus, robust support for the validity of pediatric onset bipolar I disorder as a diagnostic entity.

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Author contributions: Dr Wozniak had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Wozniak substantially contributed to the conception and design, drafting, critical revision of the intellectual content, supervision, administrative/technical/material support, and funding for this manuscript. Dr Faraone substantially contributed to the conception and design, drafting, critical revision of the intellectual content, statistical analysis, and funding for this manuscript. Ms Martelon substantially contributed to the data analysis and interpretation, drafting, and statistical analysis for this manuscript. Ms McKillop substantially contributed to the data analysis and interpretation, drafting, and administrative/technical/material support for this manuscript. Dr Biederman substantially contributed to the conception and design, drafting, critical revision of the intellectual content, administrative/technical/material support, supervision, and funding for this manuscript.

Potential conflicts of interest: In 2011, Dr Wozniak received research support from McNeil and Shire. In the past, she has received research support, consultation fees or speaker’s fees from: Eli Lilly, Janssen, Johnson and Johnson, McNeil, Pfizer, Pfizer, Shire. She is the author of the book Is Your Child Bipolar, published May 2009, Bantam Books. In 2011, her spouse John Winkelman MD, PhD received consultation fees from Pfizer, UCB, Zeo, and Sunovion. He received research support from GlaxoSmithKline. In the past, he has received research support, consultation fees or speaker’s fees from: Axon Laboratories, Boehringer-Ingelheim, Covance, Cephalon, Eli Lilly, GlaxoSmithKline, Impax, Jazz Pharmaceuticals, Janssen, Medtronic, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Sepracor, Sunovian, Takeda, UCB (Schwarz) Pharma, Wyeth, Zeo. In the past year, Dr Faraone received consulting income and research support from Shire and Alcobra and research support from the National Institutes of Health (NIH). In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr Faraone received royalties from books published by Guilford Press: Straight Talk About Your Child’s Mental Health and Oxford University Press: Schizophrenia: The Facts. Dr Biederman is currently receiving research support from the following sources: Elminda, Janssen, McNeil, and Shire. In 2011, Dr Biederman gave a single unpaid talk for Juste Pharmaceutical Spain, received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course, and received an honorarium for presenting at an international scientific conference on ADHD. He also received an honorarium from Cambridge University Press for a chapter publication. Dr Biederman received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Eli Lilly, Shire, and AstraZeneca; these royalties are paid to the Department of Psychiatry at MGH. In 2010, Dr Biederman received a speaker’s fee for a single talk given at Fundación Dr.Manuel Camelo A.C. in Monterrey Mexico. Dr Biederman provided single consultations for Shionogi Pharma Inc and Cipher Pharmaceuticals Inc; the honoraria for these consultations were paid to the Department of Psychiatry at the MGH. Dr Biederman received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course. In previous years, Dr Biederman received research support, consultation fees, or speaker’s fees for/from the following additional sources: Abbott, Alza, AstraZeneca, Boston University, Bristol Myers Squibb, Celltech, Cephalon, Eli Lilly, Esai, Fundacion Areces (Spain), Forest, Glaxo, Gliatech, Hastings Center, Janssen, McNeil, Medice Pharmaceuticals (Germany), Merck, MMC Pediatric, NARSAD, NIDA, New River, NICHD, NIMH, Novartis, Noven, NeuroseaPharma, Onatras, Pfizer, Pharmacia, Phase IV Communications, Physicians Academy, The Prechter Foundation, Quanta Communications, Reed Exhibitions, Shire, the Spanish Child Psychiatry Association, The Stanley Foundation, UCB Pharma Inc., Veritas, and Wyeth. Ms Martelon and McKillop report no conflict of interest.

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REFERENCES


*Editor’s Note:* We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.