Longitudinal Assessment of Manic Symptoms (LAMS) Study: Background, Design, and Initial Screening Results

Sarah McCue Horwitz, PhD; Christine A. Demeter, MA; Maria E. Pagano, PhD; Eric A. Youngstrom, PhD; Mary A. Fristad, PhD, ABPP; L. Eugene Arnold, MD; Boris Birmaher, MD; Mary Kay Gill, MSN; David Axelson, MD; Robert A. Kowatch, MD, PhD; Thomas W. Frazier, PhD; and Robert L. Findling, MD

Objective: To describe the design of a longitudinal study of youth with elevated symptoms of mania (ESM), as well as the prevalence and correlates of manic symptoms. Bipolar disorder in youth is serious and is surrounded by controversy about its phenomenology, course, and treatment. Yet, there are no longitudinal studies of youth selected *only* for ESM, the phenomenological hallmark. The study's objective is to document the rate and sociodemographic correlates of ESM in children attending outpatient psychiatric clinics.

Method: Parents of 3,329 children aged 6–12 years visiting 10 outpatient clinics were asked to complete the Parent General Behavior Inventory 10-Item Mania Scale (PGBI-10M). Children with PGBI-10M scores ≥ 12 (ESM positive-screen [ESM+]) and a matched sample of ESM screen-negative (ESM−) children were invited to enroll in the longitudinal study. The sample was accrued from November 14, 2005, to November 28, 2008.

Results: Most of the children whose parents filled out the PGBI-10M (N = 2,622, 78.8%) participated in the study. Nonparticipants were slightly younger (mean age = 9.1 years [SD = 2.0 years] versus 9.4 years [SD = 2.0 years] for participants; $t_{3327} = 4.42$, $P < .001$). Nearly half of the participants (43%) were ESM+; these were more likely to be Latino (4.2% versus 2.5% for ESM−; $\chi^2_1 = 5.45$, $P = .02$), younger (mean age = 9.3 years [SD = 2.0 years] versus 9.6 years [SD = 1.9 years] for ESM−; $t_{2620} = 3.8$, $P < .001$), and insured by Medicaid (48.4% versus 35.4% for ESM−; $\chi^2_1 = 45.00$, $P < .001$). There were no sociodemographic differences between those who did versus did not agree to enroll in the longitudinal portion (*yes* to enrollment: n = 621, 55.2%; *no* to enrollment: n = 503, 44.8%). Four items best discriminated ESM+ children from ESM− children. Three of the 4 items were not the most commonly endorsed items, but all were indicative of behavioral extremes.

Conclusions: Data suggest that ESM+ is not rare in 6- to 12-year-olds. Children who are ESM+ show behavioral extremes, including rapid mood shifts, compared to ESM− children.

J Clin Psychiatry 2010;71(11):1511–1517

Submitted: *November 16, 2009; accepted March 2, 2010.*
Online ahead of print: *October 5, 2010 (doi:10.4088/JCP.09m05835yel).*
Corresponding author: *Sarah McCue Horwitz, PhD, Department of Pediatrics and Stanford Health Policy, Stanford University School of Medicine, 117 Encina Commons, Stanford, CA 94305-6019 (sarah.horwitz@stanford.edu).*

Bipolar disorder is a serious psychiatric disorder in youth. Lewinsohn et al[1] noted that the lifetime prevalence of bipolar spectrum disorders in older adolescents is ≈ 1%, with an additional 5.7% reporting having experienced subsyndromal symptoms of mania ("core positive subjects"). Epidemiologic studies[2–5] indicate that up to 60% of adults with bipolar disorder report their first symptoms while young (31% below the age of 14 years, 28% between the ages of 15 and 19). Such findings lend support to the possibility of a high prevalence rate of bipolar disorder in youth.[5,6]

Although identified over a century ago[7] and carefully described in 1960,[8] bipolar disorder is controversial with respect to phenomenology, course, and treatment response prior to puberty.[9] This controversy is fueled by several issues. First, the presentation of bipolar disorder may be different in youth. In adults, it typically presents with distinct mood states and interepisode recovery. However, in youth, the illness has been described as follows: (1) brief mood episodes of rapid cycling and/or mixed states and infrequent interepisode recovery and (2) chronically irritable and dysphoric mood.[9–12] Second, bipolar disorder symptoms (hyperactivity, impulsivity, irritability, and aggressive behavior) overlap with other psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD),[9,12–14] nonbipolar depression, and conduct disorder.[15–18] Third, it is often comorbid with other psychiatric disorders such as ADHD.[9,12–14] Finally, there have been few epidemiologic studies and no longitudinal studies of youth selected *only* for elevated symptoms of mania (ESM), the phenomenological hallmark of bipolar disorder.[1,19] A study by Geller et al[20] enrolled 89 consecutive outpatient utilizers selected for *DSM-IV* mania diagnoses requiring either elated mood or grandiosity plus low functioning, thus following children with a narrow phenotype of mania rather than with symptoms of mania. Strober et al[21] prospectively followed 54 adolescents consecutively admitted to a university inpatient service with a diagnosis of bipolar I disorder. This sample was selected on a diagnosis rather than on symptoms.[21] These issues make bipolar disorder in youth difficult to diagnose and have prompted the call for longitudinal studies to disentangle the diagnostic issues.[22]

A longitudinal study of children with ESM who are putatively at greater risk for developing bipolar disorder is also justified by the developmental challenges of recognizing mania; the lack of knowledge about the positive predictive

value of ESM; the increase in the rate of diagnosis of bipolar disorder in youth[23–27]; and the growing evidence that many youth suffer from symptoms (including mania) associated with bipolar disorder for years prior to diagnosis and treatment.[9,11,12,28,29] It is especially important to examine children with ESM since many of these children do not meet strict *DSM* criteria for either bipolar I or II disorder,[29–32] yet suffer from considerable psychopathology and dysfunction.[33] Further, little is known about the phenomenology or diagnostic course in children with ESM, and very little is known about the children's key prognostic features.[31]

Given the issues surrounding bipolar disorder in youth, the National Institute of Mental Health–supported Longitudinal Assessment of Manic Symptoms (LAMS) study was designed to (1) document the rate of ESM using a valid and reliable measure in children 6–12 years of age attending outpatient mental health clinics, (2) describe the longitudinal course and diagnostic evolution of ESM from childhood to adolescence by following this cohort of children over time, and (3) identify childhood risk factors that predict poor functional outcomes in adolescence among children who present with ESM at study entry. This article describes the study design for LAMS and the prevalence and demographic correlates of ESM. The characteristics of the longitudinal cohort, including exclusions, diagnoses, and treatment will be described elsewhere.

METHOD

Design

We constructed a 2-phase study design to investigate the course of ESM in children. Two-phase designs are economical when the diagnosis of the condition of interest is complex or costly: a large population is assessed with a screening instrument, and then some portion of that population is chosen for a more extensive diagnostic assessment.[34,35] A prospective design allows the evaluation of ESM as a marker for developing bipolar disorder, determining whether certain risk factors (eg, early trauma) are related to bipolar disorder and examining the course and diagnostic evolution in children with ESM.[36–38] We screened children visiting outpatient mental health clinics because of (1) the rarity of manic symptoms in the general population of children; (2) our focus on diagnostic course rather than prevalence; and (3) the cost of screening in the community, particularly for only 1 symptom complex.[39]

Sample

The source population consisted of all children between 6.00 and 12.92 years of age visiting 10 child outpatient mental health clinics (2 in Cleveland, Ohio; 2 in Cincinnati, Ohio; 5 in Columbus, Ohio; and 1 in Pittsburgh, Pennsylvania) associated with the universities (Case Western Reserve University, Cleveland, Ohio; University of Cincinnati, Cincinnati, Ohio; Ohio State University, Columbus, Ohio; and University of Pittsburgh, Pittsburgh, Pennsylvania) in the LAMS study. The lower boundary of the age range was chosen because many child assessment measures have not been validated for children less than 6 years of age. Exclusion criteria included a prior visit to any of the participating outpatient clinics within the preceding 12 months, not being accompanied by a parent or legal guardian, and having a parent who did not understand or speak English. Adults accompanying eligible children were approached, and they voluntarily provided written informed consent for participation in the screening portion of the study. The LAMS study was approved by the institutional review board at each of the participating universities.

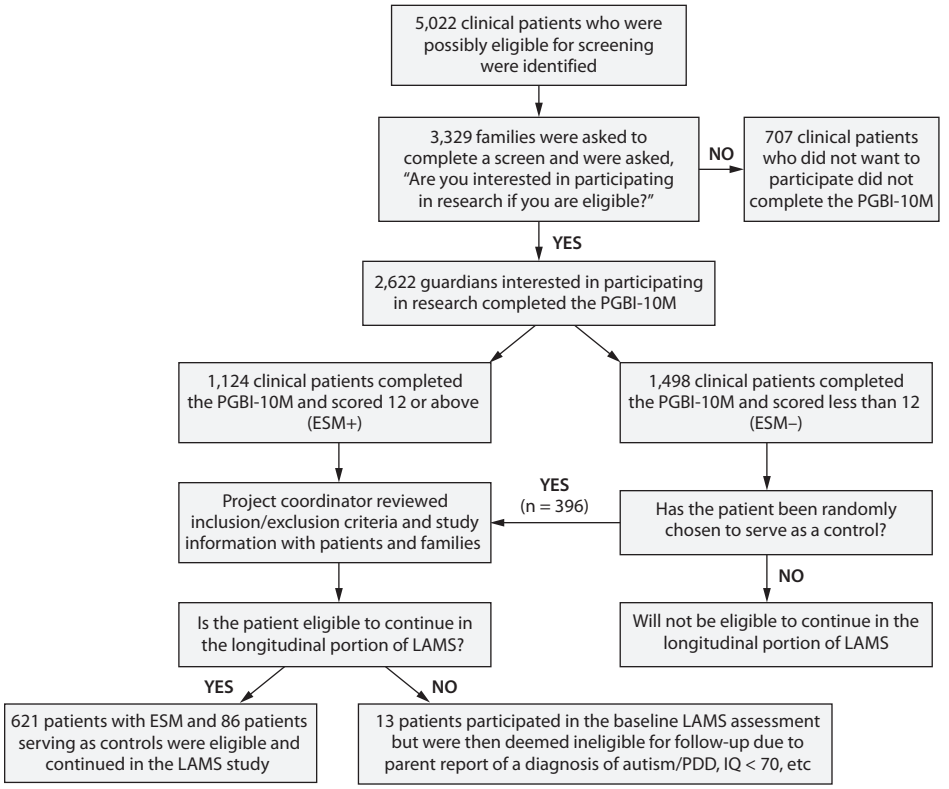
Participating adults of eligible children completed the Parent General Behavior Inventory 10-Item Mania Scale (PGBI-10M)[40,41] and a few sociodemographic questions. All children with a PGBI-10M score ≥ 12 (ie, ESM screen-positive [ESM+]) were invited to enroll in the longitudinal phase of the study. Every 3 to 4 weeks at each study site, 1 child with a PGBI-10M score of ≤ 11 (ie, ESM screen-negative [ESM−]) was selected for every 10 consecutive ESM+ children enrolled. Clinics serving a lower volume of ESM+ children enrolled children in a 1:5 negative-positive ratio. Negative screens were chosen within 3 to 4 weeks of the child's visit because our pilot experience demonstrated more participant refusal beyond this time frame. Using minimization methods, the selected negative screen was matched by age (± 2 years), sex, race/ethnicity, and insurance status of the "modal" positive child in the time segment. If more than 1 negative screen matched, the negative control was randomly selected, and, if a selected negative control refused, he or she was replaced. Considered to be the only equivalent alternative to randomization, minimization ensures balance between study groups for several patient factors.[42,43] This block size and selection method were chosen to ensure approximate balance between ESM+ and ESM− for any potential time trend changes in demographic characteristics of the "modal" ESM+ child (Figure 1). We invited to enroll in the longitudinal phase of the study parents who were informed that participation would entail ≥ 2-hour interviews twice yearly for up to 5 years.

Measures

Screening instrument. A 2-phase design requires that a psychometrically sound screening instrument be available to differentiate individuals with and without the phenomenon of interest. Prepubertal children can be screened for mania, and, as noted by Youngstrom et al,[40] the PGBI-10M performs better than other mania measures for this purpose. The PGBI-10M is a 10-item, empirically derived adaptation of the Parent General Behavior Inventory (PGBI).[44,45] Parents rate the hypomanic, manic, and biphasic mood symptoms of their children aged 5–17 years. Each item is scored from 0 ("never or hardly ever") to 3 ("very often or almost constantly"). Scores range from 0 to 30, with higher scores indicative of greater symptoms. This shortened form of the PGBI was developed by selecting items that maximally

© Copyright 2010 Physicians Postgraduate Press, Inc.

Figure 1. Flowchart of Patient Enrollment Strategy for the LAMS Screening Phase



Abbreviations: ESM = elevated symptoms of mania, ESM– = elevated symptoms of mania negative-screen, ESM+ = elevated symptoms of mania positive-screen, IQ = intelligence quotient, LAMS = Longitudinal Assessment of Manic Symptoms study, PDD = pervasive developmental disorder, PGBI-10M = Parent General Behavior Inventory 10-Item Mania Scale.

discriminated bipolar disorder from other diagnoses.[41] The PGBI-10M is highly reliable (α = 0.92) and maintains the excellent content coverage of the PGBI (correlates 0.95 with the full-length version). The PGBI-10M discriminates patients diagnosed with bipolar disorder from all others, with an area under the curve of 0.86.[39] When scores of ≥ 12 were used as the cutoff in the scale development analyses, a specificity of 88% and a sensitivity of 64% were achieved at an outpatient clinic with a sample enriched with mood disorders.[41] The diagnostic likelihood ratio[46] that a child with a score of 12 or higher on the PGBI-10M had a bipolar diagnosis was 5.5. The PGBI-10M, however, does not cover all symptoms associated with bipolar disorder. We chose the PGBI-10M because it includes a set of behaviors shown to discriminate bipolar from nonbipolar cases with a high degree of accuracy and as a way of obtaining a sample that was enriched for bipolar disorder without including all symptoms of bipolar disorder. The goal of LAMS was to develop a cohort of children with an important risk factor rather than a cohort with likely subsyndromal disorder to better understand the diagnostic evolution and key risk factors for progression to bipolar disorder.

Demographic form. Demographic characteristics reported by parents at screening included the child's age, sex, race/ethnicity, and insurance.

Analyses

Data were double-entered using SPSS Data Builder/Entry, Version 3 (SPSS Inc, Chicago, Illinois). Data discrepancies were corrected, and audits were conducted until all entry errors were corrected in the 2 entry files. Data were then exported to SPSS Version 16 (SPSS Inc, Chicago, Illinois) to examine out-of-range values, logical exclusions, and inconsistencies indicative of response bias.

Statistical analyses were conducted with SAS, Version 9.2.[47] Unweighted means, standard deviations, counts, and percentages were calculated for descriptive statistics. Variables were examined for their skewness and kurtosis. Between-group differences were assessed via the Rao-Scott χ^2 test for binary variables and *t* tests for continuous variables. The standardized effect size was calculated using Cohen *d*.[48] All hypothesis tests were considered statistically significant if the *P* value was < .05.

Sample size and power analyses. The study was designed to provide adequate statistical power for longitudinal follow-up of cases to estimate rates of diagnostic change. In order to generate a large enough sample for the longitudinal aims, a much larger sample was screened. On the basis of the obtained sample size, with α set at .05, the study had 80% power to detect very small effect sizes, Cohen *d* values of 0.11 or larger for *t* tests, and Cohen *w* values of 0.065 or larger for χ^2 tests.[49]

RESULTS

A total of 3,329 children and families visited the study outpatient clinics during sample accrual (November 14, 2005 to November 28, 2008). Of these, 79% (N = 2,622) were eligible and agreed to participate. Two-thirds of the sample were male (66%, n = 1,730) and white (67%, n = 1,743), with a mean age of 9.4 years (SD = 2.0 years; range, 6.0–12.9 years). Forty-one percent (n = 1,074) of the visits were paid for by Medicaid, and 53% (n = 1,395), by private insurance (Table 1). Institutional review board regulations allowed limited information (child age and insurance status) to be collected

Table 1. Sociodemographic Characteristics and Screening Scores of the Study Population by Screening Status

Characteristic	Total (N = 2,622)	Screen-Positive (n = 1,124)	Screen-Negative (n = 1,498)	*P* Value
Age category, n (%)				< .001
6–8 y	1,160 (44.2)	547 (48.7)	613 (40.9)	
9–10 y	758 (28.9)	299 (26.6)	459 (30.6)	
11–12 y	704 (26.8)	278 (24.7)	426 (28.4)	
Age, mean ± SD, y	9.4 ± 2.0	9.3 ± 2.0	9.6 ± 1.9	
Sex, n (%)				.28
Male	1,730 (66.0)	755 (67.2)	975 (65.1)	
Female	891 (34.0)	369 (32.8)	522 (34.8)	
Unknown	1 (0.04)	0 (0)	1 (0.1)	
Race, n (%)				.13
White	1,743 (66.5)	728 (64.8)	1,015 (67.8)	
Asian	12 (0.5)	3 (0.3)	9 (0.6)	
African American	693 (26.4)	312 (27.8)	381 (25.4)	
American Indian	10 (0.4)	3 (0.3)	7 (0.5)	
Multiracial	154 (5.9)	76 (6.8)	78 (5.2)	
Other/unknown	10 (0.4)	2 (0.2)	8 (0.5)	
Ethnicity, n (%)				.04
Latino	83 (3.2)	47 (4.2)	38 (2.5)	
Non-Latino	2,526 (96.3)	1,074 (95.6)	1,450 (96.8)	
Unknown	13 (0.5)	3 (0.3)	10 (0.7)	
Insurance status, n (%)				< .001
Public	1,074 (41.0)	544 (48.4)	530 (35.4)	
Private	1,395 (53.2)	507 (45.1)	888 (59.3)	
Public and private	90 (3.4)	52 (4.6)	38 (2.5)	
Self-pay	23 (0.9)	11 (1.0)	12 (0.8)	
Unknown	40 (1.5)	10 (0.9)	30 (2.0)	
PGBI-10M score, mean ± SD	10.6 ± 8.0	18.6 ± 4.7	4.7 ± 3.5	< .001

Abbreviation: PGBI-10M = Parent General Behavior Inventory 10-Item Mania Scale.

Table 2. Sociodemographic Characteristics and Screening Scores of the Screen-Positive Participants (N = 1,124) by Enrollment Status in the Longitudinal Study

	Screen-Positive Participants		
Characteristic	Yes to Enrollment (n = 621)	No to Enrollment (n = 503)	*P* Value
Age category, n (%)			.68
6–8 y	301 (48.5)	246 (48.9)	
9–10 y	171 (27.5)	128 (25.4)	
11–12 y	149 (24.0)	129 (25.6)	
Sex, n (%)			.61
Male	413 (66.5)	342 (68.0)	
Female	208 (33.5)	161 (32.0)	
Race, n (%)			.17
White	395 (63.6)	333 (66.2)	
Asian	2 (0.3)	1 (0.2)	
African American	171 (27.5)	141 (28.0)	
American Indian	1 (0.2)	2 (0.4)	
Multiracial	52 (8.4)	24 (4.8)	
Other/unknown	0 (0)	2 (0.4)	
Ethnicity, n (%)			.76
Latino	26 (4.2)	19 (3.8)	
Non-Latino	595 (95.8)	481 (95.6)	
Unknown	0 (0)	3 (0.6)	
Insurance status, n (%)			.21
Public	298 (48.0)	246 (48.9)	
Private	289 (46.5)	218 (43.3)	
Public and private	23 (3.7)	29 (5.8)	
Self-pay	8 (1.3)	3 (0.6)	
Unknown	3 (0.5)	7 (1.4)	
PGBI-10M score, mean ± SD	18.4 ± 4.7	18.8 ± 4.8	.22

Abbreviation: PGBI-10M= Parent General Behavior Inventory 10-Item Mania Scale.

on nonparticipants. Nonparticipating children were slightly younger (mean = 9.1, SD = 2.0 years) in comparison to participating children (mean = 9.4, SD = 2.0 years; $t_{3327} = 4.42$, $P < .001$), but payment for visits by Medicaid was similar for both groups (41.4% for nonparticipating versus 41.0% for participating; $\chi^2_1 = 0.05$, $P = .82$.) These results were consistent across sites with 1 exception: participating children in Pittsburgh were more likely to have visits paid for by Medicaid compared to nonparticipating children (54.3% versus 34.6%, respectively; $\chi^2_1 = 27.29$, $P < .0001$).

Adults completed the PGBI-10M on the 2,622 participating children; 43% of the children had PGBI-10M scores of 12 or higher (ie, a positive screen). When compared to negatively screened children, children with positive screens were more likely to be Latino (4.2% versus 2.5%, respectively; $\chi^2_1 = 4.43$, $P = .04$, $d = 0.09$), younger (mean = 9.3 years [SD = 2.0 years] versus mean = 9.6 years [SD = 1.9 years], respectively; $t_{2620} = 3.8$, $P < .001$, $d = 0.15$), and supported by Medicaid (48.4% versus 35.4%, respectively; $\chi^2_1 = 45.00$, $P \leq .001$, $d = 0.28$). There were no significant differences between screen-positive and screen-negative children in terms of sex or race. Similarities and differences were largely consistent across sites with a few exceptions. Whites were less likely to be screen-positive at the Pittsburgh, Pennsylvania, and Cleveland, Ohio, sites, and boys were more likely to be screen-positive in the Columbus, Ohio, sites (data not shown).

Positive Screens

Children with positive screens whose families did (55.2%, n = 621) and did not (44.8%, n = 503) agree to participate in phase 2 of the study were examined. As shown in Table 2, no significant demographic differences emerged between groups in terms of child age, sex, race/ethnicity, or insurance status. These findings were consistent across sites with 1 exception. In Pittsburgh, whites were more likely to refuse participation in phase 2. These comparisons were not done for the screen-negative children because they were sampled with replacements if they did not agree to participate in the longitudinal phase of the study.

Positive Versus Negative Screens

Finally, we examined symptoms endorsed on the PGBI-10M for those who screened positive compared to those who screened negative (Table 3). As would be expected, all 10 items on the PGBI-10M were more frequently endorsed by those who screened positive. Among the screen-positive children, 4 items were endorsed more frequently (listed by item number): (2) unusually happy and intensely energetic, but everything gets on nerves and makes angry; (3) mood/energy shifts rapidly from happy to sad or high to low; (4) feelings/energy are generally up or down but rarely in the middle; and (5) days unusually happy and intensely energetic, yet also physically restless, shifting activities. However, the items with the largest effect sizes, that is, those that best

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 3. Symptoms Endorsed on the Parent General Behavior Inventory 10-Item Mania Scale (PGBI-10M) by Screening Status[a]

Symptom	Screen-Positive, n (%)	Screen-Negative, n (%)	Cohen *d* Effect Size	*P* Value
1. Days or more depressed/irritable, then days or more extremely high, elated, overflowing with energy	658 (58.5)	52 (3.5)	2.24	<.001
2. Unusually happy and intensely energetic, but everything gets on nerves and makes angry	836 (74.4)	136 (9.1)	2.15	<.001
3. Mood/energy shifts rapidly from happy to sad or high to low	898 (79.9)	273 (18.2)	1.82	<.001
4. Feelings/energy are generally up or down but rarely in the middle	850 (75.6)	191 (12.8)	1.92	<.001
5. Days unusually happy and intensely energetic, yet also physically restless, shifting activities	863 (76.8)	270 (18.0)	1.71	<.001
6. Days or more of extreme happiness or energy, yet also anxious or tense	627 (55.8)	56 (3.7)	2.23	<.001
7. Days or more when others tell parent that child seems unusually happy or high—clearly different self	433 (38.5)	27 (1.8)	1.92	<.001
8. Times when thoughts/ideas come so fast child cannot get them all out, or others complain they cannot keep up	635 (56.5)	156 (10.4)	1.47	<.001
9. Days or more unusually happy and energetic, yet also struggles with rage or urge to smash/destroy	745 (66.3)	89 (5.9)	2.27	<.001
10. Days or more of extreme happiness and energy, and it takes over an hour to get to sleep at night	722 (64.2)	140 (9.3)	1.90	<.001

[a]PGBI-10M adapted with permission from Youngstrom et al.[41]

discriminated between the positive-screen and negative-screen children, were items 1, 2, 6, and 9. eAppendix 1 contains the full distribution of responses for ESM+ and ESM− subjects.

DISCUSSION

Data from these 6- to 12-year-old first-time utilizers of general outpatient mental health clinics participating in this study suggest that symptoms of mania are common and that their prevalence may differ by demographic characteristics. Of the 2,622 families who agreed to complete the PGBI-10M, 1,124 or 42.9% scored their children as positive for symptoms of mania. Although a *DSM-III-R* diagnosis of mania has been reported in about 16% of outpatient users 12 years of age or younger,[12] these data suggest that manic symptoms (as opposed to a *DSM-IV* diagnosis of bipolar disorder) may be even more common in young outpatient utilizers. Participating children who scored positive for symptoms of mania display very different behavior than children who scored negative, as noted in a number of previous studies examining symptoms in bipolar youth compared to youth with other diagnoses.[11,33,50]

The children who scored positive for symptoms of mania showed no sex difference but were more likely to be younger, Latino, and publicly insured. The lack of any sex difference is consistent with prior reports[51] of similar rates of bipolar diagnoses in boys and girls, and the findings also correspond with prior work indicating that higher levels of mania are found at younger ages.[51] There is documentation that 10%–20% of adults with bipolar disorder report onset before the age of 10.[5,52] However, whether the relationship of age to manic symptoms is due to the relationship of these symptoms to other common psychiatric problems such as ADHD, nonpathological age-related differences in behavior, or age trends for decreasing levels of mania as reported by Cicero et al[53] cannot be determined by these data but, rather, by tracking subjects' diagnostic evolution over time.

Although the relationships of ethnicity and poverty (approximated by public insurance) have not been previously reported, the more general relationship of socioeconomic status and psychopathology in children has been documented.[54–56] Given that the vast majority of investigations of diagnostic efficiency come from European-American middle and upper class samples, and that few Latinos participated in a study examining the performance of the screening instrument in subpopulations,[41] this finding, although a small difference, needs to be replicated and explored.[57] Unfortunately, as previously identified,[52,58,59] while very good data are available from regional epidemiologic studies, data on prevalence and correlates of psychopathology from a national sample are scarce. However, the National Comorbidity Survey Replication Adolescent Supplement (NCS-A)[58,60] will provide critical data on the correlates of psychopathology for 13- to 17-year-olds. It will be informative to compare these ethnicity and socioeconomic findings to the NCS-A when they become available.

Examining the symptoms endorsed, we find that every symptom was endorsed more frequently in those scoring positive, but 4 symptoms contributed most strongly to the differences (listed by item number): (1) days or more depressed/irritable, then days or more extremely high, elated, overflowing with energy; (2) unusually happy and intensely energetic, but everything gets on nerves and makes angry; (6) days or more of extreme happiness or energy, yet also anxious or tense; and (9) days or more unusually happy and energetic, yet also struggles with rage or urge to smash/destroy. Taken together, these symptoms describe children with considerable extremes in behavior; further, as pointed out by Youngstrom et al[57] in an extensive review of the evidence on the phenomenology of bipolar disorder in youth, these symptoms are highly specific to the disorder although, as reported by Shankman et al,[61] the diagnostic evolution may not be homotypic. That every symptom was endorsed more frequently in those scoring positive is not surprising given that Youngstrom et al[40] selected items from the PGBI that best discriminated between bipolar and nonbipolar cases.

Limitations

The data were generated from eligible children visiting general mental health outpatient clinics. Consequently, although representative of the 6- to 12-year-old utilizers, the data may not be representative of all outpatient utilizers, nor are they representative of children in the community. Although the screening portion of the study achieved a very good response rate (79%), only 55% of families with ESM+ children agreed to participate in the longitudinal portion of the study, usually because of the time commitment demanded by the twice-yearly ≥ 2-hour assessments. While there are no differences on the demographic variables available from the screening data for those who did and did not agree to enroll in phase 2, with just over one-half of those eligible agreeing to participate in the follow-up, there may be differences between participating and nonparticipating families. Finally, these data were all self-reported. There is no gold standard for identifying mania, and the PGBI-10M, although psychometrically sound and with better performance than other mania measures, contains questions with multiple characteristics embedded within each item.[40] Consequently, even though the exceptionally high internal consistency reliability argues against the item content being too heterogeneous, we do not know precisely to what portion of a question parents are responding.

CONCLUSIONS

This cohort of 6- to 12-year-old first-time utilizers of participating outpatient mental health clinics enriched for symptoms of mania—the hallmark symptom of bipolar disorder—will provide the data necessary to determine the positive predictive power of early symptoms of mania for the development of bipolar disorder and identify risk factors associated with poor functional outcomes. Given the functional impairment and suffering caused by bipolar disorder in children, accurate diagnosis and treatment are critical. Data generated by this cohort of children and their families have the potential to inform both of these important areas.

Author affiliations: Department of Pediatrics and Stanford Health Policy, Stanford University School of Medicine, Stanford, California (Dr Horwitz); Department of Psychiatry, Division of Child and Adolescent Psychiatry, Case Western Reserve University, Cleveland, Ohio (Ms Demeter and Drs Pagano and Findling); Department of Psychology, University of North Carolina at Chapel Hill (Dr Youngstrom); Department of Psychiatry, Division of Child and Adolescent Psychiatry, Ohio State University, Columbus (Drs Fristad and Arnold); Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, University of Pittsburgh, Pennsylvania (Drs Birmaher and Axelson and Ms Gill); Division of Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Dr Kowatch); and Center for Pediatric Behavioral Health and Center for Autism, Cleveland Clinic, Cleveland, Ohio (Dr Frazier).

Potential conflicts of interest: **Dr Arnold** has received research support, has been a consultant to, and/or has served on speakers bureaus for Abbott, Celgene, Eli Lilly, McNeil, Novartis, Neuropharm, Organon, Shire, Sigma Tau, and Targacept. **Dr Birmaher** has received research support from the National Institute of Mental Health (NIMH); has been a consultant for Schering-Plough; has participated in a forum sponsored by Forest; and has received or will receive royalties for publications from Random House, Inc (*New Hope for Children and Teens With Bipolar Disorder*) and Lippincott Williams & Wilkins (*Treating Child and Adolescent Depression*). **Dr Kowatch** has received research support from NARSAD, the National Institute of Child Health and Human Development, NIMH, and The Stanley Foundation; has been a consultant for Forest, AstraZeneca, Medscape, and Physicians Postgraduate Press; has served on the speakers bureau for AstraZeneca; and is an editor for *Current Psychiatry*. **Dr Frazier** has been a consultant to Shire Development. **Dr Findling** has received grant/research support from Abbott, Addrenex, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, Eli Lilly, Neuropharm, Otsuka, Pfizer, Shire, Supernus, and Wyeth; has been a consultant for Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm, Eli Lilly, Lundbeck, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracor, Shire, Solvay, Supernus, Validus, and Wyeth; and has served on speakers bureaus for Bristol-Myers Squibb, Johnson & Johnson, and Shire. **Drs Horwitz, Pagano**, **Youngstrom**, **Fristad**, and **Axelson** and **Mss Demeter and Gill** have no competing financial interests to disclose.

Funding/support: This study was supported by NIMH grant R01-MH073967.

Disclaimer: We acknowledge that the findings and conclusions presented in this article are those of the authors alone and do not necessarily reflect the opinions of NIMH.

Acknowledgment: We thank NIMH for its support.

REFERENCES

1. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry*. 1995;34(4):454–463.
2. Grant BF, Stinson FS, Hasin DS, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and Axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2005;66(10):1205–1215.
3. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of *DSM-III-R* psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8–19.
4. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2007;64(5):543–552.
5. Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. *J Affect Disord*. 1994;31(4):281–294.
6. Leverich GS, Post RM, Keck PE Jr, et al. The poor prognosis of childhood-onset bipolar disorder. *J Pediatr*. 2007;150(5):485–490.
7. Greves EH. Acute mania in a child of five years: recovery; remarks. *Lancet*. 1884;2:824–826.
8. Anthony J, Scott P. Manic depressive psychosis in childhood. *J Child Psychol Psychiatry*. 1960;1(1):53–72.
9. Findling RL, Gracious BL, McNamara NK, et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord*. 2001;3(4):202–210.
10. Geller B, Sun K, Zimerman B, et al. Complex and rapid-cycling in bipolar children and adolescents: a preliminary study. *J Affect Disord*. 1995;34(4):259–268.
11. Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 1997;36(9):1168–1176.
12. Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry*. 1995;34(7):867–876.
13. Geller B, Zimerman B, Williams M, et al. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2000;10(3):157–164.
14. Kowatch RA, Youngstrom EA, Danielyan A, et al. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. *Bipolar Disord*. 2005;7(6):483–496.
15. Bowring MA, Kovacs M. Difficulties in diagnosing manic disorders among children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1992;31(4):611–614.
16. Carlson GA. Mania and ADHD: comorbidity or confusion. *J Affect Disord*. 1998;51(2):177–187.
17. Geller B, Williams M, Zimerman B, et al. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms,

grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord*. 1998;51(2):81–91.
18. Kim EY, Miklowitz DJ. Childhood mania, attention deficit hyperactivity disorder and conduct disorder: a critical review of diagnostic dilemmas. *Bipolar Disord*. 2002;4(4):215–225.
19. Carlson GA, Kashani JH. Manic symptoms in a non-referred adolescent population. *J Affect Disord*. 1988;15(3):219–226.
20. Geller B, Craney JL, Bolhofner K, et al. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry*. 2002;159(6):927–933.
21. Strober M, Schmidt-Lackner S, Freeman R, et al. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry*. 1995;34(6): 724–731.
22. Biederman J, Klein RG, Pine DS, et al. Resolved: mania is mistaken for ADHD in prepubertal children. *J Am Acad Child Adolesc Psychiatry*. 1998;37(10):1091–1096, discussion 1096–1099.
23. Naylor MW, Anderson JR, Kruesi MJ, et al. Pharmacoepidemiology of Bipolar Disorder in Abused and Neglected State Wards. Presented at the 49th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 22–27, 2002; San Francisco, CA.
24. Harpaz-Rotem I, Leslie DL, Martin A, et al. Changes in child and adolescent inpatient psychiatric admission diagnoses between 1995 and 2000. *Soc Psychiatry Psychiatr Epidemiol*. 2005;40(8):642–647.
25. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among US child, adolescent, and adult inpatients, 1996–2004. *Biol Psychiatry*. 2007;62(2):107–114.
26. Olfson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry*. 2006;63(6):679–685.
27. Moreno C, Laje G, Blanco C, et al. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry*. 2007;64(9):1032–1039.
28. Thuppal M, Carlson GA, Sprafkin J, et al. Correspondence between adolescent report, parent report, and teacher report of manic symptoms. *J Child Adolesc Psychopharmacol*. 2002;12(1):27–35.
29. Carlson GA, Youngstrom EA. Clinical implications of pervasive manic symptoms in children. *Biol Psychiatry*. 2003;53(11):1050–1058.
30. Nottelmann E, Biderman J, Birmaher B, et al. National Institute of Mental Health research roundtable on prepubertal bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):871–878.
31. Hazell PL, Carr V, Lewin TJ, et al. Manic symptoms in young males with ADHD predict functioning but not diagnosis after 6 years. *J Am Acad Child Adolesc Psychiatry*. 2003;42(5):552–560.
32. Findling RL, Youngstrom EA, McNamara NK, et al. Early symptoms of mania and the role of parental risk. *Bipolar Disord*. 2005;7(6):623–634.
33. Carlson GA, Loney J, Salisbury H, et al. Young referred boys with DICA-P manic symptoms vs two comparison groups. *J Affect Disord*. 1998;51(2):113–121.
34. Shrout PE, Newman SC. Design of two-phase prevalence surveys of rare disorders. *Biometrics*. 1989;45(2):549–555.
35. Costello EJ, Egger H, Angold A. 10-year research update review: the epidemiology of child and adolescent psychiatric disorders, 1: methods and public health burden. *J Am Acad Child Adolesc Psychiatry*. 2005;44(10):972–986.
36. Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev Psychopathol*. 2006;18(4):1181–1211.
37. Kessler RC. Psychiatric epidemiology: selected recent advances and future directions. *Bull World Health Organ*. 2000;78(4):464–474.
38. Jablensky A. Research methods in psychiatric epidemiology: an overview. *Aust N Z J Psychiatry*. 2002;36(3):297–310.
39. Kelsey JL, Thompson WD, Evans AS. *Methods in Observational Epidemiology*. New York, NY: Oxford University Press; 1986.
40. Youngstrom E, Meyers O, Demeter C, et al. Comparing diagnostic checklists for pediatric bipolar disorder in academic and community mental health settings. *Bipolar Disord*. 2005;7(6):507–517.
41. Youngstrom EA, Frazier TW, Demeter C, et al. Developing a 10-item mania scale from the Parent General Behavior Inventory for children and adolescents. *J Clin Psychiatry*. 2008;69(5):831–839.
42. Scott NW, McPherson GC, Ramsay CR, et al. The method of minimization for allocation to clinical trials: a review. *Control Clin Trials*. 2002; 23(6):662–674.
43. Moher D, Schulz KF, Altman DG; CONSORT. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Med Res Methodol*. 2001;1(1):2.
44. Youngstrom EA, Findling RL, Danielson CK, et al. Discriminative validity of parent report of hypomanic and depressive symptoms on the General Behavior Inventory. *Psychol Assess*. 2001;13(2):267–276.
45. Youngstrom EA, Findling RL, Calabrese JR, et al. Comparing the diagnostic accuracy of six potential screening instruments for bipolar disorder in youths aged 5 to 17 years. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):847–858.
46. Straus SE, Richardson WS, Glasziou P, et al. *Evidence-Based Medicine: How to Practice and Teach EBM*. 3rd ed. New York, NY: Churchill Livingstone; 2005.
47. SAS Institute. *SAS 9.2*. Carey, NC: SAS Institute Inc.; 2009.
48. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Erlbaum Associates; 1988.
49. Faul F, Erdfelder E, Lang AG, et al. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175–191.
50. Carlson GA, Meyer SE. Bipolar disorder in youth. *Curr Psychiatry Rep*. 2000;2(2):90–94.
51. Duax JM, Youngstrom EA, Calabrese JR, et al. Sex differences in pediatric bipolar disorder. *J Clin Psychiatry*. 2007;68(10):1565–1573.
52. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 2005;44(9):846–871.
53. Cicero DC, Epler AJ, Sher KJ. Are there developmentally limited forms of bipolar disorder? *J Abnorm Psychol*. 2009;118(3):431–447.
54. Costello EJ, Compton SN, Keeler G, et al. Relationships between poverty and psychopathology: a natural experiment. *JAMA*. 2003;290(15): 2023–2029.
55. McLeod JD, Shanahan MJ. Trajectories of poverty and children's mental health. *J Health Soc Behav*. 1996;37(3):207–220
56. Bor W, Najman JM, Andersen MJ, et al. The relationship between low family income and psychological disturbance in young children: an Australian longitudinal study. *Aust N Z J Psychiatry*. 1997;31(5):664–675.
57. Youngstrom EA, Birmaher B, Findling RL. Pediatric bipolar disorder: validity, phenomenology, and recommendations for diagnosis. *Bipolar Disord*. 2008;10(1 pt 2):194–214.
58. Merikangas K, Avenevoli S, Costello J, et al. National Comorbidity Survey Replication Adolescent Supplement (NCS-A), I: background and measures. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):367–369.
59. Merikangas KR, Low NC. The epidemiology of mood disorders. *Curr Psychiatry Rep*. 2004;6(6):411–421.
60. Kessler RC, Avenevoli S, Costello EJ, et al. National Comorbidity Survey Replication Adolescent Supplement (NCS-A), II: overview and design. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):380–385.
61. Shankman SA, Lewinsohn PM, Klein DN, et al. Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. *J Child Psychol Psychiatry*. 2009;50(12): 1485–1494.

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.

eAppendix 1 is available at PSYCHIATRIST.COM.

eAppendix 1. Distribution of Responses to Symptoms Endorsed on the Parent General Behavior Inventory 10-Item Mania Scale (PGBI-10M) by Screening Status[a,b]

	ESM+ (N = 1,124), n (%)				ESM– (N = 1,498), n (%)			
Symptom	0	1	2	3	0	1	2	3
1. Days or more depressed/irritable, then days or more extremely high, elated, overflowing with energy	88 (7.8)	377 (33.5)	419 (37.3)	240 (21.4)	1,087 (72.6)	359 (24.0)	46 (3.1)	6 (0.4)
2. Unusually happy and intensely energetic, but everything gets on nerves and makes angry	48 (4.3)	240 (21.4)	479 (42.6)	357 (31.8)	886 (59.1)	475 (31.7)	125 (8.4)	12 (0.8)
3. Mood/energy shifts rapidly from happy to sad or high to low	31 (2.8)	194 (17.3)	409 (36.4)	490 (43.6)	631 (42.1)	594 (39.7)	234 (15.6)	39 (2.6)
4. Feelings/energy are generally up or down but rarely in the middle	30 (2.7)	243 (21.6)	505 (44.9)	346 (30.8)	809 (54.0)	498 (33.2)	161 (10.7)	30 (2.0)
5. Days unusually happy and intensely energetic, yet also physically restless, shifting activities	41 (3.6)	220 (19.6)	380 (33.8)	483 (43.0)	785 (52.4)	443 (29.6)	193 (12.9)	77 (5.1)
6. Days or more of extreme happiness or energy, yet also anxious or tense	96 (8.5)	398 (35.4)	413 (36.7)	217 (19.3)	1,142 (76.2)	300 (20.0)	50 (3.3)	6 (0.4)
7. Days or more when others tell parent that child seems unusually happy or high—clearly different self	222 (19.8)	469 (41.7)	284 (25.3)	149 (13.3)	1,238 (82.6)	233 (15.6)	24 (1.6)	3 (0.2)
8. Times when thoughts/ideas come so fast child cannot get them all out, or others complain they cannot keep up	140 (12.5)	348 (31.0)	95 (35.1)	3,241 (21.4)	932 (62.2)	410 (27.4)	117 (7.8)	39 (2.6)
9. Days or more unusually happy and energetic, yet also struggles with rage or urge to smash/destroy	112 (10.0)	266 (23.7)	387 (34.4)	359 (31.9)	1,105 (73.8)	304 (20.3)	82 (5.5)	7 (0.5)
10. Days or more of extreme happiness and energy, and it takes over an hour to get to sleep at night	116 (10.3)	285 (25.4)	315 (28.0)	408 (36.3)	1,003 (67.0)	355 (23.7)	116 (7.7)	24 (1.6)

[a]PGBI-10M adapted with permission from Youngstrom et al.[41]
[b]Responses ranged from 0 (never or hardly ever) to 3 (very often or almost constantly).
Abbreviations: ESM– = elevated symptoms of mania screen-negative, ESM+ = elevated symptoms of mania screen-positive.

doi:10.4088/JCP.09m05835yel
© Copyright 2010 Physicians Postgraduate Press, Inc.