Meta-Analysis of Epidemiologic Studies of Pediatric Bipolar Disorder

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ABSTRACT

Objective: Meta-analyze all published epidemiologic studies reporting pediatric mania or bipolar disorder to investigate whether pediatric bipolar disorder is becoming more prevalent and whether rates vary significantly by country.

Data Sources: Searches of PubMed and PsycInfo were conducted through the spring of 2010 using the following search terms: *child*, *pediatric*, *young*, *adolescent*, *epidemiology*, *prevalence*, *bipolar*, *mania*, *suicide*, and *psychiatric*. We also manually reviewed references in recent reviews of epidemiology of bipolar disorder.

Study Selection: All studies reporting rates for mania or hypomania in community epidemiologic samples with participants up to 21 years of age.

Data Extraction: All articles were coded to extract relevant variables. Prevalence rates were calculated from reported number of cases with bipolar disorders, then logit transformed. Twelve studies were included, enrolling 16,222 youths between the ages of 7 and 21 years during a period from 1985 to 2007. Six samples were from the United States; 6 were from other countries (the Netherlands, the United Kingdom, Spain, Mexico, Ireland, and New Zealand).

Results: The overall rate of bipolar disorder was 1.8% (95% CI, 1.1%–3.0%). There was no significant difference in the mean rates between US and non-US studies, but the US studies had a wider range of rates. The highest estimates came from studies that used broad definitions and included bipolar disorder not otherwise specified. Year of enrollment was negatively correlated with prevalence ($r = -0.04$) and remained nonsignificant when controlling for study methodological differences.

Conclusions: Mean rates of bipolar disorder were higher than commonly acknowledged and not significantly different in US compared to non-US samples, nor was there evidence of an increase in rates of bipolar disorder in the community over time. Differences in diagnostic criteria were a main driver of different rates across studies.

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Pediatric bipolar disorder has drawn increasing attention in recent years.[1] Accumulating research data indicate that bipolar disorder can occur both in prepubertal children and in adolescents.[2] Bipolar disorder is known to present significant health consequences for both individuals and society, with high rates of suicidality and a completion rate as much as 20 times higher than among other suicide attempters.[3,4] Additionally, early onset bipolar disorder may result in a worse long-term prognosis, including elevated rates of comorbid diagnoses and increased risk of suicide.[5–8] It is important to have an accurate picture of the prevalence of bipolar disorder in young people in order to properly allocate resources for its investigation and treatment.

The United States is widely perceived as having higher rates of pediatric bipolar disorder than other countries, but the cause of this disparity has not been explored. Differences in international rates of disorder may be due to the diagnostic criteria employed or to other clinical disparities, such as the way in which different symptoms are interpreted.[9,10] Studies have demonstrated large international differences in the labeling of case vignettes as bipolar or not[10] as well as in the manic symptom severity ratings assigned by psychiatrists to the same videotaped interviews.[11] There is debate about whether this disorder is becoming more prevalent in youth and about the perceived differences in prevalence rates internationally. Although rates of clinical diagnosis have increased 40-fold in the past decade,[12] this rise could reflect increasing awareness of bipolar disorder and better accessibility to health care, rather than increasing disease prevalence. Overall rates of psychiatric disorder in children have remained relatively constant since the 1950s.[13] Conclusions cannot currently be drawn regarding alleged increases in pediatric bipolar disorder rates or differences in rates of pediatric bipolar disorder internationally, although such differences clearly would have significant public health complications if accurate.

Epidemiologic studies are an important way by which disease rates can be disentangled from treatment seeking, service utilization, barriers to treatment, and changes in clinical practice (whether due to reimbursement or training). In order to ascertain whether bipolar disorder is becoming more prevalent among young people and whether rates vary by geographic location, we undertook this meta-analysis of published epidemiologic data on childhood psychiatric disorders. To our knowledge, this is the first meta-analysis of epidemiologic studies of pediatric bipolar disorder.

The primary objective was to analyze all available pediatric epidemiologic studies that assessed mania/bipolar in order to determine the mean rate of bipolar spectrum disorders in community youth samples. As a second goal, we tested whether rates based on samples from the United States were significantly different from rates in the rest of the world. Third, we tested whether there was evidence of a secular trend for increasing rates of pediatric bipolar disorder in community samples coinciding with the dramatic increase in the rates of clinical diagnoses. Next, we explored potential explanations for differences in rates, including diagnostic criteria (version of and adherence to *DSM*/*ICD*); the quality of reporting of study results, which was determined by using a set of guidelines for evaluating epidemiologic studies (the Strengthening

Clinical Points

- The prevalence of pediatric bipolar disorder is similar to current prevalence estimates of bipolar disorder in adults.
- The prevalence of pediatric bipolar disorder is not different in the United States, relative to other countries.
- The prevalence of pediatric bipolar disorder is not increasing over time in the community, even as it is being diagnosed more commonly in clinical settings.

the Reporting of Observational Studies in Epidemiology [STROBE] guidelines)[14]; range of participant ages; the type of interview used (Kiddie Schedule for Affective Disorders and Schizophrenia [K-SADS] or not); quality of study design with regard to assessment of bipolar disorder[15]; whether diagnostic interviews included the parent alone, child alone, or both; and whether the rater was a clinician. Finally, we tested whether any change in rate of diagnosis over time remained significant after adjusting for these study design factors.

METHOD

Search Strategy

A comprehensive search was conducted and updated in the spring of 2010 through PubMed and PsycInfo using combinations of the following search terms: *child*, *pediatric*, *young*, *adolescent*, *epidemiology*, *prevalence*, *bipolar*, *mania*, *suicide*, and *psychiatric*. Reference lists from each article were assessed for additional citations of interest. We also reviewed all epidemiologic studies described in Goodwin and Jamison,[16] along with the studies included in a recent review of epidemiologic studies.[17] In order to include as much data as possible, exclusionary criteria were minimal. Although bipolar disorder did not have to be the primary focus of a study for it to be included, a study did have to assess for symptoms of bipolar disorder specifically. As such, only studies that used diagnostic tools that systematically measure hypomanic or manic symptoms were included. Clinical samples or samples enriched for the study of specific disorders were excluded (20 studies) because the design might result in biased rates of pediatric bipolar disorder.[14] Additionally, because the goal was to report on early onset bipolar disorder, those studies that included both children and adults but did not report prevalence rates separately by age group were not included (13 studies). We requested, in the fall of 2009, raw data for studies that could not otherwise be included but did not receive any by the time of submission. Approximately 2,000 abstracts were evaluated; 150 were identified as candidate articles, based on the study parameters, and 12 in total contained the information necessary for inclusion.

Article Coding

We developed an article coding spreadsheet following recommendations from Lipsey and Wilson.[18] To better accommodate pediatric epidemiologic data, the spreadsheet was revised twice based on discussions following pilot coding of sample articles and published guidelines.[14]

Articles were coded on a range of variables, including disorder prevalence rates, method of diagnosis, diagnostic criteria, informant(s), geographic location, comorbid diagnoses, and demographic information (eAppendix 1 at PSYCHIATRIST.COM). We employed 2 methods of quality scoring, 1 for study design and 1 for study reporting (the STROBE criteria[14]), to determine whether these characteristics affect reported prevalence rates. Two raters, a resident in psychiatry and a doctoral student in clinical psychology, coded each study. All authors discussed any discrepancies to reach consensus. Reliability was calculated using κ for absolute agreement and intraclass correlation for random effects and absolute agreement (the most stringent model); values ranged from 0.86 to 1.00, with a median of 1.00.

Meta-Analysis

The first aim of the meta-analysis was to establish a mean rate of pediatric bipolar disorder in community epidemiologic samples. Prevalence rates were recalculated from raw N values. Rates were calculated for bipolar I disorder, bipolar I and II disorders, and for the full spectrum of bipolar disorders for each study with available data. The rates for bipolar I disorder were likely to be the most consistent across studies, given clearer criteria. However, it is important to include the spectrum rates in order to determine whether broad-spectrum cases are likely to convert to bipolar I or II disorder with age.[19] We used the logit transformation on the prevalence rates before calculating inverse variance-weighted averages, both of which were recommended by experts to emphasize estimates with greater precision.[18] Hedge's *Q* statistic tested whether differences across studies could be attributed to sampling error; and follow-up tests investigated whether measured study characteristics accounted for differences in findings.[18] Meta-analytic regression using restricted maximum likelihood estimation of inverse-variance–weighted random effects was used to evaluate the association between prevalence rate and year of data collection, and US versus international samples. A final set of analyses examined other potential predictors of between-study differences by estimating the variance that was shared or unique across sets of predictors.

RESULTS

The 12 studies included in this meta-analysis enrolled a total of 16,222 youths between the ages of 7 and 21 years during a period from 1985 to 2007. Six of the samples were from the United States; 6 were from other countries (the Netherlands, the United Kingdom, Spain, Mexico, Ireland, and New Zealand) (Table 1, eAppendix 2).[20–31]

What Is the Mean Prevalence Rate of Bipolar Disorder?

The mean prevalence rate of pediatric bipolar spectrum disorders was 1.8 (95% CI, 1.1%–3.0%). There was

Table 1. Studies of Pediatric Bipolar Disorder Included in the Meta-Analysis

Source	Rate of Bipolar Spectrum Disorders, %	Location	Year Collected	Diagnostic Criteria	Subtypes Included	Bipolar Disorder NOS Criteria	Total N	Diagnostic Method	Rater Degree	Informant	Participant Age, Range, y	Prevalence Period
Non-US samples												
Kim-Cohen et al,[20] 2003	1.8	New Zealand	1985	*DSM-III*	Bipolar I disorder	…	973	DISC	MD/PhD	Parent and youth	11–15	12-mo
Verhulst et al,[21] 1997	2.8	The Netherlands	1993	*DSM-III-R*	Bipolar I and II disorders	…	780	DISC	BA	Parent and youth	13–18	6-mo
Canals et al,[22] 1997	2.4	Spain	1994	*ICD-10*	Bipolar disorder NOS	Hypomania alone	290	SCAN	MD/PhD	Youth	17–18	Point
Lynch et al,[23] 2006	0.0	Ireland	2002	*DSM-IV*	Bipolar I and II disorders, cyclothymic disorder, NOS	*DSM-IV*	723	K-SADS	MD/PhD	Parent and youth	12–15	Lifetime
Benjet et al,[24] 2009	2.5	Mexico City	2005	*DSM-IV*	Bipolar I and II disorders	…	3,005	CIDI	BA	Youth	12–17	12-mo
Stringaris et al,[31] 2010	1.2	United Kingdom	2007	*DSM-IV*	Bipolar I and II disorders, NOS	*DSM-IV*, broad	5,326	DAWBA	BA	Parent and youth[a]	8–19	Lifetime
US samples												
Kashani et al,[25] 1987	0.7	Missouri	1986	*DSM-III*[b]	Mania	…	150	DICA	Master's	Parent and youth	14–16	Lifetime
Lewinsohn et al,[26] 1995	6.7	Oregon	1988	*DSM-III-R*[b]	Bipolar I and II disorders, cyclothymic disorder, NOS	*DSM-III-R*/*DSM-IV*, core	1,709	K-SADS	BA	Youth	14–18	Lifetime
Costello et al,[27] 1996	0.1	Great Smoky Mountains	1994	*DSM-III-R*	Mania, hypomania	*DSM-III-R*	1,015	CAPA	BA	Parent and youth	9–13	3-mo
Andrade et al,[28] 2006	1.5	Hawaii	1994	*DSM-III-R*	Mania, hypomania	*DSM-III-R*	619	DISC	BA	Youth	13–21	Lifetime
Gould et al,[29] 1998	1.3	United States, MECA	1996	*DSM-III-R*	Mania	…	1,285	DISC	BA	Parent and youth	7–18	6-mo
Kessler et al,[30] 2009	6.3	United States, NCS-A	2003	*DSM-IV*[b]	Bipolar I and II disorders, NOS	*DSM-IV*, broad	347	K-SADS	MD/PhD	Parent and youth	13–17	Lifetime

[a]The parents of 8–19-year-olds and the 11–19-year-olds themselves were interviewed.
[b]Criteria were modified from the published version for study purposes.
Abbreviations: CAPA = The Child and Adolescent Psychiatric Assessment, CIDI = World Mental Health Composite International Diagnostic Interview, DAWBA = The Development and Well-Being Assessment, DICA = Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents-Parent Version, DISC = Diagnostic Interview Schedule for Children, K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia, MECA = Methods for the Epidemiology of Child and Adolescent Mental Disorders, NCS-A = National Comorbidity Survey Replication Adolescent Supplement, NOS = not otherwise specified, SCAN = Schedules for Clinical Assessment in Neuropsychiatry.

significant ($P < .0005$) heterogeneity across the studies, indicating the importance of examining potential explanatory variables. Rates for bipolar I disorder, which is generally diagnosed by using more consistent criteria, fell within a more narrow range (mean = 1.2%; 95% CI, 0.7%–1.9%). The rate excluding subthreshold cases that did not meet strict *DSM* criteria was also 1.8%, (95% CI, 1.2%–2.7%). Rates tended to be higher in samples with older participants: an estimate limited to studies with participants 12 years and older yielded a prevalence rate of 2.7% (95% CI, 1.6%–4.6%).

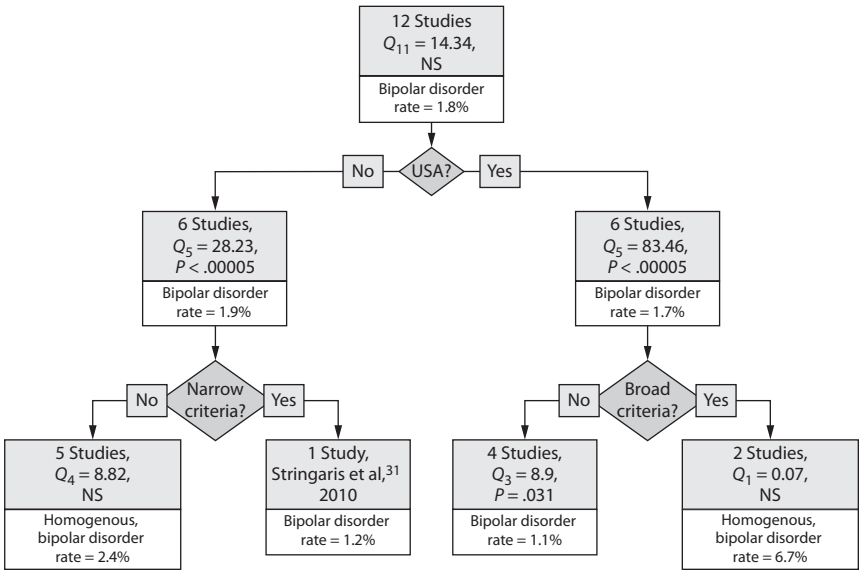
Is the Rate of Pediatric Bipolar Disorder Higher in the United States Than in the Rest of the World?

There was no significant difference in the mean rate between the 6 studies from the United States (1.7% prevalence) versus the 6 studies from outside the United States (1.9%) (Figure 1). However, there was significant heterogeneity between the studies within each subset. The majority of the difference was attributable to whether the US studies included subthreshold bipolar disorder and whether the non-US studies used a narrower definition of bipolar disorder.

Has the Rate of Pediatric Bipolar Disorder Increased in the Community Over Time?

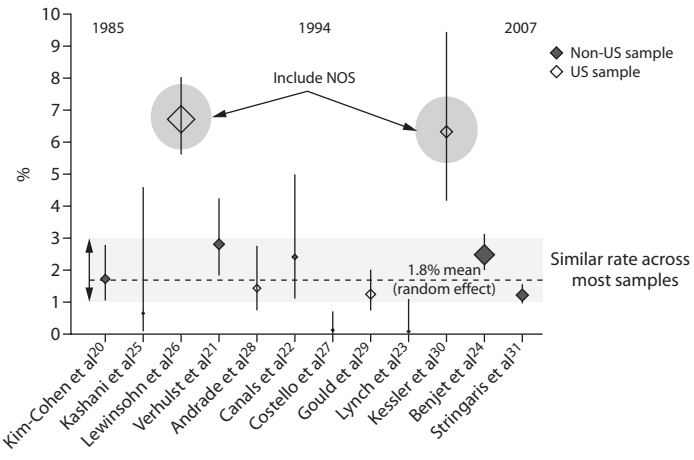
There was no relation between the year of data collection and prevalence rate ($r = -0.04$, $P > .05$), a finding that suggests that, unlike the rate of clinical diagnoses, the prevalence of bipolar disorder in the community is not increasing (Figure 2).

Figure 1. Difference Between Some US and International Rates Driven by Some Studies Using Broader-Than-*DSM* Criteria, and Not Underlying Base Rates[a]



[a]Hedges' Q statistic tests whether the differences between studies are larger than could be attributed to sampling error.
Abbreviation: NS=nonsignificant.

Figure 2. Weighted Bipolar Prevalence Rates Sorted by Year of Data Collection and Denoting US Versus International Samples[a]



[a]The size of the diamond corresponds with sample size.

Do Any Other Study Characteristics Explain Differences in Pediatric Bipolar Disorder Rates?

Several study features were associated with prevalence estimates: minimum age enrolled (r = 0.44), whether diagnoses were based on a K-SADS interview (r = 0.67), and whether the study employed strict *DSM* criteria (r = –0.36). The use of K-SADS was associated with significant variability; the 3 studies using the K-SADS included the lowest and 2 highest estimates (Q_2 = 9.89, P = .0071).

Meta-regression evaluated the unique contribution of the design variables to differences in bipolar rates. Study characteristics accounted for 96% of the variance in prevalence estimates. Even after adjusting for other factors, we found that participant age was a significant predictor of prevalence, resulting in change in R^2 of over 10% (P < .005). Additionally, the use of strict *DSM* criteria, rather than modified, study-specific criteria, was a significant predictor (β = –1.05, P < .00001). Finally, after controlling for minimum enrollment age and use of strict versus broad *DSM*/*ICD* criteria, we found that the quality of study reporting also made a significant contribution to prediction. The other variables included were not significant (Table 2).

DISCUSSION

The goals of the present study were to synthesize the rates of pediatric bipolar disorder from published epidemiologic studies, to test whether the rate observed in the United States was significantly different from that observed in the rest of the world, to see whether the rate of prevalence has increased over time in the community, and to examine the extent to which methodological factors could account for differences in rates across studies. The key finding that bipolar disorder occurs in 1.8% of youths in community samples is plausible given recent rates ranging from 3.5% to 6% in young adult samples[32] and current data about the frequency of childhood and adolescent onset in adult cases of bipolar disorder.[5] Though these results reflect the best possible estimate given the data available, the 12 studies were heterogeneous not only in prevalence rates reported but also in methodology and sample as well.

Table 2. Correlations and Regression Weights for Potential Predictors of Differences in Rates of Bipolar Across Studies[a]

Predictor	*r*	*P*	β	*P*
A priori predictors				
Year of primary data collection	−0.04	NS	−0.12	.2837
Study located in United States?	0.04	NS	−0.26	.0971
Significant predictors in final regression				
Were strict *DSM*/*ICD* diagnostic criteria used?	−0.36	NS	−1.05	.0000
STROBE reporting quality	0.12	NS	0.86	.0000
Youngest age enrolled	0.44	<.00005	0.35	.0046
Other potential predictors examined				
K-SADS interview?	0.67	<.00005		
Oldest age enrolled	0.44	NS		
Kowatch Bipolar Study Quality Rating	0.15	NS		
ICD-10 criteria?	0.09	NS		
DSM-IV criteria?	0.06	NS		
Rater clinical degree?	0.03	NS		
DSM-III-R criteria?	−0.03	NS		
DSM-III criteria?	−0.12	NS		
Both parent and child interviewed	−0.28	NS		

[a]All values based on weighted restricted maximum likelihood estimation.
Abbreviations: *ICD-10* = *International Classification of Diseases, Tenth Revision,* K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia, NS = not significant, STROBE = Strengthening the Reporting of Observational Studies in Epidemiology.

Results do not align with the theory that rates of bipolar disorder are higher in the United States than in other countries. There is a perception that pediatric bipolar disorder is an "American problem,"[9] but present findings indicate no difference in the rates in the United States versus the rest of the world. Furthermore, higher rates reported in some US samples could be attributed entirely to a tendency of the researchers to include bipolar not otherwise specified (NOS) and use broader, non-*DSM* definitions of bipolar disorder. Removing those studies that use broad definitions from the prevalence rate analyses resulted in essentially identical rates for both US and non-US samples (see Figure 1). The disparity introduced by inconsistent criteria underscores one of the fundamental challenges in pediatric bipolar disorder research.[2,26,30,33]

The year of enrollment was of great interest, given the recent rise in clinical diagnoses of pediatric bipolar disorder. The correlation (nonsignificant) between year of enrollment and prevalence of pediatric bipolar disorder was negative and failed to support the commonly held belief that the rise in rates of clinical bipolar diagnoses is attributable to an actual increase in the community prevalence of pediatric bipolar disorder. Interestingly, although rates of clinical diagnosis have increased, the reported incidence statistic of approximately 1.0%[12] still falls short of the estimate provided by epidemiologic data. This finding supports the theory that pediatric bipolar disorder is most likely both underdiagnosed and overdiagnosed in different settings.[34,35]

Participant age made a unique contribution to the prevalence rate, even after controlling for all other design features. Although, historically, bipolar disorder has been considered an adult disorder, its presence in prepubescent children is now widely accepted. Unfortunately, the ages included in most of the studies reported here reflect this now-outdated perception. As such, the results may appear to be more representative of the rate of bipolar disorder in adolescents. Studies with a younger minimum age had lower prevalence estimates, those with more adolescents tended to have higher prevalence estimates. Although findings indicate that bipolar disorder can have onset in childhood, it appears to be much more likely in adolescence.[5,36,37]

Studies that used the K-SADS produced the widest estimates of disorder rate. Differences in rater training and in calibration of what behaviors might be considered hypomanic or manic could be influential in semistructured interviews such as the K-SADS. Previous studies have found that the diagnosis of bipolar disorder is highly susceptible to differences in symptom interpretation by the rater.

Limitations of the Available Pediatric Epidemiologic Literature

Although there are 4 subtypes of bipolar disorder for characterizing patients (bipolar I disorder, bipolar II disorder, cyclothymia, and bipolar disorder NOS), the majority of studies reported only bipolar I disorder or lumped all bipolar spectrum disorders together. This failure to fully explore the entire range of bipolar spectrum disorders is a shortcoming in the field.[38] The epidemiologic studies that have assessed bipolar NOS have found that it is both prevalent and impairing.[19,26,30,39] Additionally, cyclothymic and NOS cases, which are often combined under 1 "subthreshold" label, may represent the best opportunity for preventive intervention.[40]

Two studies[26,30] included cases that did not meet severity and/or duration criteria but were symptomatic. For example, 1 study used the following "broad criteria" for pediatric bipolar disorder:

> The reduction in number of required symptoms for a determination of subthreshold hypomania was confined to two criterion B symptoms (compared with the *DSM-IV* requirement of 3 or 4 if the mood is irritable) to retain the core features of hypomania in the subthreshold definition. Recurrent hypomania and subthreshold hypomania absent MDE [major depressive episode] were included in the definition because hypomania in the absence of MDE is part of the *DSM-IV* definition of bipolar disorder not otherwise specified.[30(p394)]

Similarly, another broad definition of bipolar disorder was as follows: "Subjects who reported experiencing an abnormally and persistently elevated, expansive or irritable mood, but never met criteria for bipolar disorder."[26(p456)] These different operational definitions contributed to higher estimates of bipolar disorder rates. It remains for clinical validation studies and longitudinal follow-up to determine whether persons meeting these broader definitions have a similar etiology and course to those with presentations satisfying more narrow criteria.

The use of modified *ICD* or *DSM* criteria makes the results particularly difficult to interpret broadly. Specifically, the study reported by Stringaris et al[31] used a narrow

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definition of bipolar disorder, contingent on elated mood. Participants were not asked any additional mania-related questions if their parents did not endorse the following description:

> Some young people have episodes of going abnormally high. During these episodes they can be unusually cheerful, full of energy, speeded up, talking fast, doing a lot, joking around, and needing less sleep. These episodes stand out because the young person is different from their normal self.[31(p32)]

Irritability is often considered a key characteristic of pediatric mania[15]; focusing on other symptoms of mania, to the exclusion of irritability, most likely contributed to the low rate of bipolar disorder in this sample.

The fact that few studies included youth under the age of 12 years limits our knowledge of the rate of bipolar disorder in children. Diagnoses in prepubescent children are particularly controversial; future studies including youth as young as preschool-aged, will provide a more complete picture of the rate of bipolar disorder across development. Similarly, no study stratified its sample by pubertal status. Given questions regarding the role of puberty in the onset of mood disorder, the assessment of participants' pubertal stage would contribute valuable information to the field.

Limitations of the Meta-Analysis and Future Directions

Limitations of the present study include the rarity with which epidemiologic data on pediatric bipolar disorder have been reported, restricting the conclusions that can be drawn. Out of nearly 150 articles on the epidemiology of childhood psychiatric disorders from the past 50 years, only 12 included specific information on mania and/or bipolar disorder. Additionally, incomplete reporting of diagnostic criteria and comorbid disorders made it impossible to assess differences between the "narrow" (elated or grandiose), the intermediate *DSM* phenotype, and the broad spectrum model of bipolar disorder[41] or to explore the impact of frequently comorbid disorders, such as attention-deficit/hyperactivity disorder, on findings.

Future epidemiologic studies should assess manic symptoms more systematically and in a way consistent with current clinical nosology. Moreover, longitudinal studies will be pivotal—particularly those that assess for the full spectrum of bipolar subtypes using standard tools, in order to facilitate replication and evaluate long-term stability and course. Present data indicate that pediatric bipolar disorder occurs at a higher rate than often taught and at similar rates in US and non-US samples. Clinicians should assess for the possibility of bipolar disorder, yet also be mindful of the fact that the rising rate of clinical diagnosis is not linked to an observed increase in rates of bipolarity in community samples. Although clinical diagnoses of bipolar disorder in children are increasing at a rapid rate,[12,13] the epidemiologic sample averages are similar or higher than the US national averages for clinical diagnoses in primary care. Continued attention to the accurate definition and diagnosis of bipolar spectrum disorders is crucial to avoiding misdiagnosis while reducing the gap between the onset of bipolar symptoms and initiation of appropriate treatment.

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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.

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